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The association between systemic immune inflammation index and disease activity in patients with rheumatoid arthritis

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ABSTRACT

Background. Novel blood-derived indices are a potential substitute for traditional inflammatory markers which have disputable correlations and clinical applications in different immunological diseases. Hereby, we aimed to reveal the association of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) with disease activity score (DAS28) and clinically active disease according to simple disease activity index (SDAI).

Methods. We included 250 patients and they were grouped equally based on SDAI into two groups of patients in remission and with active disease. A blood sample was drawn from our patients to measure NLR, PLR, SII, rheumatoid factor, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Independent samples t-tests, chi-square, and Mann-Whitney U test were used accordingly. Logistic regression evaluated the factors that affect active RA.

Results. PLR, DAS28, rheumatoid factor, quantitative and qualitative ESR and CRP had a significant difference between patients with active RA and in remission. SII had significant correlation with DAS28 but PLR and NLR were not correlated with DAS28. Also, PLR was the only index to be correlated with clinically active disease based on SDAI. The logistic regression showed that NLR, SII, ESR, and CRP were independent factors predicting active RA.

Conclusion. We demonstrated that SII was significantly correlated with DAS28 and PLR was correlated with active RA. NLR, SII, CRP, and ESR were independent risk factors for RA flare-ups.

Keywords: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, rheumatoid arthritis, disease activity score, DAS28

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease with variable cycles of relapses and remissions with joint destruction as the major hallmark. Uncontrolled relapses may lead to bone and cartilage destruction, disability, and mortality. In recent years, the main goal of treatment has changed from the alleviation of symptoms and reduction of erosions and deformities to reaching and maintaining a state of clinical remission or minimum disease activity [1,2]. Routine general health assessment of patients, pain evaluation, tender, and swollen joint count, and serum acute phase reactants, are parameters for evaluating the activity of RA [3,4]. Several studies have demonstrated the limitations of currently used acute phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and thus measures including them such as simple disease activity index (SDAI), and disease activity score using 28 joints (DAS28). The major disadvantage in these settings is attaining a flooring effect at lower disease activity [5].

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DAS28 is formulated using ESR or CRP and studies have shown that both can be used in RA patients for evaluating active disease with a similar validity [6].

The inflammation being non-specific and multifaceted, requires an optimal, specific marker to cover almost all of the possible aspects. Anemia, thrombocytosis, and leukocytosis are hematological markers of acute phase reaction, thus often present in active RA due to inflammatory responses [7,8]. Anemia and activation of neutrophils, lymphocytes, and thrombocytes are mostly a result of inflammatory cytokines [8,9]. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII) are well acknowledged markers for evaluating the inflammation state in many chronic inflammatory diseases like ulcerative colitis, systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS) [10-12]. NLR has been reported as an inflammatory marker along with patients' perception of pain to be useful in predicting sustained remission in RA patients [13]. Also, hemoglobin (Hb) level, NLR and mean platelet volume (MPV) have been shown to be independently associated with RA disease activity [14]. These markers obtainable from a simple complete blood count test (CBC) are rather inexpensive compared to ESR and CRP. Nonetheless, it is beneficial to further evaluate this relationship with disease activity and clinical features to substantiate its daily use in practice. In the following study, we aimed to evaluate the association between NLR, PLR, and SII with DAS28 and clinically active disease in RA patients in remission compared to RA patients who were experiencing disease flare-ups at the time of our study.

METHODS

Study design

This is a case-control study approved by the ethics review board of our institute (Ethical code number: IR.SBMU.MSP.REC.1400.034). The study was performed in 18 to 75-year-old RA patients who visited the rheumatology clinic of Taleghani Hospital during March 2020 to 2021. We included 250 RA patients of which 125 patients were in remission and 125 patients had active disease with flare-ups. The exclusion criteria were patients with other autoimmune diseases, hematological diseases that affect blood cells including lymphoproliferative and coagulative diseases, renal, hepatic, and cardiac diseases, history of cancer, any infection, and those who use drugs that have proven effect on blood cell counts. All participants were provided with a written informed consent.

Data collection

Personal interviews and questionnaires were conducted and medical records were reviewed to obtain demographic characteristics and medical and drug histories. In order to examine the laboratory variables including CBC and differential of white blood cells (WBC), quantitative and qualitative ESR, quantitative and qualitative CRP, and rheumatoid factor (RF), a blood sample was drawn from patients. All blood samples were taken in the same day that DAS-28 and SDAI were calculated. NLR as neutrophil / lymphocyte count, PLR as platelets / lymphocyte count, and SII as platelets * neutrophil / lymphocyte count were calculated for all the participants.

In addition, DAS28 and SDAI were calculated using the formula below:

SDAI = SJC + TJC +PGA + EGA + CRP

DAS28 =0.56 × √ (TJC28) + 0.28 × √ (SJC28) + 0.014 × VAS + 0.70 × Ln (ESR)

SJC = swollen joint count (28 joints)

TJC = tender joint count (28 joints)

PGA = patient's global assessment (0–10 scale)

EGA = evaluator's global assessment (0–10 scale)

CRP = C-reactive protein level (mg/dl)

VAS = patient assessment of disease activity using a 100 mm visual analogue scale (VAS) with 0 indicating no pain and 100 indicating the worst pain that the patient has experienced.

ESR= erythrocyte sedimentation rate (mm/h)

Remission was defined based on American college of rheumatology/European league against rheumatism 2011 remission criteria which patients must satisfy all of the following based on Boolean measure and index-based definition [15]:

Tender joint count ≤ 1

Swollen joint count ≤ 1

CRP ≤ 1 mg/dl

PGA ≤ 1 (on a 0–10 scale)

SDAI score ≤3.3

Statistical analysis

We analyzed our data using IBM SPSS Statistics, Version 22.0 (IBM Corporation, Armonk, NY, USA). Kolmogorov–Smirnov statistics was used for checking the normal distribution assumption of continuous variables. Variables are presented as numbers and percentages for categorical variables, mean and standard deviation (SD) for continuous variables with normal distribution, and median with interquartile range (IQR) for continuous variables without normal distribution. To compare the data, independent samples t-tests, Mann-Whitney U test, and chi-square tests were used as appropriate. Binary logistic regression was conducted to evaluate the factors that affect active disease. P-value <0.05 was considered as statistically significant.

TABLE 1. Demographic and laboratory characteristics of studied groups and their distribution between active and remission groups

Variable	Total	Active (n=125)	Remission (n=125)	P-value
Gender				**0.571**
Male, n (%)	36 (14.4)	18 (14.4)	18 (14.4)	
Female, n (%)	214 (85.6)	107 (85.6)	107 (85.6)	
Age, years, mean (SD)	54.22 (13.14)	54.89 (12.00)	53.57 (14.22)	**0.43**
WBC, x10^9 cells/l, median (IQR)	6730.00 (5600.00-8100.00)	6750.00 (5405.00-8120.00)	6730.00 (5750.00-8100.00)	0.51
Hb, g/dl, median (IQR)	13.2 (12.47-14.00)	13.0 (12.3-13.9)	13.4 (12.7-14.2)	0.28
Platelets, x10^9 cells/l, median (IQR)	247.00 (209.75-287.50)	251.00 (210.00-292.00)	242.00 (210.00-278.00)	0.66
Lymphocyte count, x10^9 cells/l, median (IQR)	2.44 (1.84-3.08)	2.35 (1.74-3.10)	2.51 (1.97-3.05)	0.27
Neutrophil count, x10^9 cells/l, median (IQR)	3.47 (2.78-4.74)	3.51 (2.75-4.90)	3.43 (2.80-4.51)	0.91
NLR, %, median (IQR)	1.47 (1.07-2.03)	1.46 (1.10-2.10)	1.47 (1.06-1.92)	0.283
PLR, %, median (IQR)	97.27 (75.97-134.41)	102.84 (74.19-147.17)	94.72 (79.96-126.23)	0.028
SII, x10^9 cells/l, median (IQR)	355.78 (249.96-528.76)	366.50 (260.16-564.70)	342.14 (247.47-454.07)	0.135
DAS28 score, mean ± SD	2.75 (0.99)	3.49 (0.71)	1.98 (0.58)	0.000
RF positive, n (%)	136 (54.4)	90 (66.2)	46 (33.8)	0.000
CRP positive, n (%)	114 (45.6)	91 (79.8)	23 (20.2)	0.000
CRP amount, mg/dl, median (IQR)	1.67 (0.87)	1.00 (1.00-3.00)	1.00 (1.00-1.00)	0.01
ESR positive, n (%)	232 (92.8%)	121 (52.2)	111 (47.8)	0.03
ESR amount, mm/h, median (IQR)	19.5 (11.00-30.00)	25.00 (15.00-42.00)	15.00 (10.00-25.00)	0.001
SDAI				0.000
SDAI > 3.3	124 (49.6)	124	0	
SDAI < 3.3	126 (50.4)	1	125 (99.2)	
Drug use				
Corticosteroids		98 (39.2%)		
MTX		106 (42.4%)		
Adalimumab		42 (16.8%)		
Etanercept		11 (4.4%)		
Sulfasalazine		37 (14.8%)		
Hydroxy Chloroquine		13 (5.2%)		
Colchicine		10 (4.0%)		

Abbreviations: Cr, creatinine; CRP, C reactive protein; DAS28, disease activity score using 28 joints; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; IQR, interquartile range; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RF, rheumatoid factor; SD, standard deviation; SII, systemic immune inflammation index; SDAI, simple disease activity index; WBC, white blood cells

RESULTS

The studied group was composed of 125 patients with active RA and 125 patients in remission. 36 patients (14.4%) were male and the other 214 patients (85.6%) were female. The participants were distributed equally between "active" and "remission" group. The mean age of all of our participants were 54.22 years old which was not significantly different between the two groups.

In laboratory variables, WBC, hemoglobin, neutrophil count, lymphocyte count, platelets, SII, and NLR didn't have significant difference between the two groups (p-value). However, PLR and DAS28 had a significant difference between those with active RA and those in remission (p-value=). Moreover, RF, qualitative ESR and CRP were significantly different between the two groups (p-value=) (Table 1).

TABLE 2. Correlation between SII, NLR, and PLR with DAS28 and clinically active rheumatoid arthritis

Variable	Clinically active RA		DAS28	
	r	p-value	r	p-value
NLR	-0.068	0.283	0.105	0.112
PLR	-0.139	0.028	0.116	0.08
SII	-0.095	0.135	0.148	0.025

Abbreviations: DAS28, disease activity score using 28 joints; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RA, rheumatoid arthritis; SII, systemic immune inflammation index

The correlation analyses showed that SII had significant correlation with DAS28 (p-value <0.05) but PLR and NLR were not correlated with DAS28. Also,

TABLE 3. Binary logistic regression for rheumatoid arthritis activity

		B	S.E.	Wald	df	Sig.	Exp(B)	5% C.I. for Exp(B)	
								Lower	Upper
Step 1[a]	RF	-0.323	0.289	1.249	1	0.264	0.724	0.411	1.275
	CRP	-2.008	0.327	37.717	1	0.000	0.134	0.071	0.255
	ESR	1.327	0.365	13.206	1	0.000	3.770	1.843	7.714
	PLR	-0.001	0.001	0.472	1	0.492	0.999	0.997	1.002
	NLR	1.089	0.311	12.277	1	0.000	2.972	1.616	5.466
	SII	-0.002	0.001	4.506	1	0.034	0.998	0.996	1.000

a. Variable(s) entered on step 1: PLR, NLR, and SII.

Abbreviations: CRP, C-reactive protein; CI, confidence interval; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RF, rheumatoid factor; SII, systemic immune inflammation index

PLR was the only index to be correlated with clinically active disease (Table 2). The binary logistic regression showed that ESR, CRP, NLR, and SII were independent factors for active RA (p-value <0.05) (Table 3).

DISCUSSION

ESR, CRP, and other inflammatory indices are widely used to evaluate disease activity in systemic rheumatologic diseases; however, they lack sensitivity and specificity as they are altered by numerous conditions, and also, being within normal range, do not necessarily rule out active disease. ESR and CRP are best applied to conditions that have a high or low clinical probability of the disease [16,17]. ESR and CRP are well-known markers for measuring acute phase response because they are reliable and cost-effective. In our study, these two markers were significantly different between active RA and in remission groups. Moreover, ESR were independently associated with clinically active RA, along with CPR.

In a study by Chandrashekara et al., the NLR values were correlated with DAS28-CRP rather than CRP and ESR, implementing that they might not be suitable to measure the disease activity levels in conditions like chronic inflammatory diseases [18]. Recent studies attempted to introduce other markers that reflect disease activity with more specificity; due to previously described limitations of traditional acute phase reactants, CBC-derived parameters like NLR, lymphocyte-to-monocyte ratio (LMR), SII, and PLR are now drawing attention as markers of unapparent inflammation and activity [14,19]. These markers are simple, affordable, and available, and any laboratory can measure them, yet they are not widely used in clinical settings, because clinicians are unfamiliar with these leading indices.

In this study, we revealed the possible associations between these factors and disease activity, with our control group being RA patients in remission. Our results demonstrated that PLR levels were significantly different between the active RA and the remission groups. Furthermore, our findings suggested that SII and NLR are independently associated with clinically active disease in RA patients, respectively.

These markers are relatively recently brought to attention and the few studies that have been conducted demonstrated different results. In a study by Lijuan et al., NLR and PLR had lower sensitivity and specificity than ESR and CRP for differentiation of active RA from in remission patients [20]. Uslu et al. found significantly different NLR and PLR in active and in remission patients; however, the number of patients in each of the studied groups (40 patients in remission, 64 patients with active disease) was fewer than in our study [21]. Other studies also demonstrated that NLR and PLR are associated with RA disease activity [21-23]. A meta-analysis showed a significantly higher NLR and PLR in active RA patients compared to healthy individuals and RA patients in remission [24]. Another meta-analysis with 13 NLR and 8 PLR studies, showed significantly higher NLR and PLR levels in patients with RA than healthy controls. However, this study did not investigate the relationship between these two markers and RA activity [25].

NLR, PLR, and SII are easily obtainable markers from the absolute neutrophil, lymphocyte, and platelet counts in CBC. The utility of these indices in the assessment of systemic inflammation has been investigated in numerous other rheumatologic disorders including adult-onset Still disease, SLE, and AS [12,26,27]. To our knowledge, only three major studies were performed enrolling SII. Satis performed a study on two groups of active and in remission RA patients, divided by DAS28-ESR, and the results showed that SII can predict RA activity with the area under the curve in the ROC curve of 0.643. Taha et al. found that SII is higher in RA patients compared to healthy population [19,28]. In another recent study that evaluated the effects of Janus kinase (JAK) inhibitors on RA disease activity, RA patients had a significantly higher SII, NLR, and PLR compared to healthy controls at baseline. All of these makers were also associated with DAS28-ESR at baseline [29]. These results are in concordance with the results of our study, suggesting SII as a simple blood-derived marker that is associated with RA disease activity and DAS28. However, the studies that evaluate the use of SII as a marker for disease activity in RA patients are limited and the utility of these markers merits further investigation.

There are some noteworthy strengths in this study. It included a large number of RA patients

compared to other similar studies. To the best of our knowledge, this is the second study that investigates the difference and correlation of SII in RA between patients in remission and patients with active disease. Furthermore, we measured all the laboratory tests with the same analyzer machine with regular calibration to increase accuracy and reliability. Also, we evaluated the association of NLR, PLR, and SII with not only DAS28 but also clinically active disease which was based on SDAI. However, there might be some limitations to our study; this is a single-center, retrospective study and some data such as quantitative CRP may have been missed. Moreover, this study is related to this population/ethnicity and needs further studies to validate our results.

CONCLUSION

In this study, we demonstrated that PLR and DAS28 had a significant difference between RA flare-ups and RA remission. Also, SII was significantly correlated with DAS28, and PLR was the only index to be correlated with clinically active disease based on SDAI. ESR, CRP, NLR, and SII were independent factors influencing active RA. We demonstrated that SII, as a novel inflammatory marker, has a significant role in active RA; however, further studies are warranted to investigate the diagnostic and prognostic predictive role of SII.

Conflicts of interest:
The authors of the present study declare no conflict of interests.

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Ethics approval statement: All of the authors declare that this manuscript is not published elsewhere.

Patient consent statement:
A written informed consent was obtained from the patients to perform this study. The protocol and consent forms were approved by the institutional review board at Shahid Beheshti University of Medical Sciences (Ethical code number: IR.SBMU.MSP.REC.1400.034). All of the authors declare that confidentiality of the patient was respected.

Data availability statement:
The data that support the findings of this study are available on request from the corresponding author.

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