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Evaluation of the Systemic Immune-Inflammation Index and Systemic Inflammatory Response Index in Ankylosing Spondylitis Patients

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ABSTRACT

Introduction: The aim of this study was to investigate the relationship between the Systemic Immune-Inflammation Index (SII) and Systemic Inflammation Response Index (SIRI) and disease activity in patients with ankylosing spondylitis (AS).

Methods: In our study, 104 AS and 51 healthy controls (HC) were analyzed. The SII and SIRI differences between AS and HC were investigated. Those with BASDAI <4 were defined as remission (BASDAI-r) and those with BASDAI >4 as active (BASDAI-a). SII, SIRI, and other parameters were compared between the groups. As a second classification, patients were divided into two groups according to the Ankylosing Spondylitis Disease Activity Score (ASDAS) scores. Those with ASDAS <2.1 were defined as low-grade disease activity (ASDAS-l) and those with ASDAS >2.1 were defined as high-grade disease activity (ASDAS-h). SII, SIRI, and other parameters were compared between the groups.

Results: The median SIRI value was significantly higher in the patient group than in the HC group. The mean SIRI value was significantly higher in the BASDAI-a group than in the BASDAI-r group and in the ASDAS-h group than in the ASDAS-l group, but the median SIRI levels did not differ significantly between the groups. The optimal cut-off value of SIRI for identifying active patients was 1.12.

Conclusion: These results suggest that SIRI may be considered in the evaluation of patients with AS and may be a new biomarker to identify patients with active disease activity.

Keywords: Ankylosing spondylitis, SIRI, SII

Introduction

Ankylosing spondylitis (AS) is a progressive, persistent, and systemic inflammatory disorder. The common clinical findings of AS include restriction of mobility of the spine and inflammatory low back pain (1). Although its etiology has not yet been fully elucidated, it has a strong relationship with human leukocyte antigen (HLA) B27. HLAB27 positivity is observed in approximately 90% of patients with AS (2).

Although AS is a slowly progressing disease, it can cause mobility problems. For this purpose, reliable methods are needed to monitor disease activity. Some scales have been developed to evaluate disease activity. Evaluating the level of disease activity and assessing the effectiveness of treatment in AS is a multifaceted and challenging undertaking. Laboratory biomarkers, particularly C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are consistently used to assess disease activity. However, it cannot completely distinguish between infection and disease activity and has low sensitivity and specificity (3-6). Therefore, new parameters have been studied in recent years to determine disease activity [Systemic Immune-Inflammation Index (SII) and Systemic Inflammatory Response Index (SIRI)].

SII has been demonstrated to be related to activity as well as prognosis in Behcet's disease, rheumatoid arthritis (RA), and AS (7-9). SIRI has been used in cardiovascular diseases and malignancies; the determination of its association with disease activity and prognosis has been established (10,11). SIRI was investigated in patients with RA and was not associated with disease activity (9). However, SIRI did not conduct a previous study on AS patients. This study examined the association between SII and SIRI, two novel markers of inflammatory conditions, and disease activity in patients with AS.

Methods

This retrospective study included AS patients who were followed up in University of Health Sciences Turkey, İstanbul Training and Research

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Hospital between June and July 2023. Approval of the study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 262, date: 19.08.2022). This study was registered on clinicaltrials.gov under NCT05914532.

Participants

The study included a sample of 104 individuals diagnosed with AS, ranging in age from 18 to 65 years old. The diagnosis was established using the classification criteria of the Assessment of SpondyloArthritis International Society (ASAS) in 2009. In addition, a group of 51 healthy individuals was included as a control for comparison. Patients with infections, coronary artery disease, kidney and liver dysfunction, cancer diagnosis, surgery in the last three months, hypertension, and diabetes mellitus were not included. Age, gender, disease duration, and complete blood counts (ESH, CRP, and HLAB27) were recorded. SIRI and SII were calculated from complete blood counts. To calculate the SII, multiply the platelet count by the neutrophil count and divide by the lymphocyte count. SIRI is computed by dividing neutrophil and monocyte counts by lymphocyte counts.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) were employed to assess disease activity. The BASDAI questionnaire comprises a total of six questions. Higher than 4 points are defined as active disease. The ASDAS consists of five questions. We preferred ASDAS-CRP in our study. The ASDAS is categorized into four distinct groups based on disease activity levels. These groups are defined as follows: "low disease activity" for ASDAS values below 1.3, "moderate disease activity" for ASDAS values between 1.3 and 2.1, "high disease activity" for ASDAS values between 2.1 and 3.5, and "very high disease activity" for ASDAS values exceeding 3.5. The functional status of the participants was assessed using the Bath Ankylosing Spondylitis Functional Index, a 10-item measurement tool. The Ankylosing Spondylitis Metrology Index (BASMI), which consists of 5 items, was used in our study. The Maastricht Ankylosing Spondylitis Enthesitis Score was determined by assessing the occurrence of enthesitis susceptibility in 13 anatomical sites (6).

Initially, the patients were categorized into two distinct groups based on their BASDAI scores: individuals in a state of remission and those with active disease. Those with a BASDAI score below 4 are in remission (BASDAI-r); those with a BASDAI score above 4 are considered active (BASDAI-a). As a second classification, patients were divided into two groups based on their ASDAS-CRP scores. Those with an ASDAS-CRP score below 2.1 were considered low grade (ASDAS-l), and those above 2.1 were considered high grade (ASDAS-h). Comparisons of SIRI and SII were made between the groups. In addition, the relationship between SIRI and SII and disease activity was investigated. The optimal cut-off values of the parameters evaluated to differentiate AS patients from healthy controls and to differentiate active AS patients from remission AS patients were investigated.

Sample Size

NCSS, LLC.'s Power Analysis, and Sample Size Software 15 (2017) (Kaysville, UT, USA; www.ncss.com/software/pass) was used to determine the sample size. To calculate the sample size in our study, a power analysis was performed with 95% power according to the SIRI in a previous retrospective study (9).

Statistical Analysis

For statistical analysis, IBM SPSS 22.0 was used. The Kolmogorov-Smirnov/Shapiro-Wilk test was used to check for normal distribution. While descriptive analyses are presented, the mean and standard deviation or median and 1. quartile/3. quartile values are given for quantitative variables. Mann-Whitney U or Student's t-test was used when comparing data. While presenting the categorical variables, we performed the chi-square test. Correlation analyses were performed using the Spearman or Pearson test. Researchers examined receiver operating characteristic (ROC) curves to determine the best cut-off values. It was determined that $p<0.05$ was statistically significant.

Results

This study included 104 patients and 51-HCs. The mean age of the patients was 41.27±10.46 years and 35 of them were female. The mean age of HCs was 41.9±9.0 years and 14 of the HCs were female. There was no statistically significant difference between patients and HC in terms of gender or age (p=0.61; p=0.441, respectively). The mean disease duration of the patients was 9.23±7.52. 46 (44.2%) of the patients were receiving biological treatment, whereas 58 (55.8%) were receiving non-biological treatment or no medical treatment (Table 1).

Median SIRI was significantly higher in AS than in HC (p=0.001). The median SIRI was not significantly different between AS and HC (p=0.472). The median SIRI was significantly higher in BASDAI-a than in BASDA-r (p=0.005). Although the median SII was higher in BASDAI-a than in BASDA-r, there was no significant difference (p=0.256). The median SIRI was significantly higher in ASDAS-h than in ASDAS-l (p=0.015). Although the median SIRI was higher in ASDAS-h than in ASDAS-l, there was no statistically significant difference (p=0.113).

There was a positive linear correlation between SIRI and ASDAS-CRP (r=0.379; p=0.001), BASDAI (r=0.314; p=0.001), CRP (r=0.421; p=0.001), BASMI (r=0.296; p=0.002) in AS patients. In patients with AS, there was a positive linear correlation between SII and ASDAS-CRP (r=0.226; p=0.021) and CRP (r=0.293; p=0.003). The relationship among SIRI, SII, and other variables is shown in Table 2.

ROC curve analysis was performed to determine the optimal cut-off values of SIRI, CRP, and ESR to differentiate AS patients from HC; the optimal cut-off values of SIRI and CRP to differentiate BASDAI-a from BASDAI-r; and the optimal cut-off values of SIRI to differentiate ASDAS-h from ASDAS-l. SIRI is more sensitive and specific than other parameters for assessing disease activity. The optimal cut-off value of SIRI to differentiate BASDAI-a from BASDAI-r is 1.12. The optimal cut-off value of SIRI to differentiate ASDAS-h from ASDAS-l is 1.07. The area under the curve (AUC), sensitivity, specificity, and cut-off values are shown in Table 3.

Table 1. Comparisons between the groups			
Comparison of SIRI and SII between the patient and healthy control (HC)			
	Patient, (n=104)	**HC, (n=51)**	**p**
SIRI Median (1Q-3Q)	1.13 (0.76-1.51)	0.69 (0.54-0.92)	**0.001**
SII Median (1Q-3Q)	468.2 (315.44-595.2)	435.5 (352.5-573.5)	0.472
CRP (mg/L) Median (1Q-3Q)	4.83 (1.9-9.1)	0.92 (0.45-1.70)	**0.001**
ESR (mm/h) Median (1Q-3Q)	9 (5-20)	7 (3-12)	**0.021**
Comparison between the BASDAI-r and BASDAI-a groups			
	BASDAI-r, (n=49)	**BASDAI-a, (n=55)**	**p**
SIRI Mean ± SD	1.01±0.46	1.26±0.46	**0.005**
SII Median (1Q-3Q)	427.8 (304.4-592.0)	492.2 (365.2-601.4)	0.256
CRP (mg/L) Median (1Q-3Q)	4.36 (1.46-7.45)	5.56 (2.37-14.93)	**0.045**
ESR (mm/h) Median (1Q-3Q)	8 (4.5-7)	9 (5-25)	0.606
Comparison between ASDAS-r and ASDAS-a			
	ASDAS-r, (n=32)	**ASDAS-a, (n=72)**	**p**
SIRI Mean ± SD	0.98±0.52	1.22±0.43	**0.015**
SII Median (1Q-3Q)	420.1 (301.1-547.2)	485.7 (341.4-614.0)	0.113
CRP (mg/L) Median (1Q-3Q)	0.88 (2.18-4.80)	6.47 (2.62-14.25)	**0.001**
ESR (mm/h) Median (1Q-3Q)	9 (4-14,7)	5 (9-24)	0.131

SIRI: Systemic Inflammatory Response Index, SII: Systemic Immune Inflammation Index, HC: Healthy control, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

Table 2. Correlation analysis of SIRI and SII with the scales and laboratory findings									
	ASDAS-CRP	**BASDAI**	**CRP**	**ESR**	**BASFI**	**MASES**	**BASMI**	**VAS**	**DD**
SIRI									
r	**0.379***	**0.314***	**0.421***	0.101	0.182	-0.006	**0.296***	**0.248***	0.118
SII									
r	**0.226***	0.101	**0.293***	0.132	-0.031	0.038	0.137	0.188	0.007

*p<0.05 was considered significant. SIRI: Systemic Inflammatory Response Index, SII: Systemic Immune Inflammation Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, CRP: C-reactive protein, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ESR: Erythrocyte sedimentation rate, BASFI: Bath Ankylosing Spondylitis Functional Index, MASES: Maastricht Ankylosing Spondylitis Enthesitis Score, BASMI: Bath Ankylosing Spondylitis Metrology Index, VAS: Visual analog scale, DD: Disease duration

Discussion

Biological therapies are widely used to suppress disease activity for treating AS. Therefore, there is a need for early diagnosis and new parameters with higher sensitivity and specificity to prevent deformities and loss of functionality in patients with AS. ASAS recommends the use of acute-phase reactants as a tool to assess the level of disease activity and monitor the efficacy of therapeutic interventions (12). However, according to available reports, CRP and ESR have low sensitivity and specificity in AS patients (13). Therefore, normal CRP and ESR levels do not exclude the presence of inflammation.

A complete blood count is an inexpensive, rapid, and easily accessible test used to obtain information about the immune system. Previous studies have shown that neutrophils, monocytes, lymphocytes, and platelets assessed from a complete blood count play an important role in inflammatory events during AS development. Increased transcription and protein expression of inflammation-related genes in monocytes are effective in abnormal responses in monocytes of patients with AS (14). Neutrophils play an important role in the immune response by acting as the first protection against inflammatory stimulation caused by external pathogens. In many previous studies, cytokines and chemokines,

Table 3. ROC curve analysis

To differentiate patients from controls					
	AUC	**Cut-off**	**p**	**Sensitivity, (%)**	**Specificity, (%)**
CRP	0.848	1.77	0.000	76.0	76.5
ESR	0.614	8.5	0.021	52.9	52.9
SIRI	0.734	0.87	0.000	69.2	68.6
Differentiating BASDAI-a from BASDAI-r					
	AUC	**Cut-off**	**p**	**Sensitivity, (%)**	**Specificity, (%)**
CRP	0.614	4.83	0.045	54.5	55.1
SIRI	0.659	1.12	0.005	65.5	65.3
Differentiating ASDAS-h from ASDAS-l					
	AUC	**Cut-off**	**p**	**Sensitivity, (%)**	**Specificity, (%)**
SIRI	0.660	1.07	0.010	62.5	62.5

ROC: Receiver operating characteristic, AUC: Area under the curve, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SIRI: Systemic inflammatory response index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score

including interleukin-8 (IL-8), IL-17, interferon-gamma, and GM-CSF, have been shown to be effective in promoting the activation and viability of neutrophils. In another study, it was reported that the expression of genes such as ANXA3 and SORL1 differed significantly in AS patients compared with the control group. A significant positive correlation between these genes and neutrophil count was also found (15). Lymphocytes are also an important part of the immune system. Abnormal lymphocyte function is effective in the development of autoimmune diseases. An increase in the number of neutrophils in systemic inflammation corresponds to a decrease in the number of lymphocytes in immune system dysfunction (16,17).

Taha et al. (3) found the SII value to be significantly higher in AS patients than in HC patients. However, they used only ASDAS instead of BASDAI to assess disease activity. In addition, they divided AS patients into 3 groups according to their ASDAS scores: inactive, low activity, and high activity. They found that the SII value was significantly higher in the highly active disease group than in the inactive disease group. However, they did not find a significant difference between the other groups. Wu et al. (8) found the SII value to be significantly higher in AS patients than in the control group, unlike our study. In addition, they found the SII value to be significantly higher in active AS than in remission AS. Taha et al. (3) found SII to be positively correlated with CRP, ESR, and ASDAS in patients with AS, and Wu et al. (8) found SII to be positively correlated with CRP, ESR, and BASDAI in patients with AS. Similar to these studies, we found SII to be correlated with ASDAS and CRP levels. However, in this study, we did not find the SII value to be significantly different in AS patients than in healthy controls and in active AS patients than in remission AS patients. This may be because of the difference in the number of patients receiving biological therapy in the patient group. It has been previously reported that the use of TNF-alpha inhibitors may cause changes in cell counts (18). Another reason may be the difference in the cut-off values of the disease activity scales used. While Taha et al. (3) analysed 3 groups according to ASDAS in their study, we analysed in 2 groups according to ASDAS in this study. In our study, we also evaluated SIRI, unlike these studies. In our study, we also found SIRI to be correlated with ASDAS, BASDAI, CRP, BASMI, and VAS.

Satis (9) found that SII was significantly higher in RA than in HC. They also found that SII was significantly higher in patients with active disease than in those in remission. However, no significant difference was found between the disease groups in terms of SIRI. In contrast to this study, Xu et al. (19) reported that SIRI may help in the diagnosis of RA and that SIRI is associated with disease activity. In the same study, the author stated that SIRI could be used to predict tumor development and RA-related interstitial lung disease. In another study, Jin et al. (20) found that SIRI levels in patients with RA were much higher than those in patients with HC. They also found a strong correlation between SIRI and disease activity. In this study, they emphasized that high SIRI levels should be closely monitored for ischaemic stroke in RA.

In our study, we suggest that SIRI can be used to assess disease activity in RA. According to the ROC curve analysis, SIRI may be a more reliable parameter than CRP in determining disease activity by calculating the AUC. Its sensitivity and specificity in predicting disease activity were higher than those of CRP. In addition, the positive correlation of SIRI with scales assessing disease activity and mobilization in AS patients, such as BASDAI, ASDAS, and BASMI, emphasized that our findings should be considered.

Study Limitations

The limitations of our study are that it was retrospective and the number of patients was small and in a single center. Second, we could not evaluate the use of tobacco products by the patients, and the importance of this is that it has been previously reported that the neutrophil-to-lymphocyte ratio was associated with smoking, whereas the platelet-to-lymphocyte ratio was not affected by smoking (21). It would be appropriate to conduct additional studies to confirm the findings and evaluate the effect of SIRI and SIRI on the treatment responses of patients.

Conclusion

There is no doubt that new parameters are required to manage the difficulties in assessing disease activity in AS. These results show that SIRI can be taken into account when evaluating AS, and maybe a novel biomarker has been identified for evaluating disease activity.

Ethics Committee Approval: Approval of the study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 262, date: 19.08.2022).

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