Can Complete Blood Count Picture Tell Us More About the Activity of Rheumatological Diseases?

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ABSTRACT

BACKGROUND: In clinical practice, distinguishing disease activity in patients with rheumatological illnesses is challenging.

OBJECTIVES: We aimed to investigate clinical associations of hemogram-derived indices, namely: red cell distribution width (RDW), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII) with disease activity in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS).

METHODS: In 250 patients with rheumatological disease and 100 healthy age-matched controls, we investigated disease activity scores and indicators and evaluated their association with hemogram-derived indices values.

RESULTS: Compared with the control group, RDW, MPV, and PLR significantly increased ($P < .001$) in the three studied disorders (RA, SLE, and AS), but LMR dramatically decreased. SII was considerably higher in RA and AS patients compared with controls but not in SLE patients. On the other hand, NLR rose dramatically in SLE patients compared with controls ($P = .043$), but did not change much in RA and AS patients ($P > .05$). RDW and MPV showed significant changes ($P < .001$) in the three studied diseases (RA, SLE, and AS) according to disease activity. They significantly increased across worsening activity scores. Only in the SLE group, PLR was significantly increased with disease activity ($P < .001$), while LMR showed a significant decrease ($P = .016$).

CONCLUSIONS: Clinicians must pay close attention to complete blood count (CBC) analysis and its various derived ratios to better characterize the activity of rheumatological disorders and anticipate the disease course and prognosis.

KEYWORDS: Ankylosing spondylitis, complete blood count, hemogram-derived ratios, rheumatoid arthritis, systemic lupus erythematosus

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Introduction

Inflammation is the primary determinant and the critical pathogenic mechanism in many connective tissue diseases; the inflammatory process, if uncontrolled, can result in significant disabilities with increased mortality.[1] Systemic lupus erythematosus (SLE) is an inflammatory disease characterized by the generation of autoantibodies and immune complexes with end-organ damage (especially the kidneys).[2] Even with appropriate management, SLE patients may continue to have disease activity up to 10 years after diagnosis.[3] Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder affecting several organs, particularly the synovial membranes of joints, which results in joint degeneration, and poor quality of life.[4] Ankylosing spondylitis (AS), the archetype of spondyloarthropathies, is a chronic inflammatory condition that mostly affects the sacroiliac joint and spine.[5] Although AS is a slowly progressive disorder, spine involvement is progressive, and the inflammation can persist even years after the diagnosis,[6] leading to serious mobility problems and restricted social life.[7] As a result, using reliable markers to measure inflammation in collagen and connective tissue diseases is critical for monitoring disease activity and predicting patient outcomes. The most commonly used markers in daily practice are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

On the other hand, these indicators have a limited ability to distinguish between disease flare and superimposed infections.[8]

The complete blood count (CBC) is a simple, inexpensive, and time-effective test used routinely for rheumatology patients to monitor medication side effects and possible disease-related changes. Systemic inflammation is linked to changes in circulating blood cells. Many inflammatory disorders are accompanied by normochromic anemia, thrombocytosis, neutrophilia, lymphopenia, and monocytosis. As a result, inflammatory activity can be assessed using the characteristics of circulating blood cell components.[9] Neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR) are widely accepted and useful tools for the evaluation of inflammatory activity in many chronic inflammatory disorders.[9-11] Moreover, the red cell distribution width (RDW), the mean platelet volume (MPV), and the systemic immune-inflammation index (SII) have emerged as biomarkers of inflammation and disease activity in a variety of diseases.[11-14]

MPV is a surrogate marker of platelet activation,[15] and has been associated with a number of inflammatory conditions, including functional bowel diseases,[16] obesity,[17] infections,[18] diabetes mellitus (DM),[19] vertebral disk conditions,[20] and cardiac diseases.[21] On the other hand, RDW is a marker of anisocytosis[22] and is associated with certain inflammatory conditions, such as thyroiditis,[23] autoimmune hepatitis,[24] malignant conditions,[25] and type 2 DM.[26]

As a hemogram-derived marker, NLR has been reported to be associated with inflammatory bowel disease,[27] irritable bowel syndrome,[28] Hashimoto's disease,[29] and type 2 DM.[30] Similarly, PLR has been introduced as an inflammatory marker in thyroid conditions,[31] DM,[32] and liver fibrosis.[33] Finally, LMR is suggested to be related with diabetic nephropathy,[34] critical limb ischemia,[35] and cerebral venous sinus thrombosis.[36]

Our study was intended to detect whether the hemogram-derived ratios and indices (NLR, LMR, PLR, RDW, MPV, and SII) in RA, SLE, and AS patients were affected and whether they were related to the activity of the disease.

Methodology

Study subjects and settings

The PASS 11 Program was used for sample size calculation, setting power at 80% and α-error at 0.05. It was estimated that a sample size of 75 patients will be adequate to detect an expected area under receiver operating characteristic (ROC) curve of 0.70 for measured ratios to differentiate between active and inactive cases (assuming 30% of patients have active disease according to Kisacik et al).[37]

This case-control study included; 250 adult patients (age ⩾ 18 years old) with rheumatological diseases (100 patients with SLE, 100 with RA, and 50 with AS), who visited the outpatient clinic or were admitted to the inpatient unit of the Rheumatology Department of Ain-Shams University, Cairo, Egypt, during the period from April 1 to June 30, 2021 (within 6 months from their first diagnosis). The study also included 100 healthy adult age-matched subjects as control. All included participants were subjected to detailed history taking stressing on age, gender, and presenting symptoms, and a thorough clinical examination. Patients with SLE were diagnosed using the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria,[38] RA patients with the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria,[39] and AS patients with the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria.[40] Those who were pregnant or up to 6 months postpartum or had blood, liver, kidney, heart, or thyroid disorders, concomitant autoimmune diseases, infections, or malignancies were all excluded from the study.

Evaluation of disease activity

The disease activity of SLE patients was assessed using the systemic lupus erythematosus disease activity index (SLEDAI) scoring system,[41] which classified patients with a score of <6 as clinically inactive, 6 to 12 as having mild to moderate disease activity, and >12 as having severe disease activity.

The disease activity of RA patients was assessed using the disease activity score-28 (DAS-28),[42] which classified patients with a score of <2.6 as remitted, patients with a score of 2.6 to 3.1 as low active, patients with a score of 3.2 to 5.0 as moderately active, and patients with a score of >5.1 as highly active.

Regarding AS patients, we rated pain on a 10-point scale (1 being the least severe and 10 being the most severe) and by the ankylosing spondylitis disease activity score (ASDAS),[43] we used three cut-offs (1.3, 2.1, and 3.5) to distinguish AS inactive and moderate, high and very high disease activity.

Laboratory investigations

Two ml EDTA anticoagulated venous blood samples from each participant were aseptically withdrawn for CBC with differential count analysis, using the Sysmex XT-1800i autoanalyzer (Sysmex, Japan). We calculated ratios between neutrophil and lymphocyte counts (NLR), lymphocyte and monocyte counts (LMR), and platelet and lymphocyte counts (PLR). We also calculated the SII by multiplying the neutrophil count by platelet count and dividing by the lymphocyte count. RDW, which reflects the variability in red cell sizes, was calculated by the instrument by dividing the standard deviation of mean cell size by the mean corpuscular volume (MCV) of the red cells and multiplying by 100. Also, the MPV was calculated by the instrument by dividing the total mass of the platelets (plateletcrit) by the total number of platelets.

In SLE patients, an additional 3 ml of blood was collected into a serum separation tube. Serum samples were used to determine anti-double-stranded DNA antibody titer

(anti-dsDNA) by indirect immunofluorescence technique (slides were supplied by Inova Diagnostics, Inc., San Diego, USA, REF: 508200.10) and complement levels by a COBAS Auto-analyzer (Roche Diagnostics, Mannheim, Germany).

In RA patients, an additional 3 ml of blood was collected into a serum separation tube. Serum samples were used for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) determination by a COBAS Autoanalyzer (Roche Diagnostics, Mannheim, Germany).

An additional 2 ml of blood was collected in AS patients into an EDTA tube used for HLA-B27 typing by the serological method using Terasaki microtiter plates (Inno-Train Diagnostik GmbH, Kronberg, Germany) and Leica DMI3000B Inverted Fluorescence Phase-contrast Microscope (Wetzlar, Germany).

Statistical analysis

For data analysis, IBM SPSS statistics (V. 26.0, IBM Corp., USA, 2019) was used. After describing the data, we used the Wilcoxon rank sum test, Kruskal-Wallis test, and chi-square test to make comparisons. The correlation between parameters was detected using the ranked Spearman correlation test. ROC curve was built and the area under the curve (AUC) was determined to detect the most discriminating markers of disease activity. To discover the most sensitive predictors for disease activity, we used a logistic multi-regression analysis. Results were considered significant at $P < .05$.

Results

This case-control study comprised 100 healthy control and 250 adult rheumatological patients (100 SLE, 100 RA, and 50 AS). Patients and controls were age-matched with no significant differences. More female patients were in RA (81.0%) and SLE (84.0%) groups, while 66.0% were males in the AS group. RDW, MPV, and PLR significantly increased in the three studied groups (RA, SLE, and AS) compared with the control group, while LMR significantly decreased. SII significantly increased in RA and AS patients than controls, while SLE patients showed no significant change. On the other hand, NLR significantly increased in SLE patients than controls but showed no significant change in RA and AS patients. Table 1 demonstrates characteristics and CBC parameters of the included control subjects and RA, SLE, and AS patients.

Disease-specific markers and activity scoring are shown in Table 2. The median (interquartile range [IQR]) DAS 28 score of the included RA patient was 4.4 (2.8–5.9) with a range of 2–8.3, the median (IQR) SLEDAI score of the included SLE patients was 9 (6–13), and ranged from 4 to 20, and the median (IQR) ASDAS score of the included AS patients was 1.9 (1.17–2.82) and ranged from 1 to 3.8.

RDW and MPV showed significant changes in the three studied diseases (RA, SLE, and AS) according to disease activity. They significantly increased across worsening activity scores. Only in the SLE group, PLR was significantly increased with worsening SLEDAI, while LMR showed a significant decrease (Table 3).

Furthermore, RDW and MPV showed significant positive correlations with CRP, ESR, DASs, namely, DAS-28, SLEDAI, and ASDAS in RA, SLE, and AS, respectively. RDW and MPV were also significantly positively correlated with RF and anti-CCP levels in the RA group and anti-ds-DNA titer in the SLE group. PLR in the SLE group, and NLR and SII in the AS group were also significantly positively correlated with activity markers (CRP and ESR) and scores (SLEDAI and ASDAS, respectively). On the contrary, LMR in the AS group significantly negatively correlated with CRP and ESR only but not with the ASDAS score (Table 4).

According to multi-regression analyses, RDW and NLR were the best predictors of RA activity with a regression coefficient of 0.040 and −0.027, and a P of .002 and .049, respectively (F ratio: 7.144; $P = .001$). On the other hand, RDW and MPV were the best predictors of SLE activity with a regression coefficient of 0.035 and 0.058 and a P of .035 and .051, respectively (F ratio: 9.816; $P < .001$). Similarly, RDW and MPV were the best predictors of AS activity; regression coefficients were 0.084 and 0.058; P of $< .001$ and .003, respectively (F ratio: 32.079; $P < .001$).

Figures 1 to 3 illustrate ROC curve analysis to detect the best cut-off points for the prediction of disease activity. In the multi-ROC analysis, prediction of disease activity by combined markers showed better performance than the single prediction by one biomarker. The diagnostic sensitivity, specificity, negative and positive predictive values, and accuracy of RA activity prediction increased to 100% when RDW at 13.7% and NLR at 3.4 were combined. SLE activity prediction by RDW at 14.0% with MPV at 10 fl showed 100% diagnostic specificity, 96.9% diagnostic sensitivity, 84.8% negative predictive value, 100% positive predictive value, and 97.3% diagnostic accuracy. In AS, combined activity prediction by RDW at 16.0% and MPV at 8.8 fl showed 100% diagnostic specificity, 98.5% diagnostic sensitivity, 96.8% negative predictive value, 100% positive predictive value, and 99.0% diagnostic accuracy.

Discussion

ESR and CRP levels and other indices are extensively employed as indicators of disease activity in systemic autoimmune rheumatological diseases; still, serum levels are affected by various other conditions, and normal levels do not consistently exclude active disease.[44,45] Researchers are looking for other parameters that reflect disease activity because of the shortcomings of traditional acute-phase reactants (APRs).

Table 1. Demographic characteristics and CBC parameters and derived ratios in the control subjects, RA, SLE, and AS patients.

VARIABLE	CONTROL (*N* = 100)	RA (*N* = 100)	*P*1	SLE (*N* = 100)	*P*2	AS (*N* = 50)	*P*3
Age (years)	73 (71–86)	67 (59–71)	.104	65 (57–66)	.092	68 (64–70)	.122
	64–94	57–77		55–68		62–73	
Sex, n (%)	Females: 51 (51.0%)	81 (81.0%)	**< .001**	84 (84.0%)	**< .001**	17 (34.0%) 45.3%	**.049**
	Males: 49 (49.0%)	19 (19.0%)		16 (16.0%)		33 (66.0%)	
TLC ($\times 10^3$/µl)	7.95 (5.92–11)	7.4 (4.92–10.57)	.108	5.3 (3.3–8.5)	**< .001**	8.65 (6–13.07)	.233
	2.9–18	2.2–21.5		0.9–24		3.6–20.7	
Neut ($\times 10^3$/µl)	5.05 (3.32–6.95) 1.1–12.3	3.85 (2.6–6.8)	.073	3.2 (1.9–5.675)	**< .001**	5.1 (3.27–7.72)	.388
	1.1–12.3	1.1–16		0.5–12.4		2.1–15.4	
Lymph ($\times 10^3$/µl)	2.55 (1.82–3.1)	1.9 (1.2–2.6)	**.001**	1.25 (0.9–2.25)	**< .001**	2.25 (1.5–2.925)	.154
	0.8–5.9	0.2–4.8		0.2–4.8		0.5–5.3	
MON ($\times 10^3$/µl)	0.6 (0.4–0.9)	0.8 (0.5–1.2)	**.007**	0.6 (0.3–0.9)	.360	1.05 (0.575–1.95)	**< .001**
	0.2–2.6	0.1–2.6		0.05–2.2		0.2–3.2	
HB (gm/dl)	12.35 (10.02–13.6)	11.55 (8.92–12.7)	**.008**	9.55 (8.02–11.27)	**< .001**	11.05 (9.07–12.5)	**.006**
	6.2–16.7 6.2–16.7	6.5–17		5–13.4		6.9–15.2	
Plt ($\times 10^3$/µl)	243 (181.5–294.75)	296 (212.25–376.75)	**.001**	237 (139–302.75)	.268	341.5 (263–453.5)	**< .001**
	11–716 11–716	34–655		30–538		106–615	
RDW (%)	13.6 (12.4 –14.55)	16 (13.9–17.15)	**< .001**	16 (14–18)	**< .001**	17.5 (15–20)	**< .001**
	11–17.5	9.5–22.6		12.5–22		12–22	
MPV (fL)	8.4 (7.7–9)	9.5 (8.8–11)	**< .001**	9.4 (8.8–11)	**< .001**	11 (9–14)	**< .001**
	7–13	7.5–15		7.4–15		8–19.7	
NLR	2.04 (1.63–2.58)	2.31 (1.51–3.38)	.067	2.3 (1.62– 3.57)	**.043**	2.21 (1.79–2.98)	.134
	1–4.41	0.95–15.5		1–9.5		1.09–18.83	
PLR	97.44 (72.19–138.29)	156.19 (117.27–226.09)	**< .001**	140 (84.21–270.87)	**< .001**	166.22 (115.21–220.41)	**< .001**
	9.32–358	1.133–1 345		2.72–1 495		34.83–642	
SII	506.57 (362.89–660.88)	664.97 (433.74–1 099.9)	**< .001**	468.53 (250.71–890.57)	.903	800.0 (582.02–1 133.0)	**< .001**
	13.44–1 516.66	3.51–4 467.69		19–2 840.5		180.37–6265.09	
LMR	4.06 (2.52–6)	2.34 (1.42–3.65)	**< .001**	2.23 (1.5–4.27)	**< .001**	2 (1.27–3.06)	**< .001**
	1.09–13	0.22–21		0.286–27		0.33–9.66	

HB, hemoglobin; LMR, lymphocyte-to-monocyte ratio; Lymph, lymphocytes; Mon, monocytes; MPV, mean platelet volume; Neut., neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelets; RDW, red cell distribution width; SII, systemic immune-inflammation index; TLC, total leukocytic count.
P1: control vs rheumatoid arthritis (RA); P2: control vs systemic lupus erythematosus (SLE); P3: control vs ankylosing spondylitis (AS). *P*-value > .05: non-significant; *P*-value < .05: significant; *P*-value < .01: highly significant.
Non-parametric quantitative results are expressed in medians (interquartile range [IQR]) and ranges while qualitative results are expressed in numbers (*n*) and percentages (%). Bold *P*-values indicate statistical significance.

Table 2. Disease-specific markers and activity scores in RA, SLE, and AS patients.

VARIABLE	RA (*N* = 100)		
	MEDIAN (IQR)	MIN.	MAX.
ESR	55.5 (34–94.25)	10	150
CRP	24 (12–48)	6	132
RF	56 (23–153.25)	1.666	947
Anti-CCP	44 (12–99.75)	5	500
DAS-28	4.4 (2.8–5.9)	2	8.3
Positive RF	92 (92.0%)		
Positive anti-CCP	96 (96.0%)		
SLE (*n* = 100)			
ESR	59 (38–89.5)	15	140
CRP	16.5 (12–30)	6	225
Anti-dsDNA	45 (29–78)	10	143
SLEDAI	9 (6–13)	4	20
Low C4	35 (35.0%)		
Low C3	31 (31.0%)		
Positive anti-dsDNA	98 (98.0%)		
AS(n = 50)			
ESR	57.5 (34.75–89.25)	20	140
CRP	14.5 (8–36.5)	6	98
ASDAS	1.9 (1.17–2.82)	1	3.8
HLAB27 +	23 (46.0%)		

Anti-CCP, anti-cyclic citrullinated peptide; anti-dsDNA, anti-double-stranded DNA antibodies; ASDAS, ankylosing spondylitis disease activity score; CRP, C-reactive protein; DAS-28, disease activity score for RA; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SLEDAI, systemic lupus erythematosus disease activity index.
Non-parametric quantitative results are expressed in medians (IQR) and ranges (Min. and Max.) while qualitative results are expressed in numbers (*n*) and percentages (%).

Inflammatory changes in rheumatological autoimmune disease involve changes in the number, shapes, and sizes of peripheral blood cells; accordingly, CBC-derived parameters like NLR, LMR, SII, and PLR have been recently shown to be markers of occult inflammation and activity in these diseases.[46,47] These markers are simple, available, cheap, and can be done in any laboratory, yet clinicians rarely use them when studying hemograms, perhaps because they are unfamiliar with these important parameters.

Previous research looked into the relationship between various CBC-derived parameters and autoimmune diseases on an individual basis. To the best of our knowledge, this is the first study to examine the relationship between multiple hemogram-derived biomarkers, such as MPV, RDW, NLR, SII, LMR, and PLR, and the activity of various autoimmune rheumatological diseases. Furthermore, the relationship between hematological indices and rheumatologic diseases is still debatable. As a result, in our research, we attempted to collect all these biomarkers in a single study and examine their relationship to disease activity in three major autoimmune inflammatory diseases: RA, SLE, and AS.

The proportion of women in the study groups of SLE and RA patients was higher than men because both diseases are more common in women.[48,49] However, because AS is more common in men, the percentage of males in our 'study's AS patients was substantially larger than the number of females.[50]

In our RA patients, RDW, MPV, PLR, and SII, were significantly increased while LMR was significantly decreased compared with healthy controls ($P < .001$). NLR showed no significant difference between RA patients and controls. Only RDW and MPV were strongly correlated with disease activity markers and indicators, such as ESR, CRP, and DAS-28 ($P < .001$), indicating that they can be useful markers of active autoimmune inflammation. The findings of previous studies on the association of RDW and MPV with ESR and CRP were inconclusive. In their studies, Al-Rawi et al[51] and Lin et al[52] reported a significant increase in RDW in RA patients and a positive correlation with CRP levels. Another study by Remalante et al[53] discovered no link between RDW and ESR.

Partially consistent with our findings, Yildirim et al[54] discovered that MPV was significantly higher in RA patients when compared with healthy controls. Still, there was a negative relationship between MPV and disease activity. Some of the inconsistencies could be explained by sample characteristics, such as age and sample size.

Very few studies investigated the ability of CBC parameters to differentiate between active RA and RA in remission,[53,55,56] and most of the studies focused on the diagnostic value of CBC parameters in differentiating healthy controls from RA patients.

Accordingly, we investigated the discriminative ability of CBC-derived parameters for RA disease activity using an ROC analysis. In our study, RDW and MPV had a fair RA activity predictive performance. At the same time, NLR and SII showed poor performance. Remalante et al[53] found that RDW and NLR had poor performance (AUC: 0.516, 0.629, respectively) with low sensitivity and specificity for predicting RA activity. Furthermore, patients with high activity RA had significantly higher RDW and MPV levels than those with low activity in our study, implying higher levels of inflammation in the former group and supporting our findings that RDW and MPV can help with clinical follow-up and activity prediction in RA patients.

Table 3. Comparison of median (IQR) values of different activity groups in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS).

RA						
		INACTIVE	LOW	MODERATE	HIGH	*P*-VALUE
		(*N* = 13)	(*N* = 16)	(*N* = 38)	(*N* = 33)	
RDW		13.7 (12.85–14.7)	13.6 (12.97–13.87)	16 (15–17)	17 (16.6–20)	**< .001**
MPV		8.8 (8.55–9.25)	8.75 (8.4–9.3)	9.5 (8.97–10.77)	10.5 (9.9–11.55)	**< .001**
NLR		3.37 (2.13–5.97)	1.82 (1.34–3.37)	2.19 (1.24–2.83)	2.81 (1.53–3.46)	.064
PLR		162 (124.75–188.53)	159.77 (118.71–206.83)	136.66 (99.73–229.84)	174.61 (110.94–349.09)	.547
SII		721.83 (552.31–1 533.38)	587.78 (412.95–1 027.39)	701.51 (421.33–1 133.04)	617.62 (391.88–1 098.93)	.46
LMR		2 (1.03–5.25)	2.28 (1.55–3.18)	2.77 (1.62–3.91)	2 (1.38–3.56)	.487
	Inactive vs Low	**Inactive vs moderate**	**Inactive vs high**	**Low vs moderate**	**Low vs high**	**Moderate vs high**
	***P*-value**	***P*-value**	***P*-value**	***P*-value**	***P*-value**	***P*-value**
RDW	.553	**.001**	**< .001**	**.004**	**< .001**	**< .001**
MPV	.758	**.005**	**< .001**	.955	**< .001**	**.001**
SLE						
		INACTIVE	LOW	MODERATE	HIGH	*P*-VALUE
		(*N* = 18)	(*N* = 52)	(*N* = 1)	(*N* = 29)	
RDW		14 (13–15.42)	15.9 (14–17)	17 (17–17)	19 (17.4–20)	**< .001**
MPV		8.8 (8.07–8.9)	9.35 (8.8–10)	11 (11–11)	11 (9.55–11)	**< .001**
NLR		2 (1.57–3.48)	2.31 (1.65–3.59)	2.8 (2.8–2.8)	2.4 (1.35–3.81)	.68
PLR		114.02 (63.98–202.08)	117.85 (65.73–210.83)	378 (378–378)	265.33 (146.87–388.88)	**< .001**
SII		448.0 (241.73–996.29)	458.86 (250.77–849.97)	529.2 (529.2–529.2)	466.66 (168.06–1 281.63)	.965
LMR		2.15 (1.70–5.27)	2.41 (1.72–4.62)	0.55 (0.55–0.55)	1.66 (0.95–2.83)	**.016**
	Inactive vs Low	**Inactive vs Moderate**	**Inactive vs High**	**Low vs Moderate**	**Low vs High**	**Moderate vs high**
	***P*-value**	***P*-value**	***P*-value**	***P*-value**	***P*-value**	***P*-value**
RDW	**.005**	.141	**< .001**	.356	**< .001**	.35
MPV	**.001**	.098	**< .001**	.212	**.004**	.678
PLR	.605	.100	**.001**	.133	**< .001**	.525
LMR	.702	.100	**.036**	.102	**.008**	.184
AS						
		INACTIVE	LOW		HIGH	*P*-VALUE
		(*N* = 15)	(*N* = 16)		(*N* = 19)	
RDW		15 (14–15.2)	17.5 (16.12–18)		20 (19–22)	**< .001**
MPV		8.9 (8.8–9.7)	12.5 (10.25–14)		13 (10–16)	**< .001**
NLR		1.93 (1.55–2.33)	2.33 (1.75–3.37)		2.33 (1.93–3.07)	.128
PLR		145.9 (139.11–188.8)	181.0 (110.06–271.68)		160.35 (95.81–322.85)	.866
SII		697.66 (546.07–887.36)	792.73 (426.94–1 141.5)		904 (719.76–1 585.39)	.068
LMR		2.44 (1.63–3.8)	2.125 (1.22–2.81)		2 (1.11–3)	.408
	Inactive vs Low		**Inactive vs High**		**Low vs High**	
	***P*-value**		***P*-value**		***P*-value**	
RDW	**< .001**		**< .001**		**< .001**	
MPV	**< .001**		**< .001**		.359	

LMR, lymphocyte-to-monocyte ratio; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; SII, systemic immune-inflammation index.
P-value > 0.05: non significant; *P*-value < 0.05: significant; Bold *P*-values indicate statistical significance.

Table 4. Correlations of different CBC parameters with disease activity markers and scores in RA, SLE, and AS patients.

RA												
	RDW		MPV		NLR		PLR		SII		LMR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*
ESR	0.547	**<.001**	0.398	**<.001**	0.179	.074	0.09	.372	0.126	.213	−0.041	.685
CRP	0.417	**<.001**	0.348	**<.001**	0.005	.957	0.078	.442	0.116	.249	−0.064	.528
RF	0.617	**<.001**	0.532	**<.001**	0.089	.381	−0.027	.789	0.024	.812	0.045	.657
Anti-CCP	0.552	**<.001**	0.481	**<.001**	−0.03	.768	0.081	.421	0.028	.784	−0.035	.729
DAS.28	0.647	**<.001**	0.51	**<.001**	−0.046	.653	0.089	.379	−0.053	.602	−0.064	.530
SLE												
	RDW		MPV		NLR		PLR		SII		LMR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*
ESR	0.505	**<.001**	0.380	**<.001**	0.057	.574	0.266	**.008**	0.124	.217	−0.062	.540
CRP	0.375	**<.001**	0.394	**<.001**	−0.067	.509	0.264	**.008**	0.022	.831	−0.249	.013
DNA	0.603	**<.001**	0.341	**.001**	−0.078	.439	0.305	**.002**	−0.057	.572	−0.178	.076
SLEDAI	0.623	**<.001**	0.514	**<.001**	0.12	.236	0.425	**<.001**	0.072	.479	−0.221	.027
AS												
	RDW		MPV		NLR		PLR		SII		LMR	
	R	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*
ESR	0.794	**<.001**	0.697	**<.001**	0.398	**.004**	0.072	.618	0.411	**.003**	−0.284	**.045**
CRP	0.722	**<.001**	0.61	**<.001**	0.363	**.009**	0.050	.732	0.446	**.001**	−0.292	**.039**
ASDAS	0.834	**<.001**	0.612	**<.001**	0.291	**.040**	0.038	.793	0.349	**.013**	−0.176	.221

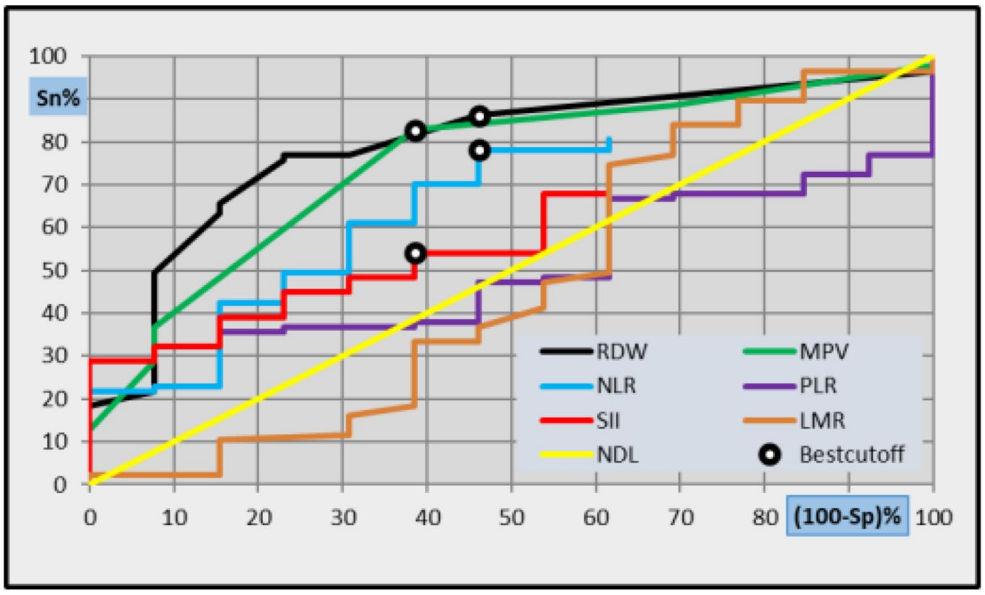
LMR, lymphocyte-to-monocyte ratio; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; SII, systemic immune-inflammation index.
P-value > .05: non significant; *P*-value < .05: significant; Bold *P*-values indicate statistical significance.

Regarding SLE patients included in our study, RDW, MPV, PLR, and NLR were significantly higher, and LMR was significantly lower than healthy controls. There was no statistically significant difference in SII between our SLE patients and controls. MPV and RDW distinguished inactive SLE patients from those with low disease activity and low disease activity from high disease activity. In addition, the AUC was higher for RDW and MPV than other indices. In contrast to our results, Peirovy et al[57] concluded that NLR, MPV, and RDW could not differentiate between SLE cases with high disease activity from those with low disease activity.

Our results regarding MPV were consistent with those of Yavuz and Ece,[58] who studied juvenile SLE patients and found that MPV was significantly higher in SLE patients than controls and increased with disease activity. In contrast, in a study on 50 SLE patients, Khan et al[59] reported that MPV decreased with SLE activity and showed an inverse relationship with ESR and SLEDAI. Also, in a study by Safak et al,[60] active SLE patients had lower MPV levels than patients in remission and healthy controls. These discrepancies could be explained by variances in patients' disease activity levels, and ongoing therapies as MPV levels are affected by disease activity and therapy.[61]

In our SLE patients, only RDW, MPV, and PLR were positively correlated with ESR, CRP, anti-dsDNA titer, and SLEDAI score, with no correlation between NLR and activity markers, which is partially against the results of Peirovy et al,[57] who found positive correlations between SLEDAI and NLR and PLR. Although the activity indices used in our study (SLEDAI) differ from those used in their study (SLEDAI-2k), our results appear to be more reliable because the aforementioned hematological indices are correlated with multiple activity markers and indicators, namely, CRP, ESR, and anti-dsDNA titer, not just the SLEDAI score.

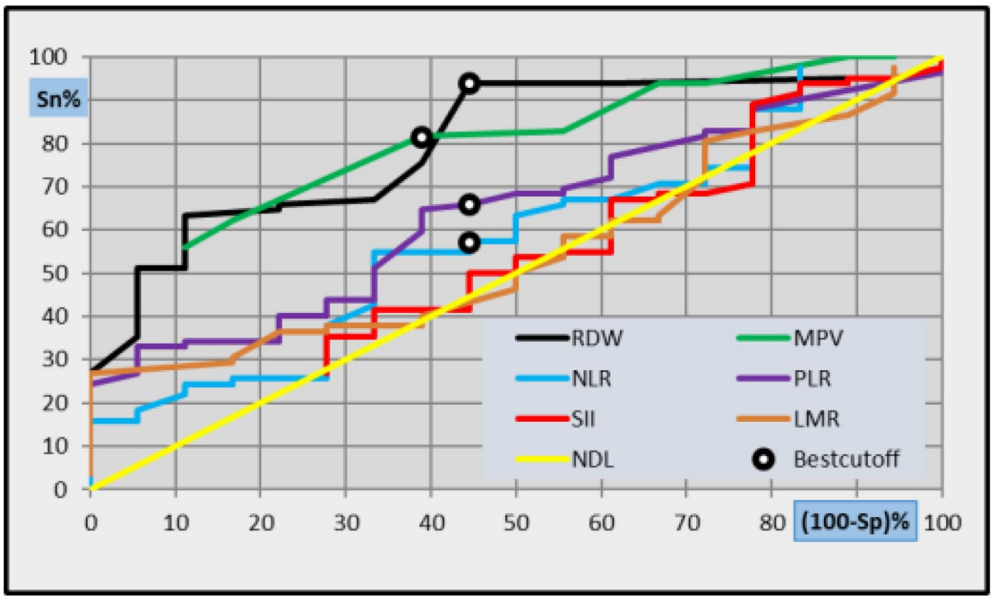
Only the SLE group from the other rheumatic inflammatory disorders studied in our study had a significantly higher



	Cut off	AUC	95% CI		SP%	SN%	PN%	PP%	Eff%
RDW (%)	13.7	0.790	0.638	0.942	53.8	86.2	36.8	92.6	82.0
MPV (fl)	8.8	0.750	0.590	0.910	61.5	82.8	34.8	93.5	80.0
NLR	3.30	0.690	0.521	0.858	53.8	78.2	26.9	91.9	75.0
SII	691.55	0.622	0.449	0.794	61.5	54.0	16.7	90.4	55.0

AUC: area under the curve; Eff: efficacy; LMR: Lymphocyte-to-monocyte ratio; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PN: Negative predictive value; PP: Positive predictive value; RDW: Red cell distribution width; SII: Systemic immune-inflammation index.SN: Sensitivity; SP: Specificity

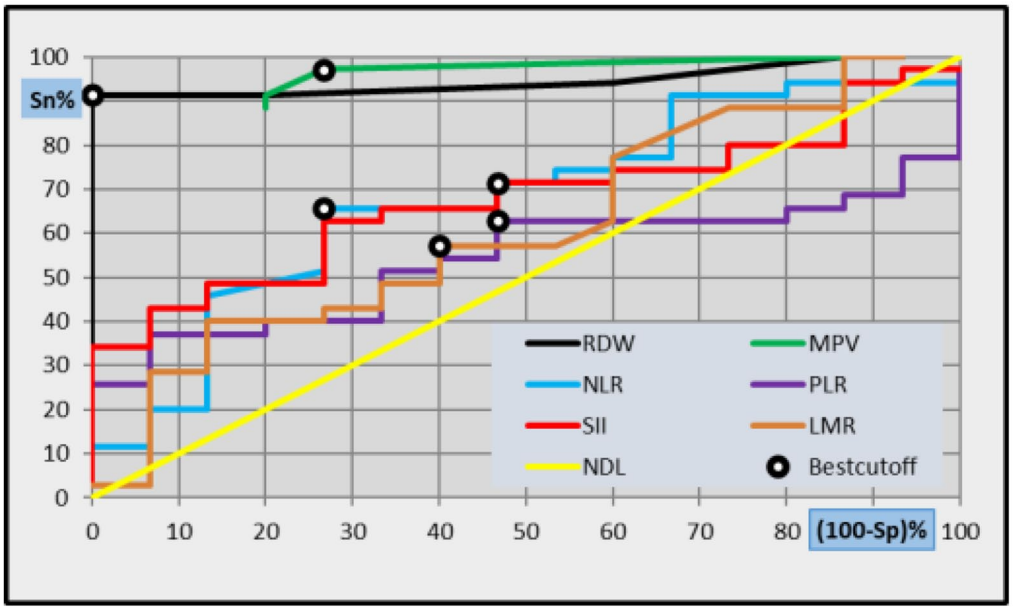
Figure 1. ROC curve analysis showing the diagnostic performance of the studied parameters for discriminating active RA patients from those inactive.



	Cut off	AUC	95% CI		SP%	SN%	PN%	PP%	Eff%
RDW (%)	14	0.696	0.529	0.864	55.6	93.9	66.7	90.6	87.0
MPV (fl)	8.8	0.697	0.530	0.865	61.1	81.7	42.3	90.5	78.0
NLR	2.13	0.418	0.248	0.588	55.6	57.3	22.2	85.5	57.0
PLR	116.66	0.638	0.464	0.812	55.6	65.9	26.3	87.1	64.0

AUC: area under the curve; Eff: efficacy; LMR: Lymphocyte-to-monocyte ratio; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PN: Negative predictive value; PP: Positive predictive value; RDW: Red cell distribution width; SII: Systemic immune-inflammation index.SN: Sensitivity; SP: Specificity

Figure 2. ROC curve analysis showing the diagnostic performance of the studied parameters for discriminating active SLE patients from those in remission.



	Cut off	AUC	95% CI		SP%	SN%	PN%	PP%	Eff%
RDW	16	0.880	0.761	0.999	100.0	91.4	83.3	100.0	94.0
MPV	9	0.721	0.557	0.885	73.3	97.1	91.7	89.5	90.0
NLR	2.18	0.676	0.506	0.847	73.3	65.7	47.8	85.2	68.0
PLR	145.90	0.541	0.363	0.718	53.3	62.9	38.1	75.9	60.0
SII	697.66	0.674	0.504	0.845	53.3	71.4	44.4	78.1	66.0
LMR	2	0.547	0.369	0.724	60.0	57.1	37.5	76.9	58.0

AUC: area under the curve; Eff: efficacy; LMR: Lymphocyte-to-monocyte ratio; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PN: Negative predictive value; PP: Positive predictive value; RDW: Red cell distribution width; SII: Systemic immune-inflammation index.SN: Sensitivity; SP: Specificity

Figure 3. ROC curve analysis showing the diagnostic performance of the studied parameters for discriminating active AS patients from those in remission.

NLR than controls, implying that the NLR could be a useful biomarker for SLE diagnosis. On the other side, NLR was not correlated with disease activity indicated by ESR, CRP, anti-dsDNA, and the SLEDAI score; also, we found no significant difference in the NLR of low active and inactive SLE patients ($P = .288$) or between low vs moderate activity groups ($P = .695$) indicating that it might be a good diagnostic marker, but not an activity marker for SLE. Consistent with our results, the findings of Oehadian et al,[62] who found no significant difference in NLR between SLE patients with mild and moderate activity, 2.59 (1.01–10.92) vs 2.01 (1.38–3.98), $P = .412$. In contrast, Papachristodoulou et al,[63] concluded that high NLR was associated with SLE activity.

In the present study, all hemogram-derived indices showed significant differences ($P < .001$) between the AS cases and healthy controls, with RDW, MPV, PLR, and SII increasing and LMR decreasing. In comparison, there was not any statistical difference regarding NLR compared with healthy controls ($P = .134$). Regarding RDW, our findings align with a recent meta-analysis study by Song and Lee.[64] They included 11 studies and concluded that RDW significantly increased in AS patients compared with controls. Still, they failed to find any difference regarding MPV and PLR, recommending further studies to clarify their findings. Also, another study on AS patients by Peng et al[65] showed increased RDW with significant difference compared with healthy individuals ($13.66 \pm 0.77\%$ vs $12.77 \pm 0.47\%$, $P < .01$). On the other hand, our findings were against another study that did not find any significant difference regarding RDW, PLR, and MPV ($P > .05$).[66]

As for NLR did not show any significant difference between AS patients and healthy controls ($P = .134$), but there was a significant difference between inactive and high disease activity patient groups ($P = .046$). Also, it was correlated with ESR, CRP, and ASDAS scores. Partially consistent with our results is a very recent study by Eroğlu et al,[67] who concluded that NLR levels were similar between AS patients and healthy controls; NLR levels were only weakly correlated with CRP levels. Similarly, Mercan et al[9] found no statistical difference between AS patients and controls regarding NLR, but found a correlation between NLR with ESR and CRP; our results seem to add more information regarding the use of NLR in AS, it might not be a diagnostic marker but is well correlated with disease activity markers and indices.

Our results can be explained by the following: AS is characterized by chronic inflammation caused by interleukin (IL)-6 and tumor necrosis factor released altering RBC maturation and life span, contributing to an increase in RDW.[68] Platelets, with their increased counts, can release a variety of mediators, including thromboxanes, which cause inflammation.[69] MPV correlates with platelet function and activation.[70]

SII, a new inflammatory marker, can provide a more comprehensive picture of the body's inflammation and immune balance.[71] SII level in patients with AS was significantly higher than that in controls ($P < .001$). The SII level was significantly higher in the AS patient group with high activity than the inactive patient ($P = .013$). In addition, it was correlated with ESR ($P = .003$), CRP ($P = .001$), and ASDAS ($P = .013$). A study by Wu et al[72] is consistent with our findings, except that they used bath ankylosing spondylitis disease activity index (BASDAI) instead of ASDAS as an activity index. Our results support Wu et al[72] results that SII could be a novel biomarker for assessing AS activity.

In terms of AS, the ROC analysis showed that RDW and MPV had the best predictive performance for disease activity. Sezgin et al[12] studied RDW and MPV in AS patients concluding at a cut-off value of 14.8% and 10.4 fl, respectively, the AUC was 0.76 and 0.58, respectively.

Our study showed that integrated markers in the multi-ROC analysis performed better than a single biomarker. Combining RDW (13.7%) and NLR (3.4%) improved the predictive performance for RA activity. RDW at 14% with MPV at 10 fl improved the predictive performance for SLE activity. In AS, combining RDW at 16.0% and MPV at 8.8 fl improved AS activity prediction.

One limitation of our study is its single-center nature; larger multicenter studies on wider scales are recommended to confirm our findings.

Clinical follow-up and disease activity prediction in patients with rheumatological diseases could be made by simple, readily available, and inexpensive indicators derived from simple CBC analysis (RDW, MPV, NLR, PLR, LMR, and SII). To which clinicians must pay attention for better prediction of disease's course and prognosis of patients.

In conclusion, of all the included CBC-derived indicators in our study, RDW and MPV had the best predictive performance for disease activity in the three studied rheumatological diseases a finding that can help with clinical follow-up

Author Contributions

All authors made major contributions to this work, whether it was in the conception, study design, data acquisition, analysis, and interpretation, or in the drafting, revising, or reviewing of the article, and they all gave final approval to the version that would be published.

Availability of Data and Materials

On request, all data will be provided.

Ethical Approval and Consent to Participate

On the basis of ethical concerns, the current study protocol was authorized by the Research Ethics Committee of Ain Shams University Faculty of Medicine (FWA 00017585). Before any of the individuals could participate in the study, all procedures were described to them and their informed consent was obtained. The Declaration of Helsinki was followed in this research.

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