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A cutoff value for the Systemic Immune-Inflammation Index in determining activity of Behçet disease

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Summary

Background. Behçet disease (BD) is an immune-mediated vasculitis-like syndrome characterized by recurrent aphthous lesions and various systemic manifestations. Inflammatory markers may be useful to assess disease severity. The Systemic Immune-Inflammation Index (SII) (neutrophils × platelets/lymphocytes) has been widely used in oncology since 2014, with promising results.

Aim. To assess the efficiency of the SII in determining activity of BD.

Methods. This retrospective cohort study was conducted on patients with BD who were admitted to the outpatient clinic of the Department of Dermatology and Venereology, Ufuk University Hospital, between 1 January 2010 and 31 December 2019. Patients were divided into two groups based on their disease status upon admission: (i) active BD (n = 103), and (ii) inactive BD (n = 63). Clinical characteristics, demographic features, type of medications, full blood count parameters, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin and SII were compared between the groups. Furthermore, receiver operating characteristic curve analysis was performed to assess the performance of the SII in determining disease severity upon admission to hospital.

Results. Higher numbers of white blood cells, platelets and neutrophils, greater red cell distribution width, higher levels of ESR, CRP and ferritin, and higher SII were observed in the active disease group ($P < 0.001$). The cutoff value of $552 \times 10^3/mm^3$ was found to have 81% sensitivity and 82% specificity.

Conclusion. The SII may be used as an additional indicator for the assessment of BD status and physicians should be cautious in patients with SII levels of $> 552 \times 10^3/mm^3$) at the initial evaluation of the patients.

Introduction

Behçet disease (BD) is an immune-mediated, vasculitis-like syndrome characterized by recurrent aphthous lesions and various systemic manifestations such as genital ulcerations, ocular disease, skin lesions, gastrointestinal (GI) involvement, neurological disease, vascular disease and arthritis.[1] Although the prevalence of BD ranges from 1 per 15 000 to 1 per 500 000 in both North American and northern European countries, the highest prevalence rates were reported in Turkey, with 80–370 cases per 100 000.[2,3]

The underlying cause of BD is not yet clear. However, altered activity of the immune system by various triggering factors in patients with genetic predisposition is thought to be the possible mechanism behind this interesting disease.[4] For this reason, no specific treatment for BD is currently available. Therapeutic approaches mostly focus on suppressing excessive immune response and preventing irreversible organ damage.[5] Additionally, treatment protocols should be individualized according to patient characteristics and

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clinical findings.[5] Thus, assessment of disease activity is very important for choosing the most appropriate management protocol for the patients.[6] However, estimating disease activity and predicting the prognosis may not be easy in some situations. Therefore, using markers of inflammation may be useful in the management of such cases.[7–9]

Estimation of inflammation based on full blood count (FBC) parameters has become a useful technique in recent years. Neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), mean platelet volume (MPV) and red blood cell distribution width (RDW) are the most commonly reported parameters in the literature.[10–18] However, there is no consensus on the reference ranges of these parameters, and interpretation of the results may be confusing for physicians.[10–18] For this reason, researchers are working on novel parameters with more consistent results. A novel index named the Systemic Immune-Inflammation Index (SII) (neutrophils × platelets/lymphocytes) has been widely used since 2014 in oncology with promising results and is being used in other branches of medicine as a prognostic factor.[19–22]

The aim of this study was to assess the efficiency of the SII in determining the disease activity of BD.

Methods

The study protocol was approved by the ethics committee of the Turkish Ministry of Health Ankara City Hospital (reference no. E1-20-699). As the study was retrospective, the requirement for informed consent was waived.

Enrolment

This retrospective cohort study was conducted on patients with BD who were admitted to the outpatient clinic of Department of Dermatology and Veneorology, Ufuk University Hospital, between 1 January 2010 and 31 December 2019. The required data were obtained from the electronic database of Ufuk University Hospital. All consecutive cases aged 16–65 years were enrolled in the study. Patients for whom there was sufficient information regarding the status of disease and required laboratory tests upon admission were excluded from the study.

Disease activity

Disease activity was evaluated based on the criteria determined by the BD Research Committee of Japan in 2003.[23] All patients were evaluated in terms of disease activity upon admission to hospital by expert dermatologists and necessary medications were arranged according to the clinical findings.

Groups

Patients were divided into two groups based on their disease activity upon admission: (i) active BD, and (ii) inactive BD. The groups were compared in terms of their demographic features and clinical characteristics. Age, sex, age at disease onset, duration of disease, clinical manifestations [rates of oral ulceration, urogenital lesions, ocular disease, neurological disease, vascular disease, pulmonary disease, arthritis and GI), laboratory parameters [haemoglobin, FBC, white blood cell count, platelet count, neutrophil count, lymphocyte count, red blood cell distribution, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, iron, total iron-binding capacity and SII] and medications administered to the patients upon admission to hospital were compared between the groups. Furthermore, a receiver operating characteristic (ROC) curve analysis was performed to assess the performance of the SII in determining the patients' status of the disease upon admission to hospital.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS V22; IBM SPSS, Armonk, NY, USA). Visual (histograms, probability plots) and analytical methods (Kolmogrov–Smirnov test) were used to determine normality of distribution. As the data were not normally distributed, medians and interquartile range values were used for descriptive analysis. Additionally, the Mann–Whitney *U*-test was conducted to compare the median values and the χ^2 test was used to compare categorical variables between the groups. ROC curves were used to assess the performance of the SII in determining disease severity upon admission to hospital. The Youden index was applied to the ROC curve to choose the best cutoff value.[24] A two-tailed $P < 0.05$ was regarded as statistically significant.

Results

Patients

There were 103 patients in the active disease group and 63 patients in the inactive disease group.

Demographic features and clinical characteristics of the patients with active and inactive BD are shown in Table 1.

Analysis of physical characteristics

The two groups were similar in terms of age, age at disease onset, rates of oral ulceration, urogenital lesions, vascular disease, pulmonary disease and GI involvement ($P < 0.14$, $P < 0.92$, $P < 1.00$, $P < 0.32$, $P < 0.10$, $P < 0.11$ and $P < 0.28$, respectively). Additionally, haemoglobin, FBC, lymphocyte, serum iron and total iron-binding capacity values were comparable between the groups ($P < 0.98$, $P < 0.60$, $P < 0.47$, $P < 0.58$ and $P < 0.43$, respectively). However, significant differences were found between the two groups for sex, disease duration, cutaneous lesions, ocular disease, neurological disease, arthritis, white blood cell count, platelet count, neutrophil count, red blood cell distribution width, ESR, CRP, ferritin and SII ($P < 0.03$, $P < 0.02$, $P < 0.003$, $P < 0.01$, $P < 0.03$ and $P < 0.001$ for the remaining parameters, respectively).

Table 1 Demographic features and clinical characteristics of the patients with active and inactive Behçet disease.

Variables	Active BD, $n = 103$	Inactive BD, $n = 63$	P
Sex (n, %)[a]			
Male	50 (48.5)	20 (31.7)	0.03
Female	53 (51.5)	43 (68.3)	
Age, years[b]	31 (18)	39 (25)	0.14
Age at disease onset, years[b]	25 (12.25)	27 (13.25)	0.92
Disease duration, months[b]	60 (102)	96 (150)	0.02
Clinical manifestion, n (%)[a]			
Oral ulceration	103 (100)	63 (100)	1.00
Urogenital lesions	76 (73.8)	32 (62.7)	0.32
Cutaneous lesions	81 (78.6)	36 (57.1)	< 0.01
Ocular disease	49 (47.6)	18 (28.6)	0.01
Neurological disease	7 (6.8)	0 (0)	0.03
Vascular disease	15 (14.5)	14 (22.)	0.10
Pulmonary disease	4 (3.9)	0 (0)	0.11
Arthritis	36 (35)	6 (9.5)	< 0.001
GI involvement	4 (3.8)	0 (0)	0.28
Laboratory parameters[b]			
Haemoglobin, g/dL	13.7 (1.7)	13.6 (1.8)	0.98
Haematocrit, %	40.8 (4.5)	40.3 (4.1)	0.60
WBC, $10^3/mm^3$	8.5 (2.7)	6.7 (2.2)	< 0.001
Platelets, $10^3/mm^3$	293 (61.1)	245 (51.5)	< 0.001
Neutrophils, $10^3/mm^3$	5.4 (2.5)	3.75 (1.5)	< 0.001
Lymphocytes, $10^3/mm^3$	2.1 (0.7)	2.1 (0.9)	0.47
RDW, %	13.7 (1.5)	13 (2.3)	< 0.001
ESR, mm/h	28 (16.5)	11 (6.25)	< 0.001
CRP, mg/dL	8.9 (8.1)	1.5 (2)	< 0.001
Ferritin, ng/mL	67.6 (92.5)	27.5 (46.5)	< 0.001
Iron, μmol/L	61 (37.3)	61 (41.9)	0.58
TIBC, μmol/L	305.3 (99.3)	326.5 (101.4)	0.43
SII, $10^3/mm^3$	753.8 (429.1)	438.5 (152.6)	< 0.001

BD, Behçet disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; IQR, interquartile range; RDW, red blood cell distribution width; TIBC, total iron-binding capacity; SII, Systemic Immune-Inflammation Index; WBC, white blood cell. [a]Statistical analysis was performed with χ^2 test. [b]Statistical analysis was performed with Mann–Whitney U-test.

Medications

Medications administered to the patients upon admission to hospital are shown in Table 2. Azothiopurine was used more commonly in patients with active BD ($P = 0.01$); however, the two groups were similar in terms of other medications.

Receiver operating characteristic curve

ROC curve analysis for assessing the performance of the SII in determining activity of BD are summarized in Fig. 1. Area under the curve was calculated as 0.84 (95% CI 0.78–0.91). The SII value in the ROC curve with the best balance of sensitivity and specificity for determining the activity of BD was $552 \times 10^3/mm^3$ (81% sensitivity, 82% specificity) according to the results obtained from the Youden index.

Discussion

The pathophysiological mechanism behind BD is not yet clearly understood. Impaired immune activity triggered by various agents in patients with a genetic predisposition to the disease seems to be the most possible

Table 2 Medications administered to the patients upon admission to hospital.

Medication	Active BD ($N = 103$), n (%)	Inactive BD ($N = 63$), n (%)	P
Colchicine	97 (94.2)	59 (93.7)	0.89
Azothiopurine	21 (20.4)	4 (6.3)	0.01
Prednisone	35 (34)	15 (23.8)	0.16
Interferon-alfa	2 (1.9)	0 (0)	0.26
MMF	1 (1)	0 (0)	0.43
Methotrexate	4 (3.9)	0 (0)	0.11
Depo-penicilin	11 (10.7)	7 (11.1)	0.93

BD, Behçet disease; MMF, mycophenolate mofetil.

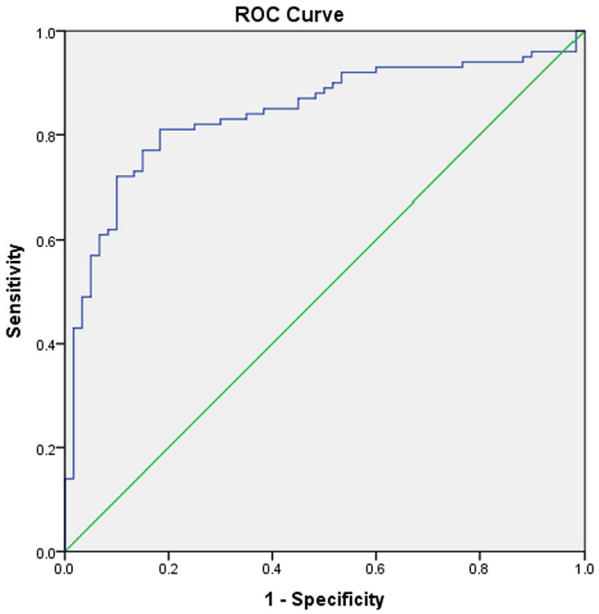

Figure 1 Receiver operating characteristic (ROC) curve analysis for assessing the performance of the Systemic Immune-Inflammation Index in determining activity of Behçet disease.

explanation, similar to other autoimmune diseases.[4] A complex cascade of events such as altered patterns of Toll-like receptors, variations in T-cell subpopulations, increased levels of various T-helper 1/2-mediated cytokines, formation of complex autoantibodies, changed activity of neutrophils and epigenetic alterations may all contribute to the pathogenesis of this specific disease.[25] For this reason, treatment and management protocols mostly focus on immunomodulatory approaches aimed at controlling the aforementioned excessive inflammatory response. However, there is no consensus on the optimal treatment strategy for these patients and clinicians should balance the benefits with the adverse effects of drugs to provide optimal healthcare.[6] Thus, more aggressive and expensive treatment options are generally reserved for cases with active disease. Our results indicated that azothiopurine was more frequently used in the active BD group compared with the inactive BD group, and this is consistent with the literature. Additionally, arranging the appropriate follow-up protocols and deciding on further ancillary tests are also associated with disease status.[6] Therefore, accurate detection of cases with active disease state is crucial. However, evaluating disease activity solely by conservative methods may be challenging in some cases,[26] and clinicians could benefit from additional parameters in order to achieve better outcomes.

Traditional laboratory tests such as CRP, ESR, ferritin and leucocyte count have long been used in clinical practice for the estimation of inflammation in disease.[7–9] Additionally, FBC indices have become more widely used in recent years for predicting the prognosis of various diseases.[27–29] As FBC is a routine, practical and cheap laboratory test, indices including various combinations of its parameters may be easily used in the assessment of inflammatory conditions.[27–29]

Various FBC indices have been used in the literature for the evaluation of BD.[10–18] In their retrospective study, Alan *et al.* compared 254 patients with BD with a control group of 173 age- and sex-matched individuals.[10] They found increased levels of white blood cell, neutrophil and platelet counts in patients with BD, and both NLR and PLR were significantly higher in the BD group. Alan *et al.* also divided patients with BD into three groups based on disease severity (mild, moderate and severe) and reported significantly increased levels of PLR and MPV. They also compared NLR, PLR and MPV values in patients with different system involvements, but found no difference between the groups. Finally, they performed a binary forward stepwise logistic regression analysis of FBC indices related to BD, and found NLR to be an independent predictor for BD ($P < 0.001$, OR = 2.535).[10] Ozturk *et al.* reported significantly higher levels of NLR in patients with BD ($n = 65$) compared with the control group ($n = 62$) in their prospective study.[13] Additionally, they calculated a cutoff value of 1.29 for NLR in predicting BD.[13] Balkarli *et al.* conducted a retrospective study evaluating NLR and MPV in patients with active BD ($n = 120$), inactive BD ($n = 66$) and healthy controls ($n = 79$), and reported higher rates of NLR in the active BD group compared with the other groups.[15] Similarly, Pancar and Kalkan reported significantly higher NLR values in the BD group ($n = 64$) compared with the control group ($n = 64$) in their retrospective study.[16] Another study by Yolbas *et al.* investigated the relationship between clinical features of various rheumatic diseases and haematological indices.[17] Higher NLR values were found in the active BD group compared with the inactive BD group. Additionally, NLR values were significantly higher in patients with neurological involvement and active genital ulcers.[17]

Lee and Kim reported decreased levels of MPV in patients with BD in their study of 325 participants (105 patients with BD and 220 controls),[11] whereas Ekiz *et al.* reported significantly higher values of MPV and ESR in patients with BD ($n = 61$) compared with healthy controls ($n = 60$) in their retrospective study.[12] Vayá *et al.* reported increased RDW, neutrophil and

leucocyte values in patients with BD (n = 89) compared with the control group (n = 94).[14] Finally, Akturk *et al.* reported significantly higher levels of RDW in patients with active (n = 40) and inactive BD (n = 70) compared with the control group (n = 46).[18]

The findings of our study are consistent with the literature as white blood cell, platelet, and neutrophil counts and RDW were significantly higher in the active BD group compared with the inactive BD group. In parallel with these findings, other inflammatory markers such as ESR, CRP and ferritin levels were also significantly higher in the active BD group.[10–18]

Additionally, we used the SII, which is a novel FBC index in this study.[19–21] The SII has been widely used in the field of oncology with promising results and it is now being used in other branches of medicine as a prognostic factor.[19–22] As the SII covers three main parameters of FBC (lymphocyte, neutrophil and platelet counts), which are strong indicators of systemic inflammation, it can be used as an additional indicator of disease activity in autoimmune diseases. Previous studies have shown that higher scores in the SII indicate increased inflammatory response and poor prognosis.[19–22] To our knowledge, the current study is the first to assess the performance of SII in rating BD activity. We found that SII readings were significantly higher in the active compared with the inactive BD group, and determined a cutoff value of 552.12 for SII with relatively high sensitivity and specificity. In our opinion, this novel, practical and cheap index may be easily used by the physicians for the assessment of BD activity.

The main strengths of this study were arelatively higher number of study parameters, first-time usage of a novel index for BD and management of cases with the same physicians. Its retrospective design, relatively low number of cases and heterogeneity in the study populations were the main limitations. Additionally, FBC indices may be affected by various factors such as anaemia, thrombocytopenia and acute infection.[10–18] Physicians should consider these factors in the assessment of inflammation with FBC indices. However, as the SII includes three parameters of FBC, it gives more accurate information about both acute and chronic inflammation,[19–22] but knowledge is still limited on this issue. For this reason, future studies with larger populations are necessary in order to confirm our results.

Conclusion

SII may be used as an additional indicator for the assessment of BD status, and physicians should be cautious about patients withSII levels of $> 552 \times 10^3/mm^3$ at the initial patient evaluation, as it could raise suspicion of severe BD.

What's already known about this topic?

- BD is an immune-mediated vasculitis-like syndrome.
- Assessment of disease activity is very important for choosing the most appropriate management protocol for the patients.
- Estimation of inflammation based on FBC parameters has become popular in recent years.

What does this study add?

- The SII may be a useful additional indicator for the assessment of BD status.

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