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Investigation of the relationship between disease activity and systemic inflammation indices in ankylosing spondylitis patients

Derya Cirakoglu[1], Ali Aslan[2]

[1]Ordu University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Ordu, Türkiye
[2]Ordu University, Faculty of Medicine, Department of Physiology, Ordu, Türkiye

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Abstract

Ankylosing Spondylitis (AS) is a long-term inflammatory rheumatic condition that mainly impacts axial regions, including the spine and sacroiliac joints. Typical symptoms consist of back discomfort, rigidity, and anterior uveitis, all of which are strongly linked to inflammatory mechanisms. Identifying reliable biomarkers for inflammation is essential for effectively monitoring the disease and determining clinical outcomes. This research seeks to assess the connection between Disease Activity (DA) and systemic inflammation markers in AS. A retrospective study was performed with 121 patients with AS and 90 participants with normal physiological and physical examination findings, who were observed at the Physical Medicine and Rehabilitation Clinic from January 1, 2023, to May 1, 2024. Demographic information and laboratory findings, including inflammatory markers, were collected. DA scores were recorded. Values for neutrophils, monocytes, lymphocytes, and platelets from hematological parameters, along with the derived indices of Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), Platelet-to-Lymphocyte Ratio (PLR), Systemic Immune Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Systemic Inflammation Aggregate Index (SIAI), were documented. No significant age difference was observed among the group of patients and the group of controls ($p=0.812$). A notable distinction was found between the two groups regarding monocyte levels ($p=0.047$). According to the Ankylosing Spondylitis Disease Activity Score (ASDAS) classification, significant variations in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels were detected between the high DA and low DA groups ($p<0.001$). In contrast, no meaningful correlations were identified for SII, SIRI, and SIAI in connection with DA ($p>0.05$). In this study, traditional inflammatory biomarkers (CRP and ESR) were associated with DA, while indices calculated from hematological parameters did not show significant associations. Additional research is required to examine the clinical relevance of these systemic inflammation indices in the assessment of AS activity.

Keywords: Ankylosing spondylitis, Systemic Immune Inflammation Index, disease activity

Introduction

Ankylosing Spondylitis (AS) is a long-term condition that impacts the spine and joints, resulting in structural damage and resulting in persistent back pain and joint restrictions in the advanced stages of the condition [1]. The prevalence of AS varies geographically, with Türkiye reporting approximately 49 cases per 10,000 individuals, compared to a prevalence of 23.8 per 10,000 in Europe [2]. Elevated scores in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which assesses DA in AS, showed a favorable correlation with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), while showing an inverse correlation with serum vitamin D levels. It is possible that most patients with AS go for many years without receiving a diagnosis. Moreover, delays in diagnosis worsen the clinical condition of the patients. The significance of timely and precise diagnosis is essential to avert structural damage and preserve a good quality of life [1].

Diagnosing spondyloarthritis is estimated to occur in every third to fifth patient presenting with chronic low back pain lasting longer than three months, especially when the onset occurs before the age of 45. This is particularly true for individuals displaying symptoms of inflammatory back pain, those who are HLA-B27 positive, or those with imaging-confirmed sacroiliitis. The effectiveness of these criteria within routine clinical practice warrants further investigation [3]. The etiology of AS and other spondyloarthritides remains elusive,

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Corresponding Author: Derya Cirakoglu, Ordu University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Ordu, Türkiye
Email: drderya79@gmail.com

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with two key phenomena needing exploration—namely, inflammation and new bone formation, particularly within the axial skeleton. Although inflammation is thought to be a precursor to new bone development, a definitive correlation between inflammatory activity and osteoproliferation has yet to be established. Additionally, there is a significant genetic predisposition to spondyloarthritides, with AS showing particularly strong hereditary influences. Male patients exhibit a greater prevalence of structural alterations, such as bamboo spine, compared to their female counterparts [3]. The connection between HLA-B27 and AS has been extensively studied for over 30 years, yet it remains poorly understood. HLA-B27 is believed to trigger autoimmune responses through the presentation of "arthritogenic" peptides shared between microbial and self-epitopes. Recent research has shifted from HLA-B27's normal peptide-presenting function to its aberrant immunobiological aspects, suggesting that its unique features may be tied to inflammatory processes and autoimmunity [4]. AS serves as a key example of immune-mediated inflammatory rheumatic disorders in the range of axial spondyloarthritis. Axial spondyloarthritis can be classified into two types according to clinical and radiological criteria: AS, characterized by specific structural alterations in the sacroiliac joints as observed in imaging, and non-radiographic axial spondyloarthritis, identified by MRI-detected inflammation of the sacroiliac joints or typical features of spondyloarthritis [5].

Currently, there are no definitive laboratory findings to diagnose AS [5]. Recent studies have reported that some parameters derived from CBC may be associated with inflammation and disease activity in rheumatic diseases such as rheumatoid arthritis and Behçet's disease [6,7]. This easily applicable and economical method has been investigated in several studies including patients with AS. In a recent study, SII levels were significantly elevated in patients with AS, suggesting that this may be a new biomarker for assessing DA [8]. However, data on this issue are still very limited and contradictory.

Therefore, the aim of this study was to investigate the levels of NLR, MLR, PLR, SII, SIRI, SIAI and their relationship with DA in patients with AS.

Material and Methods

This research was carried out retrospectively by examining the records of patients diagnosed with AS who were monitored at the Physical Medicine and Rehabilitation Clinic between January 1, 2023, and May 1, 2024. Approval for the research was obtained from the Ordu University Non-Interventional Scientific Research Ethics Committee on June 28, 2024, with decision number 2024/66. The study included 121 patients, along with 90 healthy controls. Ages <18 and ≥65 years, those with a different rheumatic disease, those with a history of acute and/or chronic infection, malignancy, or hematological disease, and those who used corticosteroids, antiplatelet agents, or anticoagulants in the prior month were not included in the study. Details are shown in Figure 1.

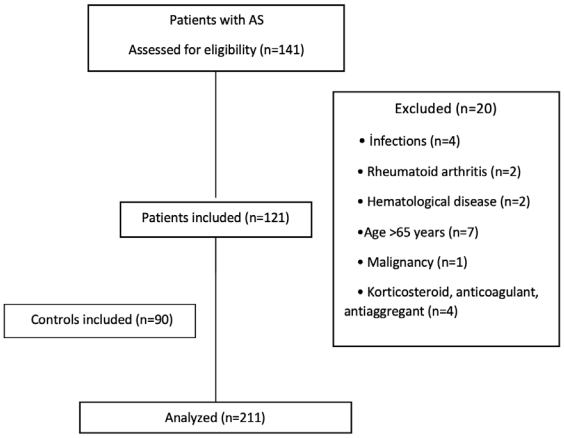

Figure 1. Flowchart of the study

Demographic data, including age and gender distribution, as well as CRP levels, ESR, and Complete Blood Count (CBC) results were documented. The CBC data collected were used to calculate systemic inflammation indices. The calculated indices included the Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), Systemic Immune Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Systemic Inflammation Aggregate Index (SIAI).

DA was evaluated through the BASDAI and the Ankylosing Spondylitis Disease Activity Score (ASDAS). The BASDAI includes six questions that assess symptoms specific to the disease, with a score of 4 or above indicating active disease [9]. A study examining the validity and reliability of the BASDAI in Turkish has been conducted [10]. Patients were classified based on their BASDAI scores, with scores ≥4 indicating active disease and scores<4 indicating remission. ASDAS in AS was developed as a combined score including measurements reported by patients and acute phase reactants to monitor the objective and subjective aspects of the disease [11]. In our study, the ASDAS-CRP and ASDAS-ESR were used.

Statistical Analysis

Data analysis was performed using the SPSS software (version 22.0, Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was employed to determine if the data followed a normal distribution. Data that were normally distributed were presented as mean and standard deviation, while data that were not normally distributed were reported as median and interquartile range (IQR). Normally distributed data were analyzed using the Student's t-test, whereas non-normally distributed data were assessed with the Mann-Whitney U test. Categorical variables were examined using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

Results

The mean age of the patient group was 40.83±10.06 years, whereas the control group had a mean age of 41.16±9.11 years, indicating that there was no meaningful disparity between the two groups (p=0.812). The gender distribution (male/female)

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also did not reveal a statistically significant difference, with patients comprising 78 males and 43 females compared to 52 males and 38 females in the control group (p=0.391).

Hematological parameters, including platelet, lymphocyte, neutrophil, and monocyte counts, as well as PLR, NLR, MLR, SIRI, SII, and SIAI were assessed. No statistically significant differences were observed in these values between the patient and control groups, with the exception of the monocyte count, which displayed a significant difference (p=0.047). Detailed results are presented in Table 1.

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

	Patients (n=121)	Control (n=90)	p-value
Age (years)	40.83±10.06	41.16±9.11	0.812
Gender (M/F)**	78/43	52/38	0.391
Neutrophil (x10^9/L)*	3.96±1.78	3.85±1.72	0.204
Lymphocyte (x10^9/L)*	2.34±0.95	2.22±0.93	0.318
Monocyte (x10^9/L)*	0.53±0.22	0.50±0.19	0.047
Platelet (x10^9/L)*	246.00±86.00	251.00±64.00	0.381
NLR (x10^9/L)*	1.68±0.72	1.62±0.73	0.539
MLR (x10^9/L)*	0.22±0.11	0.21±0.08	0.298
PLR (x10^9/L)*	106.72±44.48	114.81±41.55	0.198
SII (x10^9/L)*	415.70±246.52	431.13±204.04	0.712
SIRI (x10^9/L)*	0.90±0.67	0.89±0.54	0.245
SIAI(x10^9/L)*	211.64±195.80	236.56±114.07	0.623

*Data are presented as Median±Interquartile Range (IQR) due to non-normal distribution; **Statistical analysis was performed using the chi-square test; 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, SIAI: Systemic Inflammation Aggregate Index

According to BASDAI scores, a score of ≥4 is considered active disease, while a score of <4 indicates the disease is in remission. No meaningful difference was observed between individuals with active disease and those with the condition in remission in terms of CRP, ESR, NLR, MLR, PLR, SII, SIRI, and SIAI values.

Based on the ASDAS-ESR values, patients with a score of ≥2.1 were categorized as having high DA, whereas those scoring <2.1 were classified as having low DA. Statistically significant differences in CRP and ESR rates were noted between the groups with low and high DA (p<0.001). Nonetheless, no meaningful disparities were found in the values for NLR, MLR, PLR, SII, SIRI, and SIAI (p>0.05).

Similarly, based on ASDAS-CRP values, patients with a score of ≥2.1 were classified as having high DA, while those with a score of<2.1 had low DA. Significant differences were again found in CRP and ESR values (p<0.001), while no statistically significant differences were observed for NLR, MLR, PLR, SII, SIRI, and SIAI values (p>0.05). Detailed findings are presented in Table 2.

Table 2. Comparison of disease activity scores with laboratory findings in patients with ankylosing spondylitis

	BASDAI			ASDAS-ESR			ASDAS-CRP		
	≥4	<4	p	≥2.1	<2.1	p	≥2.1	<2.1	p
CRP (mg/l)	0.40±0.72	0.29±0.64	0.340	0.64±1.04	0.20±0.20	<0.001	0.52±0.92	0.20±0.12	<0.001
ESR (mm/h)	21.50±20.00	18.50±20.00	0.136	26.00±22.00	12.00±18.00	<0.001	26.00±22.00	10.50±13.00	<0.001
NLR (x10^9/L)	1.67±1.01	1.68±0.54	0.956	1.70±1.07	1.67±0.49	0.786	1.72±1.02	1.64±0.41	0.473
MLR (x10^9/L)	0.22±0.11	0.22±0.12	0.605	0.22±0.10	0.22±0.14	0.466	0.22±0.11	0.22±0.13	0.753
PLR (x10^9/L)	103.23±49.02	115.40±41.97	0.339	105.16±46.06	113.18±45.45	0.382	106.50±44.47	107.11±44.06	0.773
SII (x10^9/L)	395.92±269.63	439.78±234.08	0.330	431.95±296.94	408.48±198.39	0.846	437.84±303.50	397.37±178.25	0.362
SIRI (x10^9/L)	0.89±0.67	0.92±0.70	0.805	0.87±0.67	0.90±0.68	0.648	0.89±0.70	0.92±0.57	0.730
SIAI (x10^9/L)	198.67±195.25	246.12±194.02	0.281	211.81±203.58	199.96±191.13	0.812	217.35±228.41	189.52±172.93	0.544

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, SIAI: Systemic Inflammation Aggregate Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS-ESR: ankylosing spondylitis disease activity score with erythrocyte sedimentation rate, ASDAS-CRP: ankylosing spondylitis disease activity score with C-reactive protein

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Correlation analysis was performed between clinical and laboratory parameters in patients with AS. Since the data did not conform to normal distribution, Spearman correlation analysis was used. ESR values of AS patients showed statistically significant correlation with PLR (p<0.001), SII (p<0.001) and SIAI (p<0.001). CRP values showed statistically significant correlation with NLR (p=0.002), PLR (p=0.003), SII (p<0.001), SIRI (p=0.001) and SIAI (p<0.001). No significant correlation was found between BASDAI, ASDAS-CRP and ASDAS-ESR and laboratory indices. Details are shown in Table 3.

Table 3. Correlation of clinical parameters and laboratory values in patients with ankyosing spondylitis

	ESR (mm/h)		CRP (mg/l)		BASDAI		ASDAS-CRP		ASDAS-ESR	
	r	p	r	p	r	p	r	p	r	p
NLR (x10^9/L)	0.179	0.054	0.285	0.002*	0.031	0.736	0.149	0.105	0.071	0.443
MLR (x10^9/L)	0.100	0.284	0.166	0.073	-0.039	0.674	-0.019	0.840	-0.029	0.756
PLR (x10^9/L)	0.350	<0.001*	0.273	0.003*	-0.093	0.314	-0.016	0.865	0.021	0.819
SII (x10^9/L)	0.393	<0.001*	0.441	<0.001*	-0.020	0.828	0.137	0.138	0.120	0.195
SIRI (x10^9/L)	0.169	0.069	0.311	0.001*	0.039	0.676	0.130	0.160	0.083	0.369
SIAI (x10^9/L)	0.318	<0.001*	0.423	<0.001*	-0.027	0.770	0.106	0.252	0.099	0.285

r: Spearman's rank correlation coefficient; 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, SIAI: systemic inflammation aggregate index, BASDAI: bath ankylosing spondylitis disease activity index, ASDAS-ESR: ankylosing spondylitis disease activity score with erythrocyte sedimentation rate, ASDAS-CRP: ankylosing spondylitis disease activity score with C-reactive protein

Discussion

This study investigating the relationship between systemic inflammation indices and DA in AS presents several important findings. Our results indicate that we did not observe statistically significant differences in hematological parameters such as NLR, MLR, PLR, SII, SIRI, and SIAI between AS patients and healthy controls. However, our study reveals that ESR values of patients with AS are statistically significantly correlated with PLR, SII SIAI and CRP values are statistically significantly correlated with NLR, PLR, SII, SIRI, SIAI. No statistically significant difference was found between DA scores and NLR, MLR, PLR, SII, SIRI and SIAI.

Studies have examined the relationship between rheumatic diseases and systemic inflammatory indices, and different results have been presented. In a study evaluating a total of 502 fibromyalgia patients, it was emphasized that although the SII, SIRI and SIAI values of the patients were significantly higher than the control group, they did not yet have diagnostic value [12]. A study conducted on patients diagnosed with rheumatoid arthritis revealed that the pan-immune-inflammation value (PIV) and SII values were higher in RA patients with high disease activity compared to the remission group and healthy controls [13].

The classification of AS patients into active and remission stages based on the BASDAI provided a robust framework for evaluating DA. Consistent with earlier studies, our assessment using ASDAS-ESR and ASDAS-CRP values revealed significant differences in CRP and ESR rates between low and high DA groups. Yet, no corresponding significant differences were found for NLR, MLR, PLR, SII, SIRI, and SIAI values. This suggests a level of complexity in the inflammatory process associated with AS, indicating that traditional hematological parameters may not fully capture the ongoing immune response.

Kasapoğlu Aksoy et al. reported a correlation between the CRP rs3091244 C allele and higher ASDAS-CRP scores, suggesting that genetic factors could influence DA in AS [14]. Moreover, a study assessed the effectiveness of SIRI and SII, along with ultrasound evaluations of entheses and joints, in measuring DA in spondyloarthritis. Their findings indicated that both SII and SIRI were elevated in patients with high DA, supporting their potential role as biomarkers for monitoring DA. Additionally, in the study, the SII value of the patients was associated with synovitis detected on ultrasound of the peripheral joints [15]. However, Sariyildiz et al. evaluated the relationship between systemic inflammation indices and DA in AS patients and found that while these indices were significantly higher in AS, they did not effectively differentiate between DA levels or correlate with functional status or general health. Although the SII showed weak correlations with some DA scores, the study suggests that it does not indicate DA or overall patient well-being in AS [16]. In their study, Misirci et al. found that SII levels were significantly elevated in patients with AS compared to the control group. Furthermore, the same study reported that SII levels were notably higher in the active AS patient group compared to those in remission [17]. In a different study, no meaningful association was identified between SII and BASDAI scores in patients with AS [18]. In research carried out by Taha et al., the associations of RDW, MPV, NLR, PLR, LMR and SII with disease activities in rheumatology patients including AS patients were examined. Their findings revealed that RDW, MPV, and PLR were significantly elevated in all three conditions compared to controls, while LMR decreased [19]. Ibrahim et al. reported results indicating that indices like PLR, NLR and SII

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may be valuable in monitoring treatment in patients receiving biological agent treatment [20]. In a recent study examining blood parameters before and after starting biologic agents in 54 patients with AS, it was shown that NLR, PLR and MLR, CRP and ESR values were significantly lower than the initial values at 3, 6 and 12 months. However, similar to our study, although they found a correlation between hematologic markers and acute phase reactants, they did not find a correlation between hematologic markers and BASDAI scores. In our study, SII, SIRI, SIAI values were additionally examined, and a positive correlation was found between acute phase reactants and SII, SIRI, SIAI. However, no correlation was observed between BASDAI, ASDAS-CRP, and ASDAS-ESR scores and any hematological parameter [21]. In a prospective study, a positive correlation was found between PIV values and CRP, ESR, and BASDAI scores in patients with AS, and it was concluded that PIV values may be an indicator of disease activity [22]. In light of all the results, the contradictory results of the studies reveal the need for further research. Despite these insights, this research presents certain limitations. The retrospective design and small sample size are limitations of our study.. However, while this study provides valuable information regarding the relationship between DA and systemic inflammation indices, further research is essential to explore this topic in depth.

Conclusion

In summary, our study underscores the complexity of evaluating DA in AS, particularly with respect to traditional and novel biochemical markers. Continued investigation into the roles of systemic inflammation indices, alongside established clinical measures, is critical for enhancing our understanding and management of this condition.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethical approval for the research was obtained with the decision of the local Ethics Committee of Ordu University dated June 28, 2024, and numbered 2024/66.

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