Research Article

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Title: The relationship between systemic ımmune ınflammation ındex and disease activity in ankylosing spondylitis patients.

Short title: Systemic immune inflammation index in ankylosing spondylitis.

Öz

Purpose: This study aimed to investigate the relationship between the systemic immune inflammation index (SII), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and disease activity and functional status in patients with ankylosing spondylitis (AS).

Materials and methods: This cross-sectional clinical study included a total of 90 patients diagnosed with AS according to the Modified New York Criteria, aged between 18 and 65, who presented to our outpatient clinics. Demographic data and laboratory parameters, including platelet, neutrophil, basophil, eosinophil, and lymphocyte counts, mean platelet volume (MPV), red blood cell distribution width (RDW), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), were recorded. NLR and PLR values were calculated. The SII was calculated by dividing the product of neutrophil and platelet counts by the lymphocyte count.

Results: The study included 90 AS patients (mean age: 42.9±11.3 years). Positive correlations were observed between SII and CRP (p=0.010, r=0.269) and ESR (p=0.007, r=0.282). No significant correlations were found between SII and BASDAI, BASFI, or BASMI (p>0.05). NLR and PLR values didn't differ significantly between active and inactive disease groups (p>0.05). There was a significant correlation between SII and Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate (ASDAS-ESR) (rho=0.282, p=0.007).

Conclusion: The study suggests that SII correlates positively with CRP and ESR, common inflammatory markers in AS. SII could be a potential marker for assessing inflammation, especially in patients with higher disease activity.

Keywords: Ankylosing spondylitis, complete blood count, inflammation.

Makale başlığı: Ankilozan spondilit hastalarında sistemik immün inflamasyon indeksinin hastalık aktivitesi ile ilişkisi.

Kısa başlık: Ankilozan spondilitte sistemik immün inflamasyon indeksi.

Öz

Amaç: Bu çalışma, ankilozan spondilit (AS) hastalarında sistemik immün inflamasyon indeksi (SII), trombosit-lenfosit oranı (PLR), nötrofil-lenfosit oranı (NLR) ile hastalık aktivitesi ve fonksiyonel durum arasındaki ilişkiyi araştırmayı amaçlamaktadır.

Gereç ve yöntem: Bu klinik kesitsel çalışmaya, Modifiye New York Kriterleri'ne göre AS tanısı almış 18-65 yaş aralığında 90 hasta dahil edildi. Demografik veriler, trombosit, nötrofil, bazofil, eozinofil ve lenfosit sayıları, ortalama trombosit hacmi (MPV), eritrosit dağılım genişliği (RDW), C-reaktif protein (CRP) ve eritrosit sedimantasyon hızı (ESR) gibi laboratuvar parametreleri kaydedildi. NLR, PLR ve SII değerleri hesaplandı.

Bulgular: Çalışmaya dahil edilen AS hastalarının yaş ortalamaları 42,9±11,3 yıl idi. SII ile CRP (p=0,010, r=0,269) ve ESR (p=0,007, r=0,282) arasında pozitif korelasyon saptandı. SII ile BASDAI, BASFI veya BASMI arasında anlamlı bir ilişki bulunmadı (p>0,05). NLR ve PLR değerleri aktif ve inaktif hastalık grupları arasında anlamlı bir fark göstermedi (p>0,05). SII ile ESR kullanılarak hesaplanan Ankilozan Spondilit Hastalık Aktivite Skoru (ASDAS-ESR) arasında anlamlı bir korelasyon vardı (rho=0,282, p=0,007).

Sonuç: Çalışma, SII'nin AS'de yaygın inflamatuar belirteçler olan CRP ve ESR ile pozitif korelasyon gösterdiğini ortaya koymaktadır. SII, özellikle daha yüksek hastalık aktivitesine sahip hastalarda inflamasyonu değerlendirmek için potansiyel bir belirteç olabilir.

Anahtar kelimeler: Ankilozan spondilit, tam kan sayımı, inflamasyon.

Introductıon

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease belonging to the spondyloarthritis group, primarily affecting the spine and sacroiliac joints [1]. Due to its progressive nature, disease activity needs to be regularly monitored, and the treatment plan should be adjusted according to changes in activity. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly utilized markers for inflammation assessment during follow-

ups. However, their elevation can occur due to various non-specific factors like infections, malignancies, and inflammation unrelated to AS. This highlights the necessity for more specific markers in evaluating disease activity in rheumatic diseases like AS and rheumatoid arthritis. [2].

Complete blood count is an easily assessable, cost-effective, and straightforward test. There are changes in blood parameters during inflammatory processes, and these changes can be utilized to assess the level of inflammation [2]. The value obtained by dividing the number of neutrophils by the number of lymphocytes in a complete blood count, known as Neutrophil-to-Lymphocyte Ratio (NLR), has been found to be associated with the level of inflammation in diseases such as thyroid disorders [3], inflammatory bowel disease [4], and diabetes mellitus [5]. Another value obtained by dividing the platelet count by the lymphocyte count, known as Platelet-to-Lymphocyte Ratio (PLR), has found applications in conditions such as liver fibrosis [6] and diabetes [7]. The Systemic Immune Inflammation Index (SII), a novel marker, is calculated by multiplying the platelet count by the neutrophil count and then dividing this product by the lymphocyte count. SII has been found to be more successful in determining inflammation compared to NLR and PLR [8]. In studies, SII has been reported as a prognostic and activity determinant in conditions such as various types of malignancies [9,10], Behçet's disease [11], vasculitis [12], lateral epicondylitis [13], rheumatoid arthritis [14] and post-stroke depression [15].

Recent studies have reported that data obtained through calculations of laboratory parameters such as the SII, NLR, and PLR can potentially be used to assess disease activity in AS, although this remains a topic of debate [16, 17]. Additionally, in the follow-up of AS patients, parameters that include assessments of symptom severity such as 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) hold significant importance. The aim of this study is to evaluate the relationship between SII, PLR, NLR values and BASDAI, ASDAS-CRP, and ASDAS-ESR scores, which are used to determine disease activity and their applicability in patient monitoring among AS patients.

Materials and methods

Our study was designed as a cross-sectional clinical study. Between May 2, 2024, and May 20, 2024, a total of 90 patients between the ages of 18-65 who were diagnosed with AS according to the Modified New York Criteria and followed up at the Health Science University, Istanbul Physical Therapy and Rehabilitation Training and Research Hospital and Beylikdüzü State Hospital outpatient clinics were included in the study. The research received ethical approval with protocol number 2024/18 from the Clinical Research Ethics Committee of Istanbul Pyhsical Therapy and Rehabilitation Training and Research Hospital. Informed consent was obtained from all patients before the start of the research.

Exclusion criteria for our study included the presence of acute or chronic infections, autoimmune diseases other than ankylosing spondylitis, pregnancy, diabetes, chronic kidney or liver disease, and the presence of cardiovascular or hematological diseases that could lead to changes in laboratory parameters. At the beginning of the study, sociodemographic data such as age, gender, marital status, body-mass index (BMI), smoking status, duration of disease diagnosis, and age at symptom onset were recorded for all patients.

Disease activity was assessed using the BASDAI, ASDAS-CRP, and ASDAS-ESR. The Turkish version of BASDAI, which has been validated and demonstrated reliability by Akkoç et al., was utilized in the study [18]. Scores of 4 or higher were considered indicative of active disease, while scores below 4 were classified as inactive disease. For ASDAS-CRP and ASDAS-ESR scores, patients with values of 2.1 and above were categorized as active, while those with values below 2.1 were placed in the inactive group [19]. Spinal mobility was evaluated using the Bath Ankylosing Spondylitis Metrology Index (BASMI), and functional status was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) [20]. Furthermore, during the routine follow-up of patients, requested blood tests were examined to record platelet, neutrophil, basophil, eosinophil, lymphocyte counts, mean platelet volume (MPV), red blood distribution width (RDW), CRP, and ESR values. NLR, PLR and SII were calculated. SII is obtained by dividing the product of neutrophil and platelet counts by the lymphocyte count.

Statistical analysis

The study's sample size was determined based on Wu et al.'s research [21], with correlations of 0.483 for SII and CRP, 0.374 for SII and ESR, and 0.667 for

SII and BASDAI. With a significance level of 5% and 95% power, sample sizes for CRP, ESR, and BASDAI were calculated as 41, 73, and 19, respectively. A minimum of 73 participants was needed for all variables. Our study included 90 AS patients. We used G*Power 3.1.9.4 for sample size calculation. Data normality was assessed with Kolmogorov-Smirnov test. Descriptive statistics were used for quantitative data, presented as mean/standard deviation or median/min-max, and categorical data as frequency/percentage. Spearman test analyzed SII-AS disease activity correlation due to non-normality. Mann-Whitney U test compared active and inactive disease groups. SPSS 21.0 conducted statistical analyses.

Results

Our study included 90 patients diagnosed with AS. Detailed descriptive statistics are provided in Table 1. Of the participants, 61.1% were male, and 38.9% were female, with a median age of 45.5. The median BMI of the individuals was 27.7, with a minimum value of 11.5 and a maximum value of 41.6 (Table 1).

Table 2 illustrates the correlation between AS disease activity parameters and laboratory data. SII doesn't show significant relationships with BASDAI, BASFI, or BASMI scores ($p>0.05$), but it correlates positively with CRP and ESR values ($p=0.010$, r=0.269 and $p=0.007$, r=0.282, respectively). PLR and NLR ratios aren't correlated with any parameter ($p>0.05$). BASMI scores correlate significantly with CRP ($p=0.026$) and ESR ($p=0.005$), whereas BASFI and BASDAI scores don't exhibit such correlations. As expected, CRP and ESR values correlate with ASDAS-CRP and ASDAS-ESR scores ($p<0.05$) (Table 2).

In Table 3, patients were examined in two groups based on BASDAI, ASDAS-CRP, and ASDAS-ESR scores, classified as active and inactive. The calculated SII value in patients with high ASDAS-ESR scores, indicating active disease, was significantly higher than in the inactive group ($p=0.032$). There was no significant difference between the two groups in terms of NLR and PLR ratios ($p>0.05$) (Table 3).

Discussion

In this cross-sectional clinical study, a positive correlation was found between CRP and ESR values, which are frequently used in the follow-up and treatment decisions of AS patients and considered as markers of inflammation,

and the SII value. Additionally, higher SII values were found in the patient group considered active according to the ASDAS-ESR score. However, there was no significant difference in SII values between active and inactive patient groups based on ASDAS-CRP and BASDAI scores. Furthermore, in our study, we did not find a significant difference in NLR and PLR levels between active and inactive groups for all three parameters.

There are many studies in the literature investigating the use of blood parameters to determine disease activity and periodic patient monitoring in rheumatological diseases [14, 15]. However, the number of such studies in AS patients is limited. In the follow-up and determination of activity in AS patients, not only laboratory parameters but also scoring systems such as BASDAI, ASDAS-CRP, and ASDAS-ESR are used. Limitation in spinal mobility can be evaluated with the BASMI index, and the patient's functional status can be assessed with the BASFI scoring. Scoring systems that rely on the patient's self-report, such as BASDAI and BASFI, are influenced by many additional factors beyond the inflammation caused by the disease, including the patient's psychological state, perception of the disease, and central sensitization. ASDAS-CRP and ASDAS-ESR values include both laboratory parameters and patient self-report when calculated [22]. The lack of correlation between SII and scoring systems obtained from subjective questioning, but its higher values in patients considered active according to ASDAS-ESR, may be attributed to the patient's mental and psychological factors. The correlation of SII with ESR and CRP values also suggests that it could be a biomarker with the potential to predict the current level of inflammation.

In a study, the SII value in AS patients was found to be correlated with ESR, CRP, and BASDAI scores [21]. In another study, SLE, RA, and AS patient groups were compared with healthy controls. SII values were higher in AS and RA patients compared to the control group. PLR was higher in all three groups, while NLR was significantly higher only in SLE patients compared to the control group. However, when the AS group was grouped according to the level of disease activity, there was no significant difference in SII, NLR, and PLR values. Additionally, in AS patients, SII and NLR values were correlated with CRP, ESR, and ASDAS parameters, while PLR was not correlated. On the other hand, MPV and RDW values showed changes consistent with disease activity in all three disease groups [23]. In contrast, in our study, RDW and MPV values in AS

patients were not found to be associated with disease activity or laboratory parameters.

In the study by Liang et al. [24], PLR and NLR ratios were significantly higher in the AS patient group compared to the healthy group. Additionally, the AS patient group was categorized as active and inactive based on BASDAI scores, and the active group had significantly higher PLR values, but the same was not true for NLR. In our research, parallel to this study, NLR values were not found to be associated with disease activity, and similarly, PLR values were not found to be different between active and inactive patients, as was the case with NLR. In a study conducted by Osami et al. [25] in AS patients, NLR, PLR, and ESR values were found to be significantly higher in active AS patients compared to inactive ones. However, when compared to the healthy group, ESR was significantly higher, while NLR and PLR ratios were similar between the two groups. In contrast to this study, in our research, NLR and PLR values were not correlated with disease activity levels indicated by BASDAI, ASDAS-CRP, and ASDAS-ESR values.

Our study was conducted only with AS-diagnosed patients due to the absence of a control group. Additionally, the single-center nature of the study is one of its limitations. One of the strengths of our research is that we examined the correlation of markers by simultaneously using multiple methods for evaluating disease activity. The markers evaluated in this study are cost-effective parameters that can be easily obtained in all laboratories where complete blood counts are performed and are well-correlated with inflammation [23]. In our study, especially, SII has been shown to be a cost-effective marker that can be used for this purpose. Further studies with a larger number of patients and multi-center studies are needed to establish its safe use in patient follow-up.

Conflict of interest: No conflict of interest was declared by the authors.

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Ethical approval information: Ethical clearance for this research, as per protocol number 2024/18, was granted by the Clinical Research Ethics Committee of Istanbul Physical Medicine and Rehabilitation Training and Research Hospital on April 30, 2024. Prior to the commencement of the study, participants provided informed consent. The study was conducted in accordance with the guidelines outlined in the Declaration of Helsinki.

Authors' contributions to the article

The main idea and hypothesis of the study were formulated by B.S.A. and F.N.K. They also contributed to the development of the theory and organization of the material and methods section. Evaluation of the data in the Results section was conducted by B.S.A., F.N.K., N.P. and Y.C.A. The Discussion section of the article was authored by B.S.A., with input from Y.C.A., N.P. and F.N.K., who reviewed, corrected, and approved it. Furthermore, all authors collectively discussed the entirety of the study and endorsed the final version.

Table 1. Descriptive statistics

		Median (min-max) / n (%)	
Age		45.5 (21-65)	
Gender	Male	55	61.1
	Female	35	38.9
Marital status	Married	68	75.6
	Single	22	24.4
BMI		27.7 (11.5-41.6)	
Smoking	Non-smoker	48	53.3
	<10 pack-years	13	14.4
	10-20 pack-years	15	16.7
	>20 pack-years	14	15.6
Duration of diagnosis		84 (1-396)	
Age at symptom onset		24.5 (8-57)	
HLA B27	Positive	51	56.7
	Negative	39	43.3
BASDAI		5 (0-10)	
BASFI		4 (0-10)	
BASMI		2 (0-8)	
CRP		3.9 (0.2-46.4)	
ESR		9 (2-60)	
MPV		9.2 (7.1-12.5)	
RDW		13.4 (11.9-21.2)	
NLR		1.7 (0.8-4.6)	
PLR		111 (45.6-258)	
SII		478 (198.6-1503.7)	
ASDAS-CRP		2.7 (1.1-5.2)	
ASDAS-ESR		2.7 (1-5)	

BMI: Body-mass index BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein, ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PLR: platelet to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, SII: systemic immune inflammation index

Table 2. Correlation between laboratory parameters and parameters related to disease activity

	BASDAI		**BASMI**		**BASFI**		**CRP**		**ESR**		**ASDAS-CRP**		**ASDAS-ESR**	
	rho	***p***	**rho**	***p***	**rho**	***p***	**rho**	***p***	**rho**	***p***	**rho**	***p***	**rho**	***p***
CRP	-0.029	0.785	***0.234***	***0.026***	0.072	0.499	1	-	0.696**	***0.000***	***0.473***	***0.000***	***0.258***	***0.014***
ESR	0.016	0.879	***0.296***	***0.005***	0.010	0.926	0.696	***0.000***	1		***0.374***	***0.000***	***0.450***	***0.000***
RDW	-0.061	0.568	0.199	0.060	-0.100	0.348	0.124	0.245	***0.315***	***0.003***	0.055	0.605	0.131	0.218
MPV	-0.049	0.649	0.041	0.701	-0.111	0.296	0.002	0.986	0.001	0.990	-0.009	0.932	-0.021	0.845
SII	0.105	0.323	-0.045	0.673	0.163	0.124	0.269*	***0.010***	0.282**	***0.007***	0.196	0.064	0.196	0.065
PLR	0.103	0.335	-0.019	0.86	0.112	0.295	-0.006	0.953	0.133	0.212	0.031	0.771	0.098	0.357
NLR	-0.007	0.949	-0.081	0.446	0.097	0.361	0.146	0.171	0.109	0.308	0.031	0.770	0.007	0.948

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index
BASMI: Bath Ankylosing Spondylitis Metrology Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein
ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate, CRP: C-reactive protein
ESR: Erythrocyte sedimentation rate, PLR: platelet to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio
SII: systemic immune inflammation index

Table 3. Changes in laboratory and clinical parameters according to disease activity

	BASDAI				ASDAS-CRP				ASDAS-ESR		
	<4 (n=27)	**≥4 (n=63)**	***p***		**<2.1 (n=22)**	**≥2.1 (n=68)**	***p***		**<2.1 (n=25)**	**≥2.1 (n=65)**	***p***
BASFI	1 (0-6)	5 (1-10)	***0.000***	**BASFI**	1.5 (0-6)	5 (0-10)	***0.001***	**BASFI**	1 (0-7)	5 (0-10)	***0.000***
BASMI	3 (0-6)	2 (0-8)	0.535	**BASMI**	2 (0-6)	2 (0-8)	0.404	**BASMI**	2 (0-6)	2 (0-8)	0.967
RDW	13.4 (12.5-19.6)	13.4 (11.9-21.2)	0.558	**RDW**	13.2 (12.5-19.6)	13.4 (11.9-21.2)	0.305	**RDW**	13.4 (12.5-19.6)	13.4 (11.9-21.2)	0.708
MPV	9.2 (7.2-10.7)	9.1 (7.1-12.5)	0.754	**MPV**	9.2 (8-10.1)	9.1 (7.1-12.5)	0.764	**MPV**	9.2 (7.8-10.1)	9.2 (7.1-12.5)	0.435
CRP	4.2 (0.2-36.6)	3.6 (0.2-46.4)	0.853	**CRP**	1.8 (0.2-12.2)	4.9 (0.2-46.4)	***0.002***	**CRP**	2.4 (0.3-23.1)	4.7 (0.2-46.4)	0.051
ESR	8 (2-51)	10 (2-60)	0.363	**ESR**	7 (2-35)	11 (2-60)	***0.042***	**ESR**	6 (2-35)	11 (2-60)	***0.007***
NLR	1.6 (0.8-4.4)	1.8 (0.8-4.6)	0.933	**NLR**	1.6 (0.8-4.4)	1.76 (0.8-4.6)	0.639	**NLR**	1.6 (0.9-4.4)	1.8 (0.8-4.6)	0.240
PLR	105.7 (60.9-223.6)	111.6 (45.6-258)	0.708	**PLR**	110.1 (60.9-195.3)	110.9 (45.6-258)	0.858	**PLR**	105.7 (60.9-165.2)	111.8 (45.6-257.9)	0.351
SII	438.7 (214.6-1017.4)	496 (198.6-1503.7)	0.410	**SII**	412.8 (205-847.3)	491.12 (198.6-1503.7)	0.233	**SII**	357.4 (205-847.3)	496 (198.6-1503.7)	***0.032***

Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index
BASMI: Bath Ankylosing Spondylitis Metrology Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein
ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score with erythrocyte sedimentation rate, CRP: C-reactive protein
ESR: Erythrocyte sedimentation rate, PLR: platelet to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, SII: systemic immune inflammation index

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