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Evaluation of the relationship between blood cell markers and inflammation, disease activity, and general health status in ankylosing spondylitis

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SUMMARY

OBJECTIVE: The aim of this study was to assess the relation of systemic immune inflammation index, systemic inflammation response index, and systemic inflammation aggregate index with disease activity, functional status, and general health status in ankylosing spondylitis.

METHODS: Patients with ankylosing spondylitis and healthy volunteers were included in this cross-sectional study. Demographic data; disease activity measurements such as the Bath Ankylosing Spondylitis Disease Activity Index, the Ankylosing Spondylitis Disease Activity Score with C-reactive protein, and the Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate; functional status such as the Bath Ankylosing Spondylitis Functional Index; and general health status such as the Assessment of Spondyloarthritis International Society Health Index of the patients were recorded. C-reactive protein, erythrocyte sedimentation rate, platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio, systemic immune inflammation index, systemic inflammation response index, and systemic inflammation aggregate index values were recorded. Patients were grouped as active and remission according to the Bath Ankylosing Spondylitis Disease Activity Index score and as inactive-low and high-very high disease activity according to the Ankylosing Spondylitis Disease Activity Score. The correlation of laboratory parameters with disease-related parameters was tested.

RESULTS: The indexes were significantly higher in patients compared to controls ($p<0.001$, for platelet to lymphocyte ratio $p=0.03$). No significant differences existed in any blood cell-derived indexes among patient groups categorized by disease activity ($p<0.05$ for all). Systemic immune inflammation index was weakly correlated with Ankylosing Spondylitis Disease Activity Score with C-reactive protein ($\rho=0.197$ and $p=0.049$) and Ankylosing Spondylitis Disease Activity Score-erythrocyte sedimentation rate ($\rho=0.201$ and $p=0.045$). Systemic immune inflammation index was not correlated with Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, and Assessment of Spondyloarthritis International Society Health Index. No correlation was found between other indexes and disease-related variables. Platelet to lymphocyte ratio, systemic immune inflammation index, systemic inflammation response index, and systemic inflammation aggregate index showed a weak positive correlation with C-reactive protein and erythrocyte sedimentation rate ($\rho=0.200–0.381$).

CONCLUSION: Systemic immune inflammation index, systemic inflammation response index, and systemic inflammation aggregate index can be used to indicate systemic inflammatory burden in ankylosing spondylitis patients. However, these indexes are not effective in indicating patients' disease activity, general health status, and functional status.

KEYWORDS: Ankylosing spondylitis. Mediators of inflammation. Blood cell count. Lymphocytes.

INTRODUCTION

Ankylosing spondylitis (AS), the prototype of spondyloarthritis, is a rheumatic condition with an unknown etiology that causes chronic inflammation of axial structures, including sacroiliac joint, spine, and paraspinal soft tissues. Low back pain and stiffness are frequent complaints, and extra-articular signs/symptoms can be observed throughout the disease's progression. These include anterior uveitis, inflammatory bowel disease, coronary heart disease, and osteoporosis, all of which are closely related to inflammation[1,2]. Therefore, the use of reliable markers to evaluate inflammation is crucial for disease monitoring and determining clinical outcomes.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), two non-specific inflammatory biomarkers, are frequently used to assess the inflammatory process. Nevertheless, serum levels of these markers are influenced by a variety of disorders, and normal levels do not reliably prevent active disease, especially in different rheumatic conditions[3]. Complete blood cell count parameters, including neutrophil, monocyte, lymphocyte, and platelet counts, and

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their derived indexes such as the neutrophil to lymphocyte ratio (NLR), the monocyte to lymphocyte ratio (MLR), and the platelet to lymphocyte ratio (PLR), the systemic immune inflammation index (SII), the systemic inflammation response index (SIRI), and the systemic inflammation aggregate index (AISI) are cost-effective and not time-consuming tests that have served as indicators of inflammation in a variety of rheumatic diseases and other inflammatory medical conditions[4-6]. Systemic inflammation is closely connected with variations in these inflammatory indexes.

Recently, several studies and meta-analyses have provided evidence that NLR, LMR, and PLR are strong indicators of inflammation in AS[7,8]. However, research on the association between these measures and disease activity has provided contradictory results in patients with spondyloarthritis[9,10]. On the contrary, studies on SII, SIRI, and AISI focus on rheumatoid arthritis and other inflammatory conditions[6,11,12]. The data on this issue in patients with AS are still quite limited[6,13].

To the best of our knowledge, the potential of SIRI and AISI in determining chronic inflammatory burden in AS has not been previously documented. For this reason, the aim of this study was to investigate the role of cost-effective and easily calculated indexes in exhibiting systemic inflammation, disease activity, and general health status in AS.

METHODS

Participants and study concept

This study was executed between September 2022 and January 2023 at a university hospital. In this cross-sectional study, patients were enrolled in an outpatient clinic by rheumatologists and physiatrists during routine evaluations. The inclusion criteria were (i) diagnosed as AS according to Modified New York criteria[14] and (ii) ≥18 years of age. The exclusion criteria were (i) presence of concomitant inflammatory rheumatic diseases, (ii) history of acute and/or chronic infections, (iii) concomitant cardiovascular disease, (iv) history of diabetes mellitus, (vi) major organ dysfunction, (vii) recent or current use of corticosteroids, antiaggregants, and/or anticoagulants, and (viii) history of malignancy or hematological disease. A total of 50 healthy age- and sex-matched volunteers were included in this study.

The Local Ethics Committee approved the study protocol (Date: September 16, 2022, Number: 125/13). Before enrolling in the study, each participant signed an informed consent form. The Declaration of Helsinki's guiding principles were followed.

Clinical parameters

Patients' demographic information (age and sex), body mass index (BMI), current smoking, alcohol use, symptom duration (years), time of diagnosis (years), presence of peripheral arthritis, duration of morning stiffness (minutes), and medications (non-steroidal anti-inflammatory drugs [NSAIDs] and biologic agents) were recorded. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP), and the Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate (ASDAS-ESR) were used to evaluate disease activity. BASDAI scores <4 and ≥4 indicated remission and active disease, respectively[15]. Regarding ASDAS-CRP and ASDAS-ESR scores, the three cutoff values of 1.3, 2.1, and 3.5 were selected to separate inactive disease, low disease activity, high disease activity, and very high disease activity, respectively[16]. The functionality of the patients was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI)[17]. The Assessment of Spondyloarthritis International Society Health Index (ASAS HI) was used to document the functional and health status of patients. The ASAS HI is composed of 17 items concerning pain, sleep, mental health, sexual functions, mobility, self-care, daily activities, and social participation. The overall ASAS HI score varies between 0 and 17, with lower scores reflecting good health condition[18].

Laboratory parameters

After 12 h of fasting, morning venous blood samples were collected using conventional techniques and analyzed in the central laboratory of the hospital. The neutrophil, lymphocyte, monocyte, and platelet counts were used to calculate the following blood cell-based indexes and ratios:

(1) NLR=neutrophil count/lymphocyte count
(2) MLR=monocyte count/lymphocyte count
(3) PLR=platelet count/lymphocyte count
(4) SII=neutrophil count×platelet count/lymphocyte count
(5) SIRI=neutrophil count×monocyte count/lymphocyte count
(6) AISI=neutrophil count×platelet count×monocyte count/lymphocyte count

Laboratory measures other than blood-cell-based indexes included ESR (mm/h), CRP (mg/L), and human leukocyte antigen-B27 (HLA-B27).

Demographic variables, smoking/alcohol use, BMI, and laboratory examination, including a complete blood count, CRP, and ESR, were registered in the healthy volunteers' group.

Statistical analyses

The sample size was calculated using the G*Power® program (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). Based on the research in the literature[12,19], the sample sizes that will find the difference in the indexes to be measured in the study between the patient and control groups to be significant at 5% error and 90% power were calculated in numbers ranging from 20 (effect size: 1.052) to 47 (effect size: 0.679) per group. It was decided to conduct the study with 100 patients and 50 controls because there were no studies in the literature on some of the indexes to be used in the study, and the sample sizes in similar studies were 2 patients and 1 control.

The IBM® SPSS® (IBM Corp, Armonk, NY, USA) statistical software version 20.0 was used. The normality of the data was assessed by the Shapiro-Wilk test and related histograms. The demographic and clinical parameters were analyzed by descriptive tests. A comparative analysis of continuous variables between the patients and healthy volunteers, as well as among disease activity categories was performed by the Mann-Whitney U test. Pearson's chi-squared test was used to compare gender and smoking/alcohol status between groups. Data related to continuous variables were presented as either mean±standard deviation or median [25% (q1)–75% (q3) quartiles]. Spearman's correlation analysis was used to evaluate the relationship between laboratory parameters and clinical variables. Values were given as Spearman's rho (ρ). The p-values below 0.05 were accepted as "statistically significant".

RESULTS

Characteristics of the participants

A total of 100 patients with AS and 50 healthy individuals were included in this study. The demographic and laboratory characteristics of the study groups are shown in Table 1. Accordingly, there was no difference between groups in terms of age and gender (p=0.624 and p=0.806, respectively). As for the patient group, the median duration since diagnosis was 13 (6–20) years. The symptom duration, presence of peripheral arthritis, and duration of morning stiffness were 16 (8–22) years, 31% and 20 (5–33.75) min, respectively. The frequency of HLA-B27 positivity was 66%. Notably, 58% of the patients received biological therapy. The median values of BASDAI, ASDAS-CRP, ASDAS-ESR, BASFI, and ASAS HI scores were 4.6 (2.3–6.5), 2.9 (2.1–3.6), 2.8 (2–3.5), 3.8 (1.7–6.4), and 9 (5–12), respectively.

Table 1. Comparison of demographic, clinical, and laboratory parameters between groups.

Variables	AS patients (n = 100)	Control group (n=50)	p-value
Age (years)	45 (36.5–54)	45.5 (38–52)	0.624
Male gender	68 (68%)	33 (66%)	0.806
BMI (kg/m^2)	27.92±4.90	26.10±2.64	0.004
Current smoking	41 (41%)	23 (46%)	0.003
Current alcohol use	21 (21%)	15 (30%)	0.119
CRP (mg/L)	6.03 (3.34–10.60)	2.10 (1.54–2.50)	<0.001
ESR (mm/h)	18 (10.5–27)	6 (4–10)	<0.001
Neutrophil count (´10^9/L)	2.25±0.89	1.74±0.55	<0.001
Lymphocyte count (´10^9/L)	2.29±0.69	2.26±0.59	0.789
Monocyte count (´10^9/L)	0.61±0.19	0.49±0.14	<0.001
Platelet count (´10^9/L)	268.80±67.76	241.34±54.48	0.014
NLR (´10^9/L)	2.25±0.89	1.72±0.52	<0.001
MLR (´10^9/L)	0.28±0.09	0.22 ±0.06	<0.001
PLR (´10^9/L)	126.74±44.73	112.36±33.87	0.03
SII (´10^9/L)	603.41±287.78	418±164.75	<0.001
SIRI (´10^9/L)	1.11 (0.86–1.83)	0.77 (0.60–0.94)	<0.001
AISI (´10^9/L)	305.66 (196.80–125.97)	181.98 (125.97–259.76)	<0.001

Values are presented as n (%), median (q1-q3) or mean±standard deviation. AS: ankylosing spondylitis; BMI: Body Mass Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation.

Comparative analysis of laboratory parameters between groups

The comparison of laboratory findings between patients with AS and controls are given in Table 1. Accordingly, the levels of CRP and ESR were statistically higher in the patient group ($p<0.001$ for both). In addition, neutrophil, monocyte, and platelet counts were also significantly higher in patients with AS ($p<0.001$,<0.001, and 0.014, respectively). All investigated blood cell-derived indexes were remarkably higher in patients than those in controls ($p<0.001$ for all except PLR $p=0.03$).

Comparison of laboratory findings stratified for Bath Ankylosing Spondylitis Disease Activity Index and Ankylosing Spondylitis Disease Activity Score with C-reactive protein/ Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate score

When the laboratory parameters were compared between the active and remisson groups according to the BASDAI score, the ESR value was higher in the active group than in the remission group ($p=0.009$), whereas there was no significant increase in the CRP value ($p=0.150$). When the groups were compared according to ASDAS-CRP and ASDAS-ESR scores, both CRP and ESR values for both disease activity measures were significantly higher in the high-very high disease activity group compared to the inactive-low disease activity group (Table 2).

Correlation analysis of laboratory parameters with disease-related variables

The results of the correlation analysis of laboratory findings with disease-related and inflammatory parameters, including CRP and ESR, in patients with AS are displayed in Table 3. Accordingly, SII showed a weak positive correlation between ASDAS-CRP and ASDAS-ESR ($\rho=0.197$ and 0.201, respectively). However, there was no correlation between SII and BASDAI, BASFI, and ASAS HI. Other blood cell-derived indexes were not correlated with disease-related variables. PLR, SII, SIRI, and AISI, showed a weak positive correlation with CRP and ESR (ρ ranged from 0.200 to 0.381).

DISCUSSION

In this cross-sectional study, we performed an assessment of various blood cell-derived indexes to investigate the role of those in demonstrating the inflammatory burden, disease activity, functional status, and general health status in AS. Over the last decade, studies have reported the efficacy of indexes, especially in NLR, MLR, and PLR in rheumatic diseases, including AS.

Table 2. Laboratory findings of the patients with ankylosing spondylitis stratified for Bath Ankylosing Spondylitis Disease Activity IndexBath Ankylosing Spondylitis Disease Activity Index and Ankylosing Spondylitis Disease Activity scores.

Variables	BASDAI score			ASDAS-CRP score			ASDAS-ESR score		
	≥4 (n=59)	<4 (n=41)	p	≥2.1 (n=76)	<2.1 (n=24)	p	≥2.1 (n=75)	<2.1 (n=25)	p
CRP (mg/L)	6.5 (3.61–12.20)	5.46 (3.17–9.08)	0.150	6.95 (3.96–11.85)	3.76 (3.52–5.10)	<0.001	6.85 (3.62–12.2)	4 (2.79–5.61)	0.004
ESR (mm/h)	21 (12–30)	15 (8–23)	0.009	21.5 (13.5–28.5)	9.5 (5.5–16)	<0.001	22 (14–29)	9 (5–14)	<0.001
NLR (´10⁹/L)	2.25±0.85	2.25±0.95	0.998	2.26±0.89	2.19±0.89	0.731	2.27±0.89	2.15±0.90	0.543
MLR (´10⁹/L)	0.28±0.09	0.28±0.1	0.837	0.29±0.09	0.26±0.09	0.314	0.29±0.09	0.27±0.09	0.340
PLR (´10⁹/L)	128.43±45.41	124.31±44.17	0.652	129.88±45.75	116.80±40.61	0.213	130.12±44.93	116.61±43.41	0.192
SII (´10⁹/L)	542.40 (391.89–838.65)	524.32 (383.68–670.72)	0.455	559.08 (388.52–780.88)	509.34 (382.83–557)	0.265	557.33 (395.31–780.92)	505.69 (359.80–556.67)	0.89
SIRI (´10⁹/L)	1.07 (0.84–1.84	1.12 (0.92–1.79)	0.911	1.11 (0.86–1.86)	1.12 (0.91–1.35)	0.651	1.17 (0.88–1.87)	1.10 (0.78–1.36)	0.306
AISI (´10⁹/L)	307.91 (195.95–503.19)	303.41 (203.82–426)	0.563	323.18 (198.59–490.21)	289.88 (176.07–384.94)	0.239	323.35 (163–367.03)	256.50 (203.82–503.19)	0.081

Values are presented as n (%), median (q1-q3) or mean±standard deviation. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein; ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate.

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

	CRP	ESR	BASDAI	ASDAS-CRP	ASDAS-ESR	BASFI	ASAS HI
NLR (´10⁹/L)	0.236*	0.142	0.015	0.137	0.119	0.057	-0.014
MLR (´10⁹/L)	0.179	0.160	-0.23	0.46	0.060	-0.039	-0.093
PLR (´10⁹/L)	0.265**	0.272**	-0.010	0.115	0.140	-0.016	0.003
SII (´10⁹/L)	0.381***	0.348***	0.023 0.823	0.197*	0.201*	0.029	0.027
SIRI (´10⁹/L)	0.233*	0.200*	-0.026	0.077	0.079	-0.034	-0.081
AISI (´10⁹/L)	0.364***	0.351***	0.004	0.145	0.154	-0.034	-0.002
CRP (mg/L)	–	0.672***	0.228*	0.539***	0.451***	0.324**	0.305***
ESR (mm/h)	0.672***	–	0.355***	0.556***	0.667***	0.403***	0.365***

Values represent Spearman's rho. *p<0.05, **p<0.01, ***p<0.001. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; $ASDAS_{CRP}$: Ankylosing Spondylitis Disease Activity Score with C-reactive protein; $ASDAS_{ESR}$: Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate; BASFI: Bath Ankylosing Spondylitis Functional Index; ASAS HI: Assessment of Spondyloarthritis International Society Health Index.

However, the relation of SII to AS has been much less studied so far and two novel indexes, SIRI and AISI, have not yet been investigated in AS. This study revealed that SII, SIRI, and AISI were remarkably higher in patients with AS compared to healthy individuals. On the contrary, they were positively correlated with conventional systemic inflammatory markers, including CRP and ESR. These indexes may be used to indicate a chronic inflammatory state in AS. However, they had no correlation with any of the disease activity/health measures except for a very weak positive correlation of SII with ASDAS-CRP and ASDAS-ESR.

In this regard, blood cell-based indexes, including NLR, PLR, SII, SIRI, and AISI, have potential to reflect systemic inflammation in AS. However, they are not helpful in terms of the evaluation of disease activity, functional status, and general health status. The inefficiency of blood cell-derived indexes in determining disease activity and general health status can be explained in several ways. Tools like BASDAI, BASFI, and ASAS HI are solely patient-reported measures. They may not only depend on inflammation itself, but are also related to psychological status, illness perception, and sleep quality. Moreover, concomitant health conditions such as central sensitization definitely interfere with patient-reported measures of AS[20,21]. We found no correlation between patient-reported measures and blood-cell-derived indexes. Yet, ASDAS-CRP and ASDAS-ESR showed a correlation with one of these indexes (SII). This correlation could be attributed to the composite design of the ASDAS-CRP and ASDAS-ESR tools. Composite disease activity measures of AS include not only patient-reported queries but also objective markers of inflammation (CRP or ESR)[22].

A novelty of this study is related to the potential role of SIRI and AISI in defining the inflammatory status of patients with AS. To the best of our knowledge, their potential indicatory role on inflammation in AS has not been reported so far. On the contrary, we revealed potential effectiveness of SII, NLR, and PLR in reflecting inflammatory status, which had previously been demonstrated in several other studies[6-8,19]. Wu et al. reported that SII was positively correlated with CRP (r_s=0.483), ESR (r_s=0.374), and BASDAI (r_s=0.667) and also a risk factor for high disease activity in patients with AS[13]. Despite the usefulness of these indexes in determining inflammation, this study revealed that they were ineffective in the determination of disease activity and the stratification of disease severity.

One of the strengths of this study is that extensive analysis of novel indexes, SIRI and AISI, has not yet been studied in AS. The association between blood cell indexes and disease activity measures, functional status, and general health status of patients with AS has also been extensively investigated for the first time. In addition, according to the cross-sectional observational study design, the prospective collection of data from individuals enrolled in this study allowed appropriate participant selection, thereby excluding possible co-existing medical conditions that could affect these indexes. The main limitation of this study is that the study population consisted of real-life patients, and almost all received NSAIDs and/or biologics at the time of evaluation. Therefore, the impact of pharmacological therapy on these indexes could not be assessed or excluded, which might lead to confounding bias.

In conclusion, NLR, MLR, PLR, SII, SIRI, and AISI are higher in patients with AS compared to the controls, and positive

correlation exists between PLR, SII, SIRI, and AISI with CRP and ESR. Accordingly, this study provides evidence that simple, cheap, and easily calculated blood cell indexes (particularly SII, SIRI, and AISI) are reasonable measures to determine systemic inflammation in AS. On the contrary, these indexes are not effective in demonstrating disease activity, functional status, or general health status in AS.

DATA AVAILABILITY

The datasets gathered during the preparation of this article are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study protocol was approved by the Local Ethics Committee of Cukurova University Faculty of Medicine (Date of approval: September 16, 2022, Number: 125/13) and the study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from each study participant.

AUTHORS' CONTRIBUTIONS

AS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ICB:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **IT:** Conceptualization, Methodology, Writing – review & editing. **IU:** Conceptualization, Formal Analysis, Methodology, Software, Writing – review & editing. **SSZA:** Conceptualization, Methodology, Writing – review & editing.

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