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Hematological indices: potential markers of disease activity in ankylosing spondylitis patients treated with biological drugs

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Abstract

Background Some important hematological indices implement acute phase reactions. They can be used to assess disease activity and therapeutic response in many inflammatory conditions. This work aimed to determine whether different hematological indices can be used to assess disease activity and therapeutic response in patients with ankylosing spondylitis (AS) on biological drugs.

Patients and methods Ninety-seven AS patients and a similar number of controls were involved in the current study. The Ankylosing Spondylitis Disease Activity Score (ASDAS) was used to assess the disease activity. Different complete blood count parameters and indices were assessed.

Results There was a significant difference between the patients and controls as regards mean corpuscular volume, mean corpuscular hemoglobin, red blood cells count, red cell distribution width, mean platelet volume, platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). Moreover, there was a statistical correlation between ASDAS on one side and hemoglobin (Hb), hematocrit (HTC), lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), PLR, and SII on the other side. When the patient group was divided into 2 subgroups according to ASDAS, with patients with inactive and low disease activity in one subgroup and those with very high and high disease activity in another subgroup, there was a significant difference as regards Hb, HTC, mean corpuscular hemoglobin concentration, NLR, PLR, SII, and also ESR and CRP levels. Moreover, there was a significant correlation between PLR and SII levels on one side and ESR on the other side.

Conclusion Hematological indices such as PLR, NLR, and SII might be potential markers for follow-up of disease activity and therapeutic response in AS patients treated with biological therapy. This emphasizes the significance of a comprehensive approach for AS patient assessment and follow-up of therapeutic drugs, considering inflammatory markers, hematological indices, and disease activity scores.

Keywords Hematological markers, Ankylosing spondylitis, ASDAS, Biological drugs

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Background

Ankylosing spondylitis (AS) is a chronic inflammatory illness that has a prevalence rate between 0.1 and 1.4% worldwide [1]. AS typically affects the axial spine and sacroiliac joints, although it can also impact peripheral joints and entheses [2–4]. Progressive spine stiffness and persistent back pain are two of the most common clinical signs and symptoms of AS, while there is a wide variety of other manifestations as well. AS can lead to peripheral arthritis, enthesitis, dactylitis, and postural problems that result from reduced spinal movement [5, 6]. Along with skeletal involvement, AS can also present with extra-articular symptoms such as psoriasis (10%), acute anterior uveitis (25–35% of cases), and inflammatory bowel disease (IBD), which affects about 50% of cases [7]. The systemic inflammation caused by AS disease pathophysiology increases the risk of cardiovascular disease. Patients may also encounter pulmonary problems, such as restrictive pulmonary illnesses [8].

Although the pathogenic mechanism of AS is still unclear, several theories regarding the initial process have been suggested. One of them is a direct inference from "self–nonself" immunology that suggests a molecular mimicry between the foreign and self-peptide causing autoinflammation to certain arthritogenic peptides [9]. Other hypotheses propose that AS results from the conformational flexibility of the major risk gene, human leukocyte gene-B27 (HLA-B27). An error-prone folding mechanism in some HLA-B27 alleles might lead to endoplasmic reticulum stress, which in turn triggers the release of cytokines. Altered HLA-B27 molecules can activate the immune system through natural killer cells, killer immunoglobulin-like receptors expressed on CD4 + T cells, and the intrinsic HLA monitoring receptor [10].

To evaluate the activity of AS disease, the SpondyloArthritis international Society (ASAS) membership chose ASDAS with C-reactive protein (CRP) as the best method of assessment and ASDAS with erythrocyte sedimentation rate (ESR) as the alternative form. In addition to the CRP or ESR score, this index also includes four other self-reported items: back pain, peripheral pain or swelling, length of morning stiffness, and patient global assessment of disease activity [11, 12].

Although CRP and ESR levels are commonly used to assess disease activity in many rheumatic conditions, they are insufficient due to their limited specificity and sensitivity [13].

A complete blood count (CBC) is a low-cost, easy, and relatively sensitive clinical indicator of inflammatory response. CBC components, namely platelets, lymphocytes, and neutrophils, are affected by inflammation and immunological responses. These cells are powerful effectors in the inflammatory response. Essential alterations that take place in the peripheral blood in reaction to inflammation include anemia, leukocytosis, and thrombocytopenia [14, 15]. Additionally, the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) are two essential hematological indices that monitor acute phase responses [16–18].

Therefore, measuring disease activity in AS is critical not only for a better understanding of the pathophysiology of AS and predicting prognosis but also for monitoring the response to therapeutic drugs. To the best of our knowledge, this is, so far, the first study to investigate the value of hematological markers in a unique group of AS patients treated with biological therapy. This study aimed to determine whether different hematological indices can be used to assess disease activity and therapeutic response in patients with AS on biological drugs.

Patients and methods

Study design

The study design is as follows: observational (cross-sectional) study. A convenient sample of patients was recruited from the outpatient clinic of the rheumatology department.

Study setting and sampling

The study was conducted on 97 AS patients and a similar number of controls. All AS patients were diagnosed according to the Assessment of SpondyloArthritis international Society classification criteria for spondylarthritis [19].

Exclusion criteria

All patients with other inflammatory, autoimmune, infectious diseases, diabetes mellitus, malignancies, pregnancy, liver or kidney diseases were excluded. Newly diagnosed AS patients and those on biologics for less than 3 months were also excluded.

Calculation of sample size

Based on the results of a previous study [20], the mean ± SD of NLR in AS patients was 2.25 ± 0.89, and for the healthy control group, it was 1.72 ± 0.52. To detect the difference between groups with a power of 80%, a level of significance of 5%, and an effect size of 0.67, a total sample size of 72 participants was needed, at ≥ 36 participants for each study group. The sample size was calculated by G*Power (version 3.1.9.2; Germany).

Methodology

All patients were subjected to a full medical history and clinical examination. Disease activity was assessed using ASDAS [11]. Back pain, peripheral pain/swelling, duration of morning stiffness, and patient global assessment were all assessed on a numerical rating scale (from 0 to 10) according to the following formula:

$$\begin{aligned}\text{ASDAS} - \text{CRP} &= 0.12 \times \text{Back Pain} + 0.07 \\ &\times \text{Peripheral Pain/Swelling} + 0.06 \\ &\times \text{Duration of Morning Stiffness} + 0.11 \\ &\times \text{Patient Global} + 0.58 \times \text{Ln}(\text{CRP} + 1)\end{aligned}$$

The 3 cut-offs, selected to separate disease activity states, were as follows: < 1.3 between "inactive disease" and "low disease activity" < 2.1 between "low disease activity" and "high disease activity" and > 3.5 between "high disease activity" and "very high disease activity."

Laboratory investigations

Venous blood was collected from all participants who did not exhibit any clinical symptoms of fever or infection.

A CBC using the Sysmex XT1800i apparatus was done, from which the following data were collected: red blood cell count (RBCs), hemoglobin level (Hb), red cell distribution width (RDW), white blood cell count (WBCs), absolute neutrophil and lymphocyte count, platelet count, and markers of platelet activation (mean platelet volume (MPV) and platelet distribution width (PDW)) [21]. By dividing the absolute count of neutrophils by the absolute count of lymphocytes, NLR was calculated. PLR was also calculated by dividing the absolute platelet count by the absolute lymphocytic count [22]. The systemic immune-inflammation index (SII) was calculated as the product of the platelet and neutrophil counts divided by the lymphocyte count [23, 24]. ESR [25] and CRP [26] were measured immediately.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences SPSS 22.0 software (IBM Microsoft). Quantitative data normality was tested by Kolmogorov's test. Qualitative variables were presented using numbers and percent; the chi-square test was used for analysis. Numerical variables were expressed as medians (IQR), and the Mann–Whitney *U* test was used for comparison between groups. Spearman's correlation analysis was used to evaluate the relation between laboratory parameters and clinical variables. A *P*-value (< 0.05) was adopted as the level of significance.

Results

Ninety-seven AS patients and a similar number of matched controls were included in the current study. The demographical and clinical characteristics of the study groups are shown in Tables 1 and 2. The median age of the AS patients was 42 years, and the percentage of males in the AS disease group was 86.6% with age- and sex-matched controls. The median disease duration of the patients was 8 years. As regards the extra-articular manifestations of AS, 7 patients had uveitis and 8 patients had colitis. Eighty-four (86.6%) patients were HLA-B27 positive. Fifty-three (54.6%) patients used NSAIDs, while only 3 (3.1%) patients were on steroids. Six patients were on mesalamine, and only one patient used MTX. As regards ASDAS, 8 patients had inactive disease while 20 had VHDA, with nearly equal numbers of LDA and HAD (35, 34, respectively). Thirty-eight patients were on adalimumab, 29 on golimumab, 21 on secukinumab, and 9 patients on etanercept. Table 2 presents the laboratory findings of the studied groups. There was a significant difference between the patients and controls as regards MCV, MCH, RDW, RBCs, MPV, PLR, and SII. Moreover, there was a statistical correlation between ASDAS on one side and Hb, HTC, lymphocyte count, NLR, PLR, and SII on the other side (Table 3). When the patient group was divided into 2 subgroups based on ASDAS, with patients with inactive and LDA in one subgroup and those with HAD and VHDA in another subgroup, there was a significant difference as regards Hb, HTC, MCHC, NLR, PLR, SII, ESR, and CRP levels. Moreover, there was a significant correlation between PLR and SII levels on one side and ESR on the other side (Table 4).

Discussion

The etiopathogenesis of spondyloarthropathy is caused by the interplay of genetic, immunomodulatory, and ethnic factors. There are still many unanswered questions about these complex relationships, one of which is how the severity of the illness is influenced by the peak of the inflammatory state [27, 28]. To evaluate the degree of disease activity and patients' responses to biological treatment, ESR, CRP, and other disease activity scores have been widely used [29, 30]. Nevertheless, monitoring the course of the AS disease necessitates the development of further novel biomarkers, especially in patients treated with biological drugs. Since different hematological markers can be easily obtained from CBC, these markers seem promising for evaluating disease activity in AS patients, aiming for

Table 1 Clinical characteristics of disease activity among ankylosing spondylitis patients

Studied variables		AS patients ($n=97$)
Age of disease onset (years)		34 (26–40)
Disease duration (years)		8 (5–15)
Extra articular manifestations	**Absent**	82 (84.5%)
	Colitis	8 (8.2%)
	Uveitis	7 (7.2%)
DMARDs use	**No**	90 (92.8%)
	MTX	1 (1.0%)
	Mesalamine	6 (6.2%)
Steroids use	**No**	94 (96.9%)
	Yes	3 (3.1%)
NSAIDS use	**No**	44 (45.4%)
	Yes	53 (54.6%)
Biological drugs use	**Adalimumab**	38 (39.2%)
	Etanercept	9 (9.3%)
	Golimumab	29 (29.9%)
	Secukinumab	21 (21.6%)
Duration of biological drug intake (ms)		12 (6–18)
Number of failed biologics	**0**	39 (40.2%)
	1.0	18 (18.6%)
	2.0	31 (32%)
	3.0	8 (8.2%)
	4.0	1 (1%)
ASDAS score		2.8 (1.8–3.4)
Activity grade	**Inactive**	8 (8.2%)
	LDA	35 (36.1%)
	HDA	34 (35.1%)
	VHDA	20 (20.6%)
HLA-B27	**Absent**	13 (13.4%)
	Present	84 (86.6%)
ESR (mm/h)		21 (10–40)
CRP (mg/L)		5.1 (3.02–14.3)

Values are presented as number (%) and median (IQR)

DMARDs disease-modifying antirheumatic drugs, *MTX* methotrexate, *NSAIDS* nonsteroidal anti-inflammatory drugs, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *LDL* low disease activity, *HAD* high disease activity, *VHDA* very high disease activity

optimal management. Combined hematological indices of inflammation, particularly NLR, PLR, and SII, are widely used with favorable results in various diseases. Additionally, the prognosis and severity of several inflammatory disorders can be predicted by the CBC parameters and the ratios between them [31, 32].

The demographic data of the patients in this study revealed no significant difference when compared to the healthy control group. This demonstrated that the patients were correctly matched to the control group, and confounding variables that could have influenced the results were avoided.

RDW and MPV represent the degree of heterogeneity in circulating erythrocyte volume and platelet count, which are altered by inflammatory conditions [33]. Many studies have been conducted on the connections between MPV, RDW, platelet count, and other hematological parameters in rheumatic disorders; nevertheless, conflicting results have been reported [34]. In the current work, there was a statistically significant difference between the patients and controls as regard to MCV, MCH, RDW, RBCs, MPV, PLR, and SII, with decreased levels of MPV, PLR, SII, and red blood cell parameters except for RDW, which

Table 2 Comparison of demographic, clinical, and laboratory variables between the studied groups

Studied variables		AS patients ($n=97$)	Control group ($n=97$)	*P*-value
Sex	**Female**	13 (13.4%)	10 (10.3%)	0.505
	Male	84 (86.6%)	87 (89.7%)	
Age (years)		42 (37–50)	39 (35–51)	0.374
BMI (kg/m^2)		30.2 (26.7–33.1)	30.5 (25.5–34.2)	0.505
Hb		12.8 (11.7–13.9)	12.8 (12.5–13.2)	0.341
HTC		39.3 (36.3–41.6)	38.6 (36.5–39.7)	0.376
MCV		81.6 (76.5–86.7)	85.5 (81.5–88.9)	< 0.001*
MCH		27.4 (25.0–28.6)	28.6 (27.2–29.3)	< 0.001*
MCHC		32.5 (31.7–34.0)	33.3 (32.7–34.5)	0.002*
MPV		9.8 (8.4–10.8)	10.8 (9.7–11.3)	< 0.001*
RDW		13.8 (12.9–15.7)	13.3 (12.7–13.3)	< 0.001*
RBCs		4.8 (4.3–5.2)	4.5 (4.3–4.9)	0.002*
Platelet count (× 10^9/L)		255.0 (202.0–308.0)	296.0 (227.0–390.0)	0.001*
WBCs		6.5 (5.3–8.3)	6.3 (6.0–7.8)	0.953
Bas		2.2 (0.0–5.0)	0.1 (0.02–2.9)	0.009*
Eos		0.14 (0.07–0.25)	0.16 (0.10–0.19)	0.724
Neutrophil count (× 10^9/L)		3.7 (2.6–4.9)	3.7 (3.1–4.2)	0.907
Lymphocyte count (*10^9/L)		2.1 (1.7–2.7)	2.2 (1.8–2.7)	0.403
Monocyte count (× 10^9/L)		0.37 (0.29–0.53)	0.47 (0.40–0.50)	< 0.001*
PDW		12.6 (11.4–13.9)	13.0 (11.9–13.2)	0.926
NLR (× 10^9/L)		1.66 (1.24–2.31)	1.6 (1.3–1.9)	0.579
PLR (× 10^9/L)		116.5 (81.6–162.9)	149.7 (103.6–180.5)	0.014*
SII (× 10^9/L)		429.1 (274.3–574.2)	475.6 (387.0–627.5)	0.010*

Values are presented as number (%) and median (IQR)

BMI body mass index, *WBCs* white blood cells, *HCT* hematocrit, *RBCs* red blood cells, *Hb* hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *RDW* red cell distribution width, *PLT* platelets, *MPV* mean platelet volume, *PDW* platelet distribution width, *NLR*, neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *SII* systemic immune-inflammation index

* Significant at $P<0.05$

was increased in the patient group. Anemia is a common manifestation of the chronic inflammation process and has also been observed in individuals with axial SpA. The mechanism behind it is thought to be related to the inhibitory effects of cytokine secretion. TNF-α has the potential to inhibit erythropoietin's actions on hematopoietic stem and progenitor cells [35]. Since all the recruited patients were on biological treatment, with their marvelous anti-inflammatory effect, for at least 3 months and that nearly 44% of them were either in remission or low disease activity, it was expected that the PLR and SII might be of normal levels. On the other hand, the results of Liang T et al. [36] reported that the levels of PLR were significantly higher in the AS group than in the non-AS group. This discrepancy may be due to patient selection criteria. Melek Sezgin et al. [37] observed that RDW was more significant in AS patients than in controls. The impact of anemia rather than a true inflammatory index might be the reason for the elevated RDW. Consistent with the results of the present study, several studies [38–42] reported no significant difference in NLR between AS patients and healthy controls; however, comparable findings were reported by Bozan et al. [43]. This may be the result of various treatment strategies and methods used to choose AS patients for various research projects.

Moreover, there was a statistical correlation ($P<0.01$) between ASDAS on one side and Hb, HTC, lymphocyte count, NLR, PLR, and SII on the other side. Similarly, Liang T. et al. [36] and Sariyildiz A. et al. [20] found a correlation between PLR, activity indices, and disease severity. Additionally, Wu J. et al. [13] and Sariyildiz A. et al. [20] reported a correlation between SII and disease activity.

Regarding NLR, numerous studies [38, 44, 45] have reported a relationship between AS disease activity indices and NLR. Others, such as Al-Osami et al. [46]

Table 3 Correlation of laboratory parameters with disease-related variables in patients with ankylosing spondylitis

Laboratory parameters	ASDAS	Activity grade	ESR	CRP
Hb	−0.325**	−0.360**	−0.329**	0.132
HTC	−0.244*	−0.268**	−0.248*	0.134
MCV	−0.107	−0.157	−0.092	−0.228*
MCH	−0.174	−0.251*	−0.196	−0.201*
MCHC	−0.152	−0.173	−0.231*	−0.042
MPV	0.076	0.036	0.152	−0.063
RDW	0.106	0.177	0.171	0.152
RBCs	−0.180	−0.176	−0.198	0.221*
Platelet count (× 10^9/L)	0.141	0.151	0.177	0.116
WBCs	−0.042	−0.043	−0.149	0.291**
Bas	0.074	0.059	−0.045	−0.164
Eos	−0.124	−0.185	−0.233*	−0.070
Neutrophil count (× 10^9/L)	0.176	0.137	0.004	0.263**
Lymphocyte count (× 10^9/L)	−0.274**	−0.239*	−0.164	0.175
Monocyte count (× 10^9/L)	−0.022	−0.031	−0.073	0.041
PDW	0.110	0.104	−0.028	−0.128
NLR (× 10^9/L)	0.369**	0.322**	0.126	0.085
PLR (× 10^9/L)	0.333**	0.309**	0.278**	−0.062
SII (× 10^9/L)	0.379**	0.354**	0.211*	0.107
ESR (mm/h)	0.486**	0.475**	-	0.353**
CRP (mg/L)	0.354**	0.368**	0.353**	-

Values represent Spearman's rho correlation coefficient

WBCs white blood cells, *HCT* hematocrit, *RBCs* red blood cells, *Hb* hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *RDW* red cell distribution width, *PLT* platelets, *MPV* mean platelet volume, *PDW* platelet distribution width, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *SII* systemic immune-inflammation index

* Significant at $P < 0.05$

** Significant at $P < 0.01$

and Inal et al. [38], observed no correlation. Currently, CBC indices such as NLR and PLR are commonly used as indicators of inflammation. Previous studies have shown that they are associated with a variety of autoimmune disorders [47–49]. Additionally, SII can better reflect the body's balance of inflammation and immunity than NLR or PLR alone because it incorporates the three properties of neutrophils, lymphocytes, and PLTs. This allows SII to represent numerous inflammatory and immunological pathways in the body [50]. Previous researches [51–53] have observed a relationship between SII and many other rheumatologic disease activities, such as rheumatoid arthritis, vasculitis, and Behcet disease.

The current study showed that RBCs parameters, NLR, PLR, SII, ESR, and CRP levels were significantly higher in AS patients with higher disease activity. The persistent inflammation that is seen in individuals with high disease activity can help to explain this observation. Similarly, Liang T et al. [36] found a correlation between PLR and NLR on one side and disease activity grading on the other side. Moreover, they observed that PLR was associated with the severity of AS and may be used independently to diagnose AS. Also, Al-Osami et al. [46] found that NLR and PLR were significantly higher in the AS patients with active disease compared to those with inactive disease, even though there was no significant difference in the same parameters between AS patients and healthy controls. Inal et al. [38] and Kucuk et al. [45] also reported the same finding as regards NLR and PLR. Furthermore, Wu J et al. [13] reported that patients with active AS had significantly higher NLR, SII, and PLR levels than those in remission. The increase in SII level may be due to the increase in neutrophils, together with thrombocytosis and lymphopenia caused by an immune-inflammatory response.

Moreover, there was a significant correlation between PLR and SII levels on one side and ESR on the other. This emphasizes the importance of these indices for monitoring the inflammatory process in AS patients, particularly when combined with acute phase reactants such as ESR.

Table 4 Comparison of laboratory parameters in patients with ankylosing spondylitis regarding to Ankylosing Spondylitis Disease Activity Score

Laboratory parameters	ASDAS score		*P*-value
	< 2.1 (*n* = 45)	≥ 2.1 (*n* = 52)	
Hb	13.6 (12.4–14.6)	12.3 (11.5–13.1)	< 0.001*
HTC	40.8 (37.8–42.4)	37.7 (35.4–39.9)	0.003*
MCV	82.6 (78.6–87.4)	80.9 (75.8–86.1)	0.182
MCH	27.9 (26.0–29.5)	26.75 (24.6–28)	0.017*
MCHC	33.8 (31.6–34.9)	32.3 (31.7–33.3)	0.057
MPV	9.2 (8.2–10.6)	9.9 (8.6–11.0)	0.413
RDW	13.5 (12.7–15.5)	14.4 (13.2–15.8)	0.134
RBCs	4.98 (4.49–5.32)	4.66 (4.15–5.06)	0.039*
Platelet count (× 10^9/L)	244.0 (201.0–292.0)	264.5 (208.0–322.0)	0.259
WBCs	6.7 (5.2–8.3)	6.2 (5.0–7.8)	0.613
Bas	2.6 (0–5.3)	2.2 (0.0–4.9)	0.718
Eos	0.16 (0.09–0.42)	0.14 (0.06–0.20)	0.116
Neutrophil count (× 10^9/L)	3.6 (2.5–4.8)	3.7 (2.8–5.1)	0.267
Lymphocyte count (× 10^9/L)	2.5 (1.8–2.9)	1.9 (1.5–2.4)	0.023*
Monocyte count (× 10^9/L)	0.37 (0.29–0.53)	0.37 (0.29–0.54)	0.908
PDW	12.4 (11.4–13.6)	13 (11.5–14.2)	0.344
NLR (× 10^9/L)	1.52 (1.02–1.94)	1.82 (1.45–2.66)	0.003*
PLR (× 10^9/L)	95.28 (74.15–120.66)	136.45 (84.97–181.60)	0.006*
SII (× 10^9/L)	324.72 (229.30–440.36)	492.59 (342.40–705.18)	0.001*
ESR (mm/h)	12.0 (8.0–25.0)	32.5 (19.0–50.0)	< 0.001*
CRP (mg/L)	4.0 (2.9–6.4)	10.5 (4.0–19.8)	0.002*

Values are presented as median (IQR)

WBCs white blood cells, *HCT* hematocrit, *RBCs* red blood cells, *Hb* hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *RDW* red cell distribution width, *PLT* platelets, *MPV* mean platelet volume, *PDW* platelet distribution width, *NLR* neutrophil/lymphocyte ratio, *PLR* platelet/lymphocyte ratio, *SII* systemic immune-inflammation index

* Significant at $P < 0.05$

Conclusions

Hematological indices such as PLR, NLR, and SII might be potential markers for follow-up of disease activity and therapeutic response in AS patients treated with biological therapy. This emphasizes the significance of a comprehensive approach for AS patient assessment and follow-up of therapeutic drugs, considering inflammatory markers, hematological indices, and disease activity scores.

Abbreviations

AS	Ankylosing spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
CBC	Complete blood count
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
LDA	Low disease activity
HAD	High disease activity
MPV	Mean platelet volume
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
PDW	Platelet distribution width
SII	Systemic immune-inflammation index
VHDA	Very high disease activity

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None.

Authors' contributions

All authors have contributed to designing the study, collecting and analyzing, interpretation of data, and preparing and revising the manuscript. Design of the study: MA, ZS, AI. Recruitment of patients: MA, AI. Data collection: MA, AI, AE. Randomizing: MA, HA, AI, AE. Assessment: MA, AI. Statistical analysis and data interpretation: HA, AE. Manuscript preparation: MA, HA, AI, AE. Manuscript revision: MA, ZS, AI. All co-authors have approved the final version of the manuscript.

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Availability of data and materials

Available.

Declarations

Ethics approval and consent to participate

We confirm none of the present study's procedures had violated the principles stated by the latest version of declaration of Helsinki. The current study

was approved by the local ethical committee at Kafrelsheikh University with the approval code KFSIRB200-160. All patients and controls were recruited to participate and provided detailed information about the study, and those who agreed to be involved in the study were included. We confirm that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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