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Original Article / Orijinal Araştırma

Clinical Usefulness of Hematologic Indices in Evaluating Response to Treatment with Anti-Tumor Necrosis Factor-Alfa Agents and Disease Activity in Patients with Ankylosing Spondylitis

Ankilozan Spondilit Hastalarında Hastalık Aktivitesi ve Anti-Tümör Nekroz Faktörü Alfa Ajanlar ile Tedavi Yanıtını Değerlendirmede Hematolojik Endekslerin Klinik Yararlılığı

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Abstract

Aim: Ankylosing spondylitis (AS) is a chronic inflammatory disease which influences the proportion of immune cells. Tumor necrosis factor alpha (TNF-α) is essential in the pathogenesis of AS, and TNF inhibitors are the most effective treatment for AS patients. In recent years, routine blood parameters were reported as markers of systemic inflammation associated with the diagnosis and prognosis of numerous malignancies and chronic inflammatory diseases. This study aimed to investigate the relationship between haematological parameters and clinical parameters, disease severity and treatment response in AS patients treated with TNF inhibitors.

Material and Methods: A total of 326 participants were recruited from the rheumatology department in this study. Participants were divided into healthy controls (n=178) and AS (n=148). Neutrophil, lymphocyte, monocyte and platelet counts, neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), platelet crit (PCT), mean platelet volume (MPV), red cell distribution width (RDW), systemic inflammatory index (SII), systemic inflammatory response index (SIRI), cluster systemic inflammation index (AISI) and RPR levels were analyzed for each participant. They were compared between healthy control, AS patients during the pre-treatment phase and three months after the treatment.

Results: RDW, PLR, NLR, MLR, SIRI, AISI and SII were higher than healthy controls and decreased with treatment except SIRI. The decrease in AISI and SII after treatment was significant in HLA-B27 positive patients. MPV was lower than healthy controls and increased with treatment. SII, SIRI and AISI were significantly higher in the active AS patients than in the inactive patient. Also, they were correlated with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

Conclusion: SII, AISI, and SIRI may be valuable markers for demonstrating disease activation and evaluating the effectiveness of anti-TNF-α therapy.

Keywords: Ankylosing spondylitis, anti-tumor necrosis factor alpha, cluster systemic inflammation index, systemic inflammatory index, systemic inflammatory response index

Öz

Amaç: Ankilozan spondilit (AS), yüksek morbititeye sahip kronik inflamatuar bir hastalıktır. AS'nin patogenezinde TNF-α önemlidir ve TNF inhibitörleri AS hastaları için etkili tedavi ajanlarıdır.AS patogenezinde tümör nekroz faktör alfa (TNF-α) esastır ve TNF inhibitörleri AS hastaları için en etkili tedavi yöntemidir. Son yıllarda rutin kan parametrelerinin, çok sayıda malignite ve kronik inflamatuar hastalığın tanı ve prognozu ile ilişkili sistemik inflamasyon belirteçleri olduğu rapor edilmiştir. Bu çalışmada TNF inhibitörleri ile tedavi edilen AS hastalarında hematolojik parametreler ile klinik parametreler, hastalık şiddeti ve tedaviye yanıt arasındaki ilişkinin araştırılması amaçlandı.

Gereç ve Yöntem: Bu çalışmaya romatoloji bölümünden toplam 326 katılımcı dahil edildi. Katılımcılar sağlıklı kontroller (n=178) ve AS (n=148) olarak ikiye ayrıldı. Nötrofil, lenfosit, monosit ve trombosit sayıları, ortalama trombosit hacmi (MPV), plateletkrit (PTC), nötrofil lenfosit oranı (NLO), nötrofil platelet oranı (PLO), monosit lenfosit oranı (MLO), eritrosit dağılım genişliği (RDW), sistemik inflamatuar indeks (SII), sistemik inflamatuar yanıt indeksi (SIRI), sistemik inflamasyon agregat indeksi (AISI) ve RPR düzeyleri her katılımcı için analiz edildi. Sağlıklı kontrol ile AS hastalarının tedaviden önceki ve tedaviden üç ay sonraki paremetreleri karşılaştırıldı.

Bulgular: RDW, PLR, NLR, MLR, SIRI, AISI ve SII sağlıklı kontrollerden yüksekti ve SIRI dışındakiler tedavilerle azaldı. HLA-B27 pozitif hastalarda tedavi sonrası AISI ve SII'deki azalma anlamlıydı. MPV sağlıklı kontrollerden düşüktü ve tedaviyle arttı. Aktif AS hastalarında SII, SIRI ve AISI, aktif olmayan hastalara göre anlamlı derecede yüksekti. Ayrıca eritrosit sedimantasyon hızı (ESH), C-reaktif protein (CRP) ve BASDAI ile koreleydi.

Sonuç: SII, AISI ve SIRI, hastalık aktivasyonunu göstermede ve anti-TNF-α tedavisinin etkinliğini değerlendirmede değerli belirteçler olabilir.

Anahtar Kelimeler: Ankilozan spondilit, anti-tümör nekroz faktör alfa, sistemik inflamatuar indeks, sistemik inflamatuar yanıt indeksi, sistemik inflamasyon agregat indeksi

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INTRODUCTION

Ankylosing spondylitis (AS), a chronic inflammatory autoimmune disease, is diagnosed in millions of people every year globally, and it mainly occurs in young adult males. AS mostly involves the sacroiliac joints and the axial skeleton, impairing structure and function. Without effective treatment, about one-third of patients may develop severe disabilities. Its pathogenesis is still unclear. AS can be diagnosed clinically and radiographically.[1,2] However, there is no specific diagnostic test. Tumor necrosis factor alpha (TNF-α) is the most important factor in the pathogenesis of AS, and anti-TNF-α therapy is the most effective treatment for AS patients. Various clinical and laboratory markers have been used to evaluate the efficacy of anti-TNF-α therapy. Currently, two non-specific inflammatory biomarkers, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are frequently used to monitor disease activity of rheumatic diseases; however, they are unsatisfactory due to their low sensitivity and specificity. Despite the predictive function of MRI in terms of disease progression, the role of radiological imaging in follow-up is limited. Therefore, there is an urgent need for specific and sensitive biochemical markers for adjunctive diagnosis, treatment guidance and prognosis monitoring of AS.

Reports have shown that white blood cell (WBC) changes (lymphocyte, neutrophil, and neutrophil) are related to inflammatory diseases. The relative levels of circulating WBCs change in response to systemic inflammation.[3] The best known of these is relative lymphopenia accompanied by neutrophilia. Inflammatory processes usually increase the number of monocytes and platelets. Platelets have been shown to play essential roles in inflammatory reactions and immune responses. MPV, an indicator of platelet function and activation, has been reported to reflect immunological and inflammatory status. PCT refers to the percentage of platelet volume in the blood.[3,4] In recent studies, the ratio of neutrophil, monocyte and platelet counts to lymphocyte count [neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), platelet crit (PCT), mean platelet volume (MPV) and red cell distribution width (RDW) have been shown to reflect inflammation and oxidative stress in chronic inflammatory and autoimmune diseases.[3,4] These biomarkers can be used to monitor the effectiveness of treatment in the same patients or to evaluate subclinical inflammation after treatment.[5] In addition, in many inflammatory diseases, new haematological biomarkers such as the systemic inflammatory index (SII: neutrophils × platelets/lymphocytes), the systemic inflammatory response index (SIRI: neutrophils × monocytes/lymphocytes) and the cluster systemic inflammation index (AISI: neutrophils × platelets × monocytes/lymphocytes) are have been used. SII, SIRI and AISI indices have been proposed as markers of systemic inflammation with prognostic significance in patients recently undergoing major surgery and oncological treatment.[6] They may reflect systemic inflammation better than NLR or PLR alone. We aim to investigate the relationship between haematological parameters and clinical parameters, disease severity and treatment response in AS patients treated with Anti-TNF.

MATERIAL AND METHOD

Study population and design

Patients who satisfied the ASAS criteria as AS were recruited from the Department of Rheumatology between January 2018 and March 2021. We enrolled 326 patients, 148 AS and 178 were of similar age and gender without any systemic disease or drug history of healthy controls. Demographic characteristics, including age, sex, duration of disease, general medical history, involvement, laboratory parameters, imaging tests, and treatment information of the patients, were recorded. Data were obtained from the electronic registration database.

Exclusion criteria were as follows: acute and chronic infections, other connective tissue diseases, malignancy, heart failure, severe anaemia, malnutrition, blood transfusion, receiving steroid treatment, haematological disorders, thromboembolic disease, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, acute and chronic kidney failure, chronic hepatic disease.

This single-centre case-control study was approved by the Ethics Committee (Decision No:2021/118) and was performed according to the tenets of the Declaration of Helsinki.

Laboratory measurements

Blood was analyzed in ethylenediaminetetraacetic acid (EDTA) tubes to obtain CBC results, including the platelet (PLT, K/μL), lymphocyte (K/μL), neutrophil (K/μL), and monocyte (K/μL) count, RDW (normal range: 11.5%–14.5%), MPV (normal:7,5–11,5 fl) levels were determined using an automatic blood counting system (Beckman Coulter LH 780, Brea, California, USA) for each participant. ESR (normal:0-20 mm/hour) and CRP (normal:0-8 mg/L), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), were used in the assessment of AS. In addition, HLA-B27 genetic analysis was recorded for AS. MLR, PLR, NLR and were calculated. RPR was calculated by the formula RDW (%) / platelet count (10 9 /L), SII was calculated by the formula platelet counts x neutrophil counts/lymphocyte counts, SIRI was calculated by the formula neutrophil counts x monocyte counts/lymphocyte counts; AISI was calculated by the formula platelet counts x neutrophil counts x monocyte counts /lymphocyte counts, White blood cell, neutrophil, lymphocyte, monocyte and platelet counts, MPV, PTC, NLR, PLR, MLR, RDW, SII, SIRI, AISI, RPR levels were analyzed in the control group, AS patients in the pre-treatment phase and three months after the treatment for each participant.

Disease activity index

The most widely used tool for assessing disease activity in AS is BASDAI, which includes six parameters: fatigue, spinal pain, peripheral joint pain, attachment point inflammation and duration, and severity of morning stiffness. A total score

ranging from 0 to 10 is calculated based on the answers given by the patients to the six questions, and a higher score indicates a more severe disease. A BASDAI score of ≥4 represents the active stage of the disease

Statistical analysis

All statistical analysis was performed using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). To assess the normality of the data, Shapiro-Wilk's normality test and Q-Q plots were used. Moreover, Levene's test was used to check the homogeneity of the variances. Numerical variables were presented as mean±standard deviation or median with interquartile range (25th percentile – 75th percentile), as appropriate. Categorical variables were described as count (n) and percentage (%). Aspin-Welch t-test and Pearson chi-square test were used to compare the age and gender distribution of the study groups. An Aspin-Welch t-test and Mann-Whitney U test were run to determine whether there was a statistically significant difference between healthy control groups ad pre- and post-treatment of the AS groups regarding haematological parameters. Besides, Paired samples t-test and Wilcoxon signed-rank test were conducted to examine whether there was a statistically significant difference between pre-and post-treatment of the AS patients regarding haematological parameters. In addition, Spearman's rho correlation coefficient was calculated to examine the relationship between inflammatory indicators (ESR, BASDAI, CRP) and indexes. A p-value less than 5% was considered statistically significant.

RESULT

The demographical and clinical characteristics of the study groups are given in **Table 1**. The mean age of the AS patients was lower than healthy controls (41.72±10 vs 48.28±8.92, p<.001), and the percentage of males in the AS disease group was higher compared to the healthy controls (66.9% vs 30.9%, p<.001). The mean disease time of the patients was 6.94±2.95 (range: 1 – 13). Of the 148 AS patients, 148 were sacroiliitis, 65 were enthesitis, 19 were uveitis, 66 were HLA B27 positive, and 9 had a family history. **Table 2** presents the laboratory findings of the healthy controls and the patient with AS. There was a statistically significant change before and after the treatment for all laboratory findings, except for monocyte (**Table 2**). After the treatment, haemoglobin, neutrophile, lymphocyte, monocyte, RDW, and RPR values were higher than in healthy controls, while NLR and PLR values were lower. Figure 1 demonstrates the SII, SIRI and AISI scores in the study groups. The SII score was significantly higher before the treatment than the healthy controls, but the SII score was significantly reduced after treatment compared to controls and pre-treatment (**Table 2**, **Figure 1-A**). The SIRI value was significantly higher before the treatment than in healthy controls but remained higher after treatment (**Table 2**, **Figure 1-B**). The AISI value was significantly higher than healthy controls before the treatment but decreased to the level of healthy controls with the treatment (**Table 2**, **Figure 1-C**). A Mann-Whitney U test showed that SII, SIRI and AISI values were similar in both pre-and post-treatment groups in patients with AS disease according to uveitis (**Suplemantary Figure 1**). SIRI values of patients with enthesitis symptom had significantly lower both before (1.10 [IQR, 0.77 – 1.60] vs 1.36 [IQR, 0.96 – 2.09], p=.039) and after (0.82 [IQR, 0.53 – 1.08] vs 0.97 [IQR, 0.65 – 1.44], p=.049) treatment than in patients without enthesitis. There was no significant difference between the absence and presence of enthesitis according to SII and AISI levels in patients with AS (**Suplemantary Figure 2**). SII values of patients with HLA-B27 symptom had significantly lower after (315.90 [IQR, 255.65 – 436.82] vs 441.42 [IQR, 325.83 – 530.13], p=.002) treatment than in patients without HLA-B27. AISI values of patients with HLA-B27 symptom had significantly lower after (201.92 [IQR, 134.80 – 296.99] vs 244.09 [IQR, 189.63 – 363.40], p=.048) treatment than in patients without HLA-B27. There was no significant difference between the absence and presence of HLA-B27 according to SIRI (**Suplemantary Figure 3**) levels in patients with AS. There was a statistically significant and positive relationship between SII and CRP (Spearman's rho=0.335, p<.001), ESR (Spearman's rho=0.527, p<.001), and BASDAI score (Spearman's rho=0.392, p<.001) (Figure 2). Elevated CRP value (Spearman's rho=0.203, p=.013), higher ESR (Spearman's rho=0.273, p<.001), and increased BASDAI score (Spearman's rho=0.243, p=.003) significantly correlated with higher pre-treatment SIRI score (**Figure 3**). Similarly, AISI value was positively correlated with elevated CRP value (Spearman's rho=0.282, p<.001), higher ESR (Spearman's rho=0.436, p<.001), and increased BASDAI score (Spearman's rho=0.348, p<.001) (**Figure 4**).

Table 1. Demographical and clinical characteristics of the study groups

Characteristics	Healthy controls (n=178)	AS Patients (n=148)	p value
Demographical characteristics			
Age (years)	48.28±8.92 (25 – 68)	41.72±10 (20 – 65)	<.001[1]
Gender (M/F)	55 (30.9) / 123 (69.1)	99 (66.9) / 49 (33.1)	<.001[2]
Clinical characteristics			
Disease time (years)		6.94±2.95 (1 – 13)	
Sacroiliitis		148 (100)	
Enthesitis		65 (43.9)	
Uveitis		19 (12.8)	
HLA-B27 positivity		66 (55.9)	
Family history		9 (6.1)	
Treatment			
Adalimumab		52 (35.1)	
Etanercept		32 (21.6)	
Golimumab		31 (20.9)	
Infliximab		8 (5.4)	
Secukinumab		2 (1.4)	
Certolizumab		23 (15.5)	

AS: Ankylosing spondylitis, HLA: Human leukocyte Antigen, M:male, F: Female, Data were expressed as mean±standard deviation (range: min–max) or count (n) and percentage (%). [1]Aspin-Welch t-test, [2]Pearson chi-square test

Table 2. The laboratory findings of the healthy controls and the patients with AS

Parameters	Healthy controls (n=178)	AS Patients (n=148)		p-value[a]	p-value[b]	p-value[c]
		Pre-treatment (Baseline)	Post-treatment (3rd month)			
Hemoglobin (g/L)	13.70±1.40	13.49±1.87	14.10±1.91	.252[1]	.033[1]	<.001[3]
Platelet (10^9/L)	264.67±57.15	305.14±88.38	265.99±70.51	<.001[1]	.855[1]	<.001[3]
Neutrophile (10^9/L)	3.93±1.18	5.46±1.78	4.34±1.66	<.001[1]	.012[1]	<.001[3]
Lymphocyte(10^9/L)	2.37±0.62	2.47±0.86	2.84±0.85	.258[1]	<.001[1]	<.001[3]
Monocyte (10^9/L)	0.50±0.15	0.61±0.20	0.63±0.19	<.001[1]	<.001[1]	.245[3]
MPV(fL)	8.37±0.82	7.92±1.32	8.32±1.29	<.001[1]	.708[1]	<.001[3]
RDW (%)	13.6 (13.1–14.3)	15.1(13.8-17.05)	14.6 (13.4–16.6)	<.001[2]	<.001[2]	.001[4]
PCT		0.23 (0.19–0.28)	0.21 (0.17–0.26)			<.001[4]
CRP (mg/L)		9.01 (3.42–20)	3.28 (2.18–5.5)			<.001[4]
ESR (mm/H)		19 (9.75–41)	7 (3–18)			<.001[4]
BASDAI		5.65 (4.6–6.7)	4 (3.6–5.2)			<.001[4]
NLR	1.61 (1.37–1.94)	2.17 (1.65–2.85)	1.45 (1.11–1.94)	<.001[2]	.011[2]	<.001[4]
MLR	0.20 (0.18–0.25)	0.24 (0.20–0.32)	0.23 (0.17–0.28)	<.001[2]	.085[2]	<.001[4]
PLR	109.03 (93.4–140.22)	124.87 (94.67–158.13)	94.79 (78.32–114.7)	.013[2]	<.001[2]	<.001[4]
SII	414.84 (333.87–528.39)	615.75 (448.46–966.53)	387.94 (266.09–509.05)	<.001[2]	.018[2]	<.001[4]
SIRI	0.76 (0.59–1.03)	1.21 (0.86–1.86)	0.87 (0.61–1.33)	<.001[2]	.034[2]	<.001[4]
AISI	197.11 (146.02–271.69)	364.04 (242.37–569.32)	218.36 (144.47–332.68)	<.001[2]	.084[2]	<.001[4]
RPR	0.05 (0.05–0.06)	0.05 (0.04–0.06)	0.06 (0.05–0.07)	.700[2]	.004[2]	<.001[4]

AS: Ankylosing spondylitis, NLR: neutrophil-lymphocyte ratio, MLR: monocyte-lymphocyte ratio, PLR; platelet-lymphocyte ratio, RPR: Red cell distribution width to platelet ratio, PCT: platelet crit, MPV: mean platelet volüme, RDW: cell distribution width, SII: systemic inflammatory index, SIRI: systemic inflammatory response index, AISI: cluster systemic inflammation index, BASDAİ: Bath Ankylosing Spondylitis Disease Activity Index

Data were presented as mean±standard deviation or median with interquartile ranges (25th percentile – 75th percentile), as appropriate.

[1]Aspin-Welch's t-test

[2]Mann-Whitney U test

[3]Paired samples t-test

[4]Wilcoxon test

p-value[a] comparison of healthy controls and pre-treatment

p-value[b] comparison of healthy controls and post-treatment

p-value[c] comparison of pre-and post-treatment

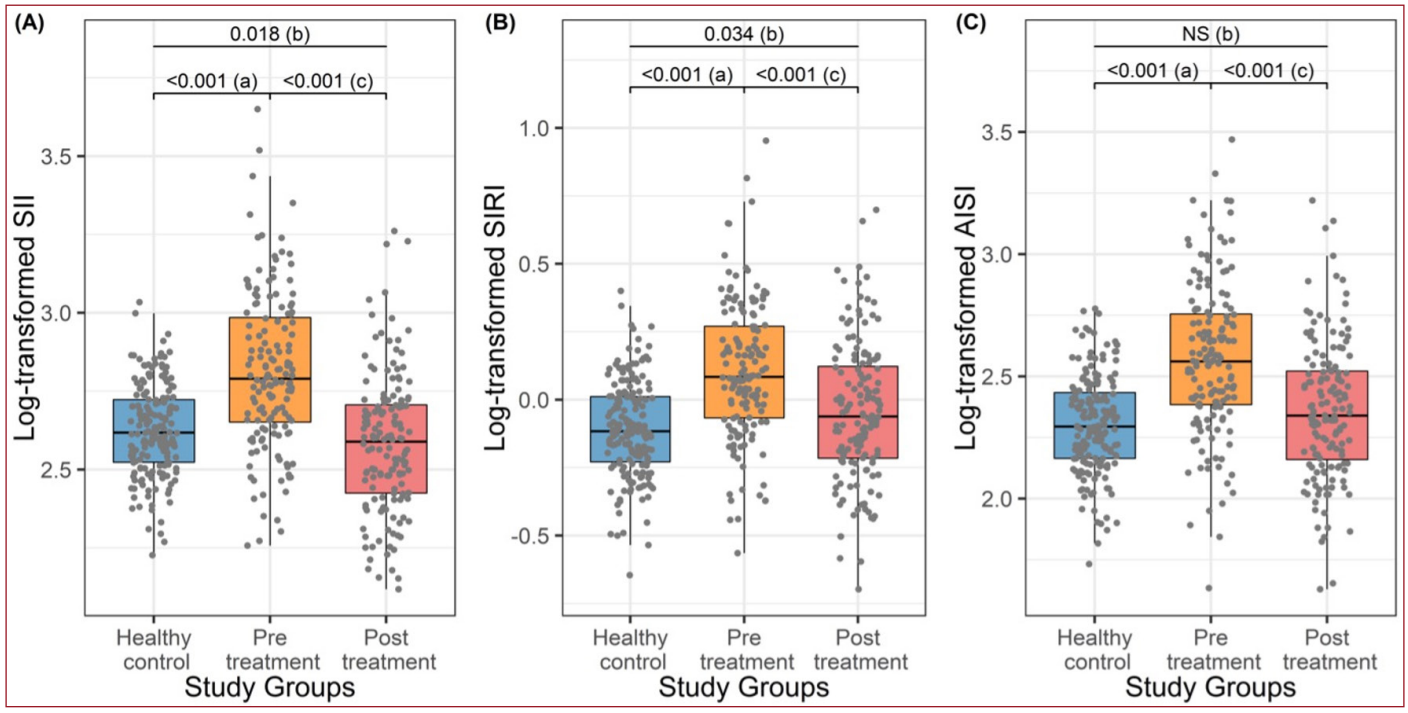


Figure 1. The box plots of (A) SII, (B) SIRI and (C) AISI scores in healthy controls (n=178) and pre- and post-treatment groups in patients with AS (n=143). Data were expressed as median with interquartile ranges (IQR, 25th–75th percentiles). Due to the right-skewness data, the SII, SIRI and AISI values were log-transformed for graphical presentation. Dots depicted the individual's samples. p<.05 was considered statistically significant. NS is not significant.
(a) represents the comparison of SII levels between AS patients before treatment and healthy control groups. Testing for differences between healthy controls and pre-treatment. Mann-Whitney U test was used for comparison. (b) represents the comparison of SII levels between AS patients after treatment and healthy control groups. Mann-Whitney U test was used for comparison. (c) represents the comparison of SII levels before and after treatment of patients with AS. Wilcoxon test was used for comparison.

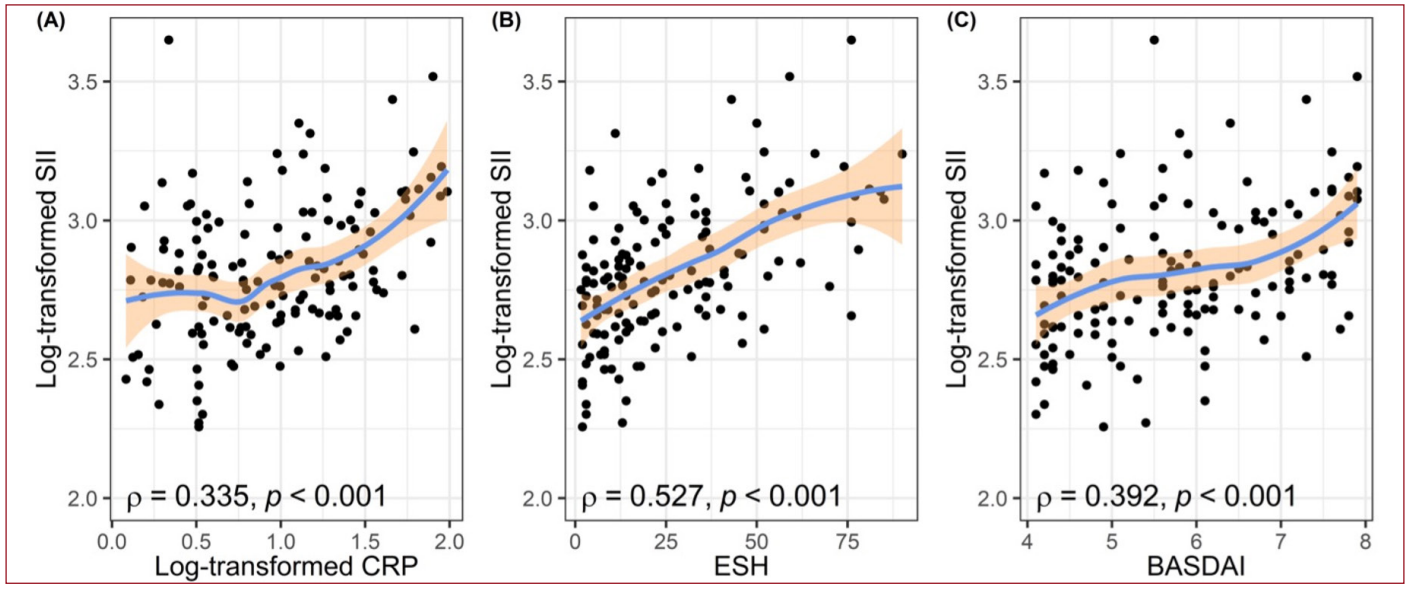


Figure 2. Scatter plots of SII, CRP, ESR, and BASDAI scores with loess regression lines and 95% confidence intervals.

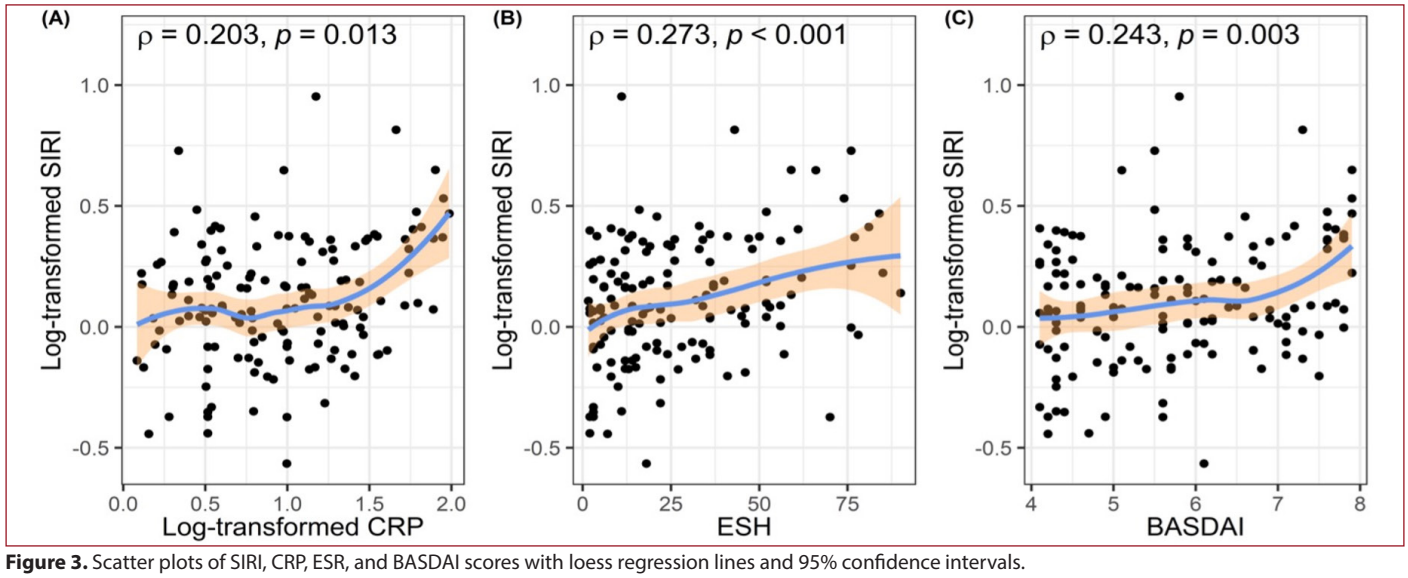


Figure 3. Scatter plots of SIRI, CRP, ESR, and BASDAI scores with loess regression lines and 95% confidence intervals.

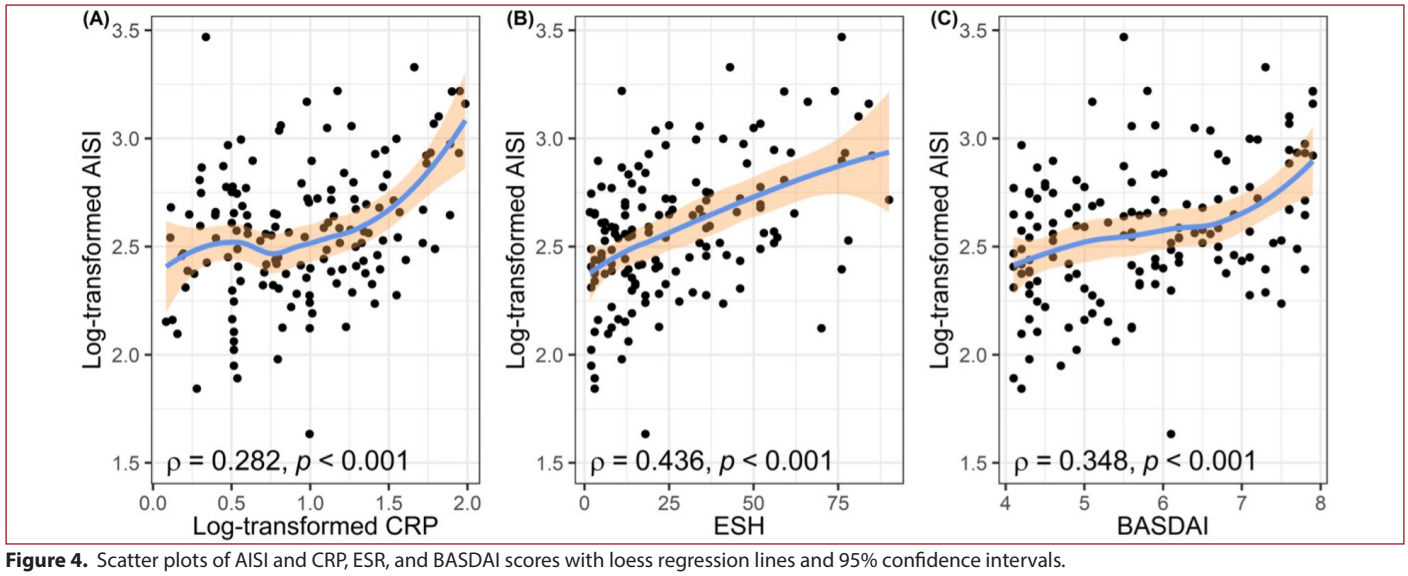
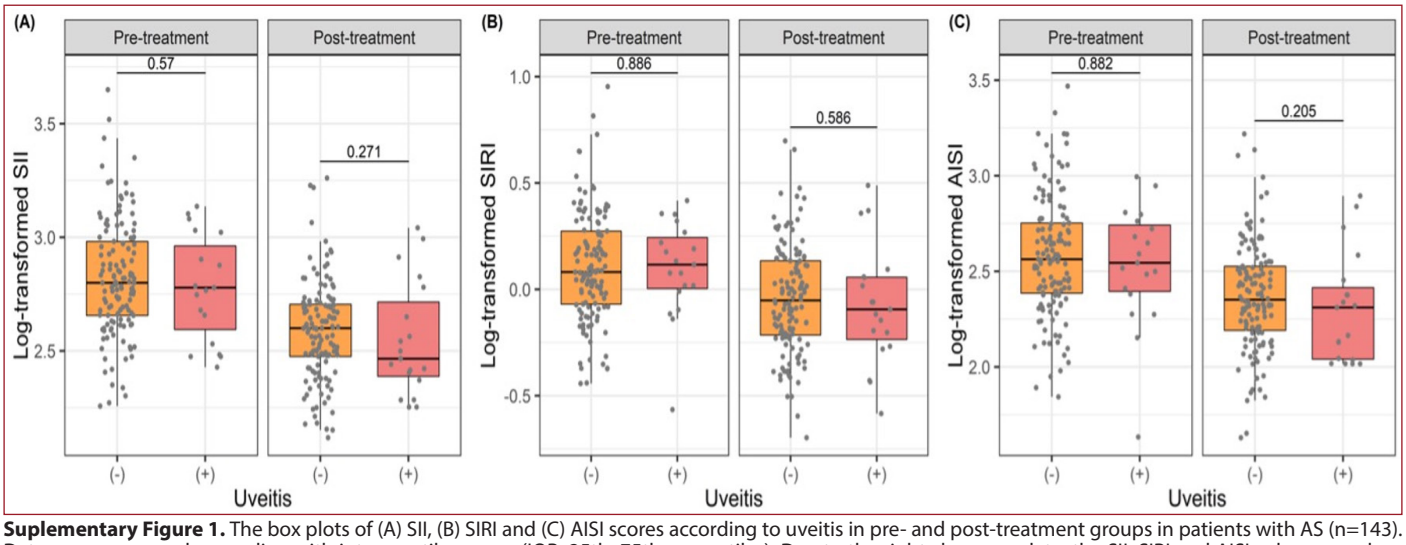
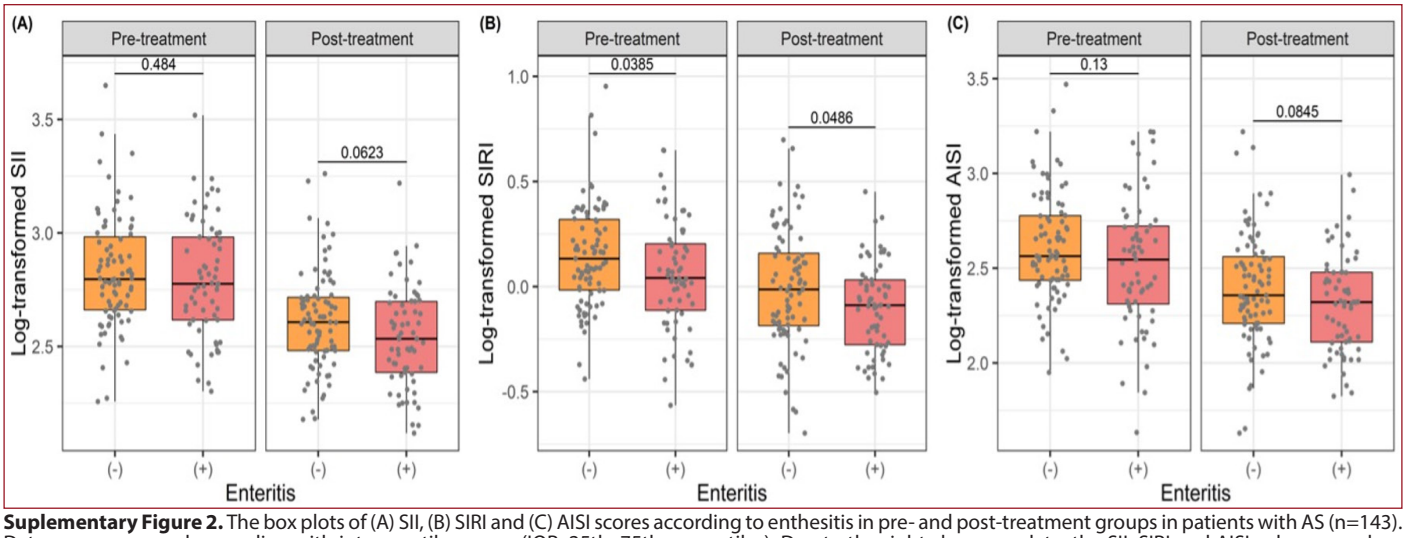


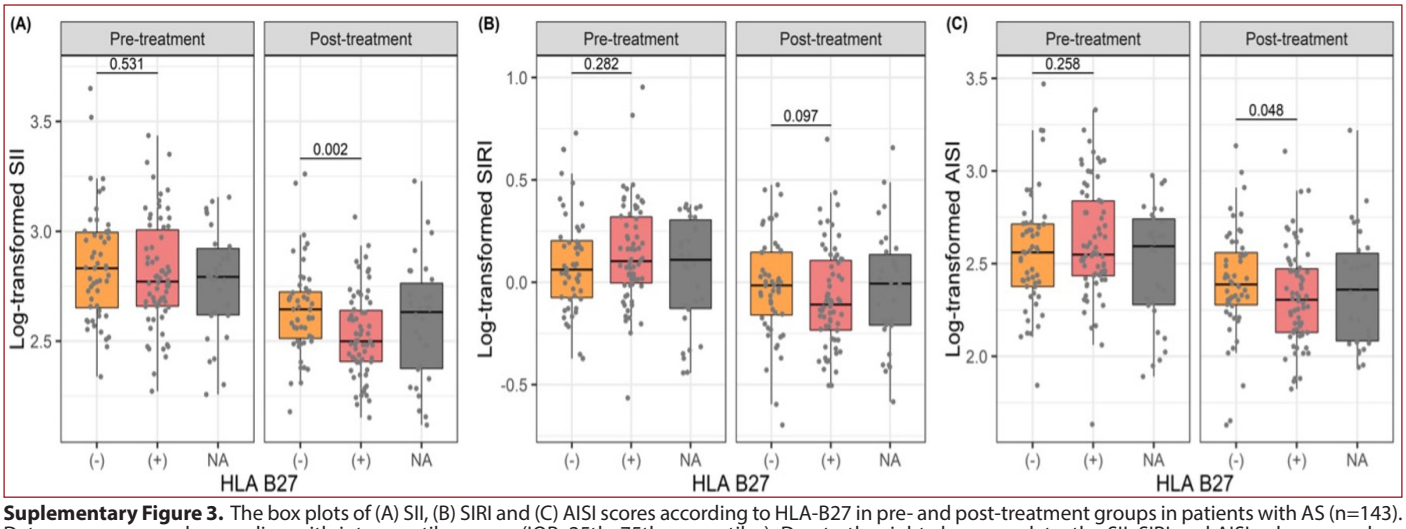
Figure 4. Scatter plots of AISI and CRP, ESR, and BASDAI scores with loess regression lines and 95% confidence intervals.



Suplementary Figure 1. The box plots of (A) SII, (B) SIRI and (C) AISI scores according to uveitis in pre- and post-treatment groups in patients with AS (n=143). Data were expressed as median with interquartile ranges (IQR, 25th–75th percentiles). Due to the right-skewness data, the SII, SIRI and AISI values were log-transformed for graphical presentation. Dots depicted the individual's samples. p<.05 was considered statistically significant. Mann-Whitney U test was used for comparisons.



Suplementary Figure 2. The box plots of (A) SII, (B) SIRI and (C) AISI scores according to enthesitis in pre- and post-treatment groups in patients with AS (n=143). Data were expressed as median with interquartile ranges (IQR, 25th–75th percentiles). Due to the right-skewness data, the SII, SIRI and AISI values were log-transformed for graphical presentation. Dots depicted the individual's samples. p<.05 was considered statistically significant. Mann-Whitney U test was used for comparisons.



Suplementary Figure 3. The box plots of (A) SII, (B) SIRI and (C) AISI scores according to HLA-B27 in pre- and post-treatment groups in patients with AS (n=143). Data were expressed as median with interquartile ranges (IQR, 25th–75th percentiles). Due to the right-skewness data, the SII, SIRI and AISI values were log-transformed for graphical presentation. Dots depicted the individual's samples. p<.05 was considered statistically significant. Mann-Whitney U test was used for comparisons. NA, not applicable, shows missing values.

DISCUSSION

AS is a common kind of autoimmune disease which influences the proportion of immune cells.[1] Therefore, identifying the immune status changing associated with AS can improve the diagnosis of AS. In recent years, routine blood parameters were reported as markers of systemic inflammation associated with the diagnosis and prognosis of numerous malignancies and chronic inflammatory diseases.[3,4] White blood cells (WBCs) and their counts change in systemic inflammation, including AS. This study aimed to investigate the differences in the complete blood count parameters, which incorporated easily accessible for the diagnosis, severity and response to Anti-TNF treatment of AS.

Studies have shown that patients with AS have a higher peripheral blood PLT count than healthy individuals. PLTs are important in inflammatory reactions and immune responses by releasing proinflammatory mediators such as chemokines and cytokines.[6] Although the specific mechanisms involving PLTs in the pathogenesis of AS are unclear, it has been reported that activation of PLTs by thrombin, histamine, TNF-α and interleukin (IL)-12 leads to adhesion between activated PLTs. Regulated with the aid of TNF and upon activation, normal T-cell expressed and possibly chemokine-secreting PLT factor 4 stimulates neutrophils and monocytes to release inflammatory mediators and participate in the inflammatory response. As a subgroup of leukocytes, neutrophils are an important line of cellular immune defence against external microbial inflammatory stimulation and invasion by exogenous pathogens. Studies have shown that many cytokines and chemokines play an important role in neutrophil recruitment, activation and survival in inflammatory sites, including IL-17, IL-8, interferon-γ, TNF-α and granulocyte-macrophage colonies. Abnormal lymphocyte signalling can lead to autoimmune diseases. In systemic inflammation, an increase in neutrophils is accompanied by a corresponding decrease in lymphocytes.[1] This is consistent with our findings showing that absolute neutrophil and platelet counts are higher in patients with AS than in healthy controls. Cellular components and blood ratios can provide insight into the extent of ongoing inflammation. In recent studies, MLR, NLR, PLR, RDW, MPV, and PCT have been shown to reflect inflammation and oxidative stress in chronic inflammatory and autoimmune diseases.[3,7] These parameters have been reported to reflect disease activity and prognosis in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, Behçet's disease (BD), and psoriasis.[4,8,9] These biomarkers can be used to monitor the effectiveness of treatment in the same patients or to evaluate subclinical inflammation after treatment.[5,10,11] NLR is predictive in general and cancer-specific surveillance of stomach, lung, breast, colorectal and kidney cancers.[12] Other inflammatory diseases such as acute pancreatitis, inflammatory bowel disease, and acute appendicitis, and systemic diseases such as hypertension, diabetes mellitus, chronic kidney failure, irritable bowel syndrome, Hashimoto's disease, the cardiovascular disease had higher NLR levels. In another study, bone loss and inflammation were associated with higher NLR levels in elderly patients with osteoporosis.[3] Recently, in studies conducted on patients with familial Mediterranean fever (FMF), the NLR was thought to be a valuable marker for demonstrating subclinical inflammation and for following the development of amyloidosis.[10] Similarly, PLR has been introduced as an inflammatory marker in thyroid conditions, DM, and liver fibrosis. Multiple studies have suggested that NLR and PLR can be considered markers of disease state in RA, SLE, Takayasu arteritis, ulcerative colitis, other autoimmune diseases, and infectious diseases. MLR is another parameter used as an inflammatory and prognostic marker in many autoimmune disorders, cardiovascular diseases, cancer and tuberculosis.[13] The efficacy and safety of PCT and MPV have been investigated in various dermatological diseases such as psoriasis, Behçet's disease, recurrent aphthous stomatitis and pemphigus vulgaris.[14] In recent years, NLR, PLR, and RDW have also been found to be associated with axial SpA disease activity.[15,16] Previous studies have demonstrated that NLR levels are related to CRP and ESR. Increased NLR was found in patients with high disease activity in axial SpA patients. In addition, different levels of NLR have been found in patients exposed to different treatments, such as anti-TNF-alpha therapy and nonsteroidal anti-inflammatory drugs.[17] PLR was identified as an independent factor for diagnosing AS and was associated with the severity of AS.[18,19] Peng et al. suggested that increased RDW is associated with AS and could be a potential marker to predict AS disease activity.[7] Consistent with the literature, our study showed significant differences between AS cases and healthy controls with increased RDW, PLR, NLR and MLR. Previous study found MPV to be lower than control in patients with rheumatoid arthritis, Behçet, AS.[20] They argued that this might be related to platelet utilization in inflammatory processes. Thus resulting in smaller, inactive platelets. Similar to the previous study, MPV was lower than healthy controls and increased with treatment. PCT decreased with treatment but was not significant.

Combined haematological indices of inflammation, especially NLR, MLR, PLR, SII, SIRI and AISI, are widely used with promising results in various diseases.[8,9,14,15] SII, SIRI, and AISI indices have been proposed as markers of systemic inflammation with prognostic significance in patients recently undergoing major surgery and oncological treatment.[21,22] SIRI was significantly higher in diseases such as cancer, infectious diseases and cardiovascular disease.[23] AISI has been found to be a prognostic factor in idiopathic pulmonary fibrosis.[24] SII has been widely used in oncology since 2014 with promising results. There are studies on gastrointestinal, bone, breast, kidney and gynaecological cancers and coronary artery diseases with SII.[25,26] A study showed that SII has a high diagnostic value for moderate/severe psoriasis. Another study showed that SII, NLR, and PLR were significantly elevated and associated

with endoscopic severity in ulcerative colitis patients.[27] In a study on Covid 19, significantly lower survival was found in patients with higher AISI, dNLR, MLR, NLPR, NLR, SII and SIRI.[28,29] In the field of rheumatology, there is an increasing interest in combined haematological inflammation indices, especially in SII.[30,31] In a study conducted on rheumatological diseases, the SII value was found to be significantly higher in the active BD group than in the inactive BD group.[32] Satis et al. previously evaluated SII and SIRI as a marker of inflammation in RA patients.[6] In a study evaluating SII in ANCA-related vasculitides, SII was found to be associated with disease activity and prognosis.[33] A study in adult-onset still disease (EBSH) demonstrated that laboratory inflammatory scores could be used as a practical tool to diagnose EBSH. The same study concluded that the combination of SII and ferritin was the most powerful assessment tool.[34] Similarly, it has been shown that osteoporosis can be an important marker in the evaluation of osteoporotic fractures.[35] There are studies concerned with AISI, SII and SIRI in some rheumatological diseases. However, there is no data in the literature on SII, SIRI and AISI indices, which are used as new and more comprehensive chronic inflammatory indicators based on monocyte, neutrophil, lymphocyte and platelet counts in AS. BASDAI, ESR, and CRP have commonly used measures to determine disease activity and patients' response to therapy. New biomarkers that can monitor AS disease activity need to be identified, and the accuracy of currently available disease activity assessment tools needs to be increased. In this study, NLR, PLR, MLR, RDW, SII, SIRI and AISI were higher in AS patients compared to the healthy control group. AISI, SIRI and SII levels were significantly higher in the highly active AS patient group than in the inactive patient. Also, they were correlated with ESR, CRP and BASDAI. Regarding AS, ROC analysis showed that SII, AISI, and SIRI had the best predictive performance for disease activity. Therefore, an estimator such as SII, AISI, and AISI may better reflect the inflammatory status in specific disease states. To our knowledge, this is the first study to show the relationship between AISI, SIRI, SII and disease activity in patients with AS. It was concluded that SII, AISI and SIRI could be new biomarkers to evaluate AS activity.

TNF-α plays an essential role in the pathogenesis of AS. It is also an important element in hematopoietic progenitor cell differentiation and maturation. Various clinical and laboratory markers have been used to evaluate the efficacy of anti-TNF-α therapy. Our study found that SII, AISI, SIRI, RDW, MLR, PLR, and NLR levels in patients with AS were significantly higher than in healthy individuals and decreased after treatment, except for SIRI. The decrease in PLR and RDW was less after treatment. MPV, which was low before treatment, increased with treatment. This may indicate that inflammation inhibits platelet maturation. In AS patients, the decrease in AISI and SII after treatment was more significant in HLA-B27 positive patients than in negative. It shows that SII, AISI, MLR, PLR, NLR, MPV, and RDW may be valuable markers to evaluate the efficacy of anti-TNF-α therapy in patients with AS. Given that SII, AISI, and AISI can be easily calculated from CBC, an inexpensive, easily accessible test, are promising markers for assessing disease activity in AS patients and aiding in treatment optimization.

The study has several limitations which should be reviewed. The first limitation was the single-centre, retrospective natüre of the study. Additionally, our small sample size limited the power of the statistical analysis. Another limitation was the complexity of relations between complete blood count parameters, and immune response. Furthermore, we believe that still there might be some unknown interactions. Thus, more investigations should be conducted to clarify these complex interactions.

CONCLUSION

SII, SIRI and AISI may be seen as valuable markers for demonstrating inflammation and disease activity. Besides, SII, AISI NLR, PLR, MLR, RDW, and MPV are valuable in evaluating the effectiveness of anti-TNF-α therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Faculty of Medicine Hospital Ethics Committee (Decision No: 2021/118).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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