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# The effect of colchicine treatment on complete blood cell count-based parameters in patients with Behçet's disease

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## ABSTRACT

**Aim**: Behçet's disease (BD) is a systemic disease, with still unknown etiology and pathogenesis and varying disease presentations, characterized by recurrent oral aphthae, followed by genital ulcers, arthritis, variable skin and ocular lesions, gastrointestinal and central nervous system involvement, as well as, vascular disease. Colchicine is one of the oldest remedies still in use today. The study aimed to investigate the effect of colchicine on levels of the complete blood cell count-based parameters in BD.

**Material and Method**: A total of 117 (participants 60 healthy control and 57 patients with BD) were recruited from the rheumatology department in a single-center case-control study. The laboratory data were obtained from the electronic registration database. Laboratory findings of patients and healthy controls were evaluated. In addition, patients with BD were evaluated for these parameters before colchicine therapy and after 3-month from the beginning of colchicine treatment.

**Results**: The levels of inflammatory markers such as neutrophil count, neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and systemic immune-inflammation index (SII), significantly higher than the control group before treatment, decreased to similar levels with the control group in the third month of colchicine use. However, red blood cell distribution width (RDW), mean platelet volume (MPV), and plateletcrit (PCT) were still statistically significantly different from the control group in BD patients.

**Conclusion**: SII, CRP, ESR, and NLR are useful parameters to evaluate the colchicine response of patients with mucocutaneous BD.

**Keywords**: Behçet's disease, colchicine, neutrophil to lymphocyte ratio, plateletcrit, systemic immune-inflammation index

## INTRODUCTION

Behçet's disease (BD) is a variable vessel vasculitis with multi-system involvement that shows significant heterogeneity among patients regarding demographic features, organ manifestations, frequency and severity of relapses, disease course, response to treatment, and prognosis. Although BD is more common in "Silk Road" populations, it has a universal distribution (1). The interplay between a complex genetic background and both innate and adaptive immune systems is related to the BD clinical features (2). The well-known genetic association is with HLA-B51 (60%). It may start with mucocutaneous findings such as recurrent aphthous stomatitis and genital ulcer and convert a systemic form characterized by ocular, cardiovascular, articular, neurological and gastrointestinal symptoms. Mucocutaneous manifestations decrease the health-related quality of life, whereas major organ involvement may result in severe morbidity/mortality. The symptoms and severity of BD may vary between patients and may change over time in the same patient. Due to the lack of a universally recognized pathognomonic laboratory test, the diagnosis is based on clinical criteria (3, 4). The primary treatment goals are improved health-related quality of life, maintenance of disease remission, and prevention of organ damage. Colchicine is one of the oldest remedies still in use today (5). Many studies have been conducted on tests that may reflect disease activation, be helpful in monitoring treatment efficiency, or predict potential complications of BD. However, there is still a demand for new laboratory markers in patients with BD. Complete blood cell count parameters (CBC) have recently emerged as

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valuable biomarkers of many inflammatory diseases because of their availability and affordability. Pre-treatment CBC-based biomarkers have been reported to reflect systemic and local inflammation associated with cancer progression and prognosis inflammation and oxidative stress in chronic inflammatory and autoimmune diseases (6-9). We aimed to investigate the dynamic changes in hemogram parameters before and after colchicine treatment in BD patients and investigate the anti-inflammatory effect of colchicine on these parameters and their value for BD.

## MATERIAL AND METHOD

This study was approved by the Selçuk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 2021/295). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent forms were taken from all participants before the study.

### Study Population and Design

We selected 57 new patients with mucocutaneous BD at diagnosis. BD diagnosis was made according to The International Study Group (ISG) criteria. The ISG criteria for BD require oral aphthous ulcers and two or more additional manifestations: genital aphthous ulceration, eye lesions (uveitis, retinitis), skin lesions (folliculitis, papulopustular lesions, acneiform nodules, erythema nodosum) and/or a positive pathergy test (3). All BD patients were selected from patients who were administered only colchicine (1,5 mg /day)

The study's inclusion criteria were being 18 years old or above and not receiving any systemic treatment for BD at the time of hospital application. Healthy controls were selected from patients admitted to the outpatient checkup clinic without any known diseases. Pregnant or breastfeeding women, smoking, alcohol, oral contraceptive use, concomitant obesity (BMI >30 kg/m2), hypertension, diabetes mellitus, endocrine disorders, malignancies, acute or chronic infection, chronic haematologic disease, other autoimmune or autoinflammatory diseases, tuberculosis, heart and lung disease, major organ involvement (eye, brain, major intestinal, lung, and cardiovascular involvement) were excluded from the study. Patients' demographic characteristics (gender, age, age of disease onset, duration of illness), mucocutaneous involvement such as oral ulcer, genital ulcer, erythema nodosum and folliculitis, joint involvement, features, and clinical symptoms, physical examination findings, pathergy reaction, laboratory findings, imaging tests and treatment information received were evaluated.

### Laboratory Measurements

Hemoglobin, RDW (normal 11%-15%), MPV (normal 7.5-11.5 FL), PCT (%), platelet (K/μL), lymphocyte (K/μL), neutrophil (K/μL) and monocytes (K/μL) levels were determined using an automatic blood counting system for each participant. NLR, MLR, and PLR were calculated using the ratio of neutrophil, monocyte, and platelet counts to lymphocyte counts, respectively. Systemic Immune-Inflammation Index (SII) was calculated by the formula: neutrophil (Neu) x platelet (Plt) / lymphocyte (Lym). Also, the erythrocyte sedimentation rate (ESR; normal 0-20 mm/hour) and C-reactive protein (CRP; normal 0-8 mg/L) were recorded. Patients with BD were evaluated for these parameters before colchicine therapy and after 3-month from the beginning of colchicine treatment.

### Statistical Analysis

All data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 21.0. The normality distribution of scale variables was checked using the Shapiro-Wilk test. Data were expressed mean±standard deviation. Wilcoxon test was used for dependent samples. Independent samples were compared with the Mann-Whitney U test. Pearson's chi-square test was used for categorical variables. ESR, CRP, and SII values were compared with Spearman's correlation test and presented with a simple scatterplot. Two-sided p-values less than 0.05 were considered statistically significant.

## RESULTS

Demographic and clinical characteristics of the BD and control groups included in the study were as in **Table 1**. The groups were identical in terms of age and gender (p=0.061, p=0.603; respectively). There was no statistical difference between the control and BD groups regarding BMI and smoking (p=0.167, p=0.404; respectively). In **Table 2**, statistical differences between BD patients whose hemogram parameters were evaluated before and after treatment and healthy controls were analyzed separately. The decrease in NLR value was statistically significant (p3<0.001). There was no significant change in hemoglobin and platelet levels (p3=0.744, p3=1.000; respectively). Although the decrease in MPV values after treatment was not statistically significant, a significant decrease was observed in PCT levels (p3=0.237, p3=0.006; respectively). There was a significant decrease in inflammatory markers such as ESR and CRP (both, p3<0.001). Similarly, a significant decrease was observed in the SII value (p3=0.003). The SII calculation parameters, neutrophil, lymphocyte, and platelet counts, might already be expected to correlate with SII. Therefore, correlation analyzes of SII with

only CRP and ESR were performed. It was determined that SII had moderate correlations with CRP and high correlations with ESR (r=0.466, p<0.001, r=0.698, p<0.001; respectively) (**Figure 1**).

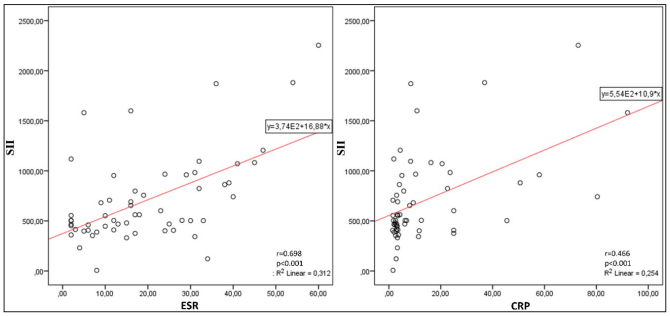


**Figure 1.** Positive correlation of SII with ESR and CRP
SII: Systemic immune-inflammation index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

**Table 1.** Presentation of demographic and clinical features

| | Healthy control (n=60) | Behçet's disease (n=57) | p value |
|---|---|---|---|
| Age (years) | 30.5±4.8 | 32.2±6.8 | 0.061* |
| Sex | | | 0.603 |
| Man | 26 (43.3%) | 22 (38.6%) | |
| Woman | 34 (56.7%) | 35 (61.4%) | |
| BMI (kg/m2) | 22.9±3.6 | 22.1±2.5 | 0.167* |
| Clinical features | | | |
| Oral aphthae | - | 57 (100.0%) | - |
| Genital ulcer | - | 15 (26.3 %) | - |
| Erythema nodosum | - | 17 (29.8 %) | - |
| Folliculitis | - | 26 (45.6%) | - |
| Arthralgia | - | 36 (63.1%) | - |
| Pathergy positivity | - | 37 (64.9%) | - |

BMI – body mass index; N/A – not applicable
Data were expressed as mean±standard deviation—Mann-Whitney U (*) and Pearson's chi-square tests were used.

The levels of inflammatory markers such as neutrophil count, NLR, CRP, ESR, and SII, significantly higher than the control group before treatment, decreased to similar levels with the control group in the third month of colchicine use. However, values such as RDW, MPV, and PCT were still statistically significantly different from the control group in patients with BD despite treatment (**Table 2**).

## DISCUSSION

Endothelial injury has been proposed as one of the main pathophysiological mechanisms underlying the BD, promoting a hyperinflammatory and prothrombotic state leading to worse clinical outcomes. The activated neutrophils may be involved in the process of tissue damage in BD. It has been recently shown that neutrophil activation promotes fibrinogen oxidation, thrombosis formation, reactive oxygen species (ROS) generation and sustains BD activity (2). Growing data suggest that neutrophils can contribute to thrombo-inflammation via ROS and through additional mechanisms, including the release of neutrophil extracellular traps (NETs) (10). According to evidence-based medicine, colchicine is a first-line effective therapy in BD's mucosal, cutaneous, pleuropericardial, and abdominal complications. Neutrophil function, which is essential in the pathogenesis of the disease, is modified by this drug. It is believed to suppress the secretion of cytokines, chemokines, and in vitro platelet aggregation by disrupting the cytoskeleton (5). Moreover, studies show that colchicine, despite the lack of an anti-oxidant power, exerts a protective effect on oxidation-induced NETs production and oxidation-

**Table 2.** Comparison of hemogram parameters before and after colchicine treatment in Behçet's disease separately with the healthy control group

| Parameters | A (n=57) BD, pre-treatment 0th month | B (n=60) Healthy control | C (n=57) BD, post-treatment 3rd month | p1-value (A vs. B) | p2-value (B vs. C) | p3-value (A vs. C) |
|---|---|---|---|---|---|---|
| Hemoglobin (g/dl) | 13.9±1.5 | 14.4±1.3 | 14.0±1.5 | 0.064 | 0.215 | 0.744 |
| MCV (fl) | 83.9±5.5 | 85.1±3.7 | 84.4±5.7 | 0.307 | 0.993 | 0.174 |
| RDW (%) | 14.4±1.7 | 12.9±1.0 | 14.1±1.6 | <0.001 | <0.001 | 0.995 |
| Neutrophil ($10^6$/l) | 5004±1882 | 4261±1690 | 4402±1462 | 0.012 | 0.367 | 0.018 |
| Lymphocyte ($10^6$/l) | 2143±533 | 2915±602 | 2297±687 | 0.266 | 0.872 | 0.153 |
| Monocytes ($10^6$/l) | 567±193 | 542±150 | 591±189 | 0.627 | 0.093 | 0.264 |
| Platelet ($10^9$/l) | 277±80 | 271±62 | 273±69 | 0.409 | 0.643 | 1.000 |
| PCT (%) | 0.24 ±0.06 | 0.28±0.06 | 0.22±0.05 | 0.003 | <0.001 | 0.006 |
| MPV (fl) | 8.45±1.21 | 10.2±1.2 | 8.14±1.19 | <0.001 | <0.001 | 0.237 |
| NLR ($10^{-2}$) | 251±137 | 194±76 | 207±96 | 0.010 | 0.593 | <0.001 |
| MLR ($10^{-2}$) | 28±12 | 24±7 | 28±14 | 0.330 | 0.252 | 1.000 |
| PLR | 136.5±49.9 | 124.7±35.6 | 130.7±68.7 | 0.168 | 0.737 | 0.141 |
| CRP (mg/l) | 14.0±20.5 | 3.8±2.1 | 4.8±5.0 | 0.003 | 0.478 | <0.001 |
| ESR (mm/hour) | 19.7±14.6 | 10.3±8.6 | 10.4±8.0 | 0.002 | 0.823 | <0.001 |
| SII | 706±442 | 532±250 | 556±251 | 0.041 | 0.624 | 0.003 |

Data were expressed as mean±standard deviation. Mann-Whitney U test was used. Significant values were shown in bold.
BD: Behçet's disease; MCV: Mean corpuscular volume; RDW: Red cell distribution width; PDW: Platelet distribution width; PCT: Plateletcrit; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte ratio; MLR: Monocytes/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; SII: Systemic immune-inflammation index

induced neutrophil apoptosis (11). Simple markers are needed for diagnosis, follow-up treatment plan, and prognosis for BD. Cellular components of blood and their ratios may give insight into the extent of ongoing inflammation. In recent years, there has been a trend in clinical practice to utilize inflammation-based indexes as assessment tools for disease activity of various kinds of inflammatory diseases and prognostic indicators in the survival of patients with malignant tumors (6-9). Furthermore, SII may be a potentially helpful index in clinical practice to follow-up and manage these patients by monitoring response to anti-inflammatory treatment modalities. The following study investigates whether hematologic parameters such as SII, NLR, RDW, MPV, and PCT are associated with colchicine efficacy in BD. It has been reported in some studies that the NLR, PLR, and RDW are significantly higher in BD patients than in the healthy group, suggesting their value as promising inflammatory biomarkers in BD (12-20). Several studies observed the significant association of NLR with BD activity. In addition, Ünlü et al. (21) reported that high NLR might be associated with endothelial dysfunction and reflect BD activity. In our study, there was a statistically significant difference between BD patients in terms of NLR, which was higher than the control group. In addition, NLR decreased in these treated patients. NLR may serve as a surrogate assay for BD response to colchicine. Djaballah-Ider et al. (16) found results similar to this study, but the patient group was under colchicine + steroid treatment, not just those under colchicine treatment. The SII, a novel inflammation-based biomarker, integrates neutrophils, platelets and lymphocytes. SII covers NLR and platelets and is calculated by the formula platelet x NLR. One of the most outstanding findings of our study was the demonstration of the positive correlation of SII with CRP and ESR. According to previous studies, SII may have a high prognostic value in cancer patients, and an elevated pre-treatment SII is associated with poor outcomes in cancer patients (9). SII is a valuable biomarker of the inflammatory status and immune response. Recently, studies have also reported using SII as an indicator for autoimmune diseases, such as an index to assess the disease activity of patients with BD or to predict the poor prognosis of antineutrophil cytoplasmic antibody-associated vasculitis (22-24). Recently, the diagnostic utility of SII has been studied in autoimmune diseases, such as adult-onset Still's disease (25). Our results showed that the SII levels in BD patients were higher than those of healthy controls and decreased in these treated patients. SII changes could predict these patients' responses to treatment and clinical outcomes. Platelets play an essential role in the integrity of normal hemostasis; MPV is the indicator of platelets' function. Changes in the MPV in many different conditions have been researched. While the MPV was not found to be associated with disease and/or disease activity in some of these conditions, it is increased or decreased in others. An increased MPV has been associated with an increased thrombotic disposition (26, 27). A higher MPV in patients with active BD has also been reported (28). Ataş et al. (11) evaluated the effect of colchicine on MPV levels, and after colchicine treatment, a decrease in MPV was obtained in their study. This study found the MPV level higher in BD patients than in healthy controls, but the difference persisted regardless of whether it changed significantly with colchicine. There was no significant difference in MPV levels among the patients with BD and healthy controls in some studies. An explanation for this discrepancy was the possibility that MPV alone was not an appropriate indicator of platelet activation following a conclusion stated. MPV reflects early platelet activation and PCT obtained by multiplying platelet with MPV, the percentage of blood volume occupied by platelets. According to recent studies, PCT provides more comprehensive data on total platelet mass and is expected to be a tumor-related biomarker (29, 30). An increased PCT has been found to be associated with an increased risk of coronary artery disease and venous thrombosis (29, 30). PCT may also be a good indicator of inflammation. A recent study found a higher PCT value than the healthy control (31). Thrombocytes play an essential role in various inflammatory disorders by activating immune cells and stimulating immune responses, consistent with the current study findings of significantly high MPV and PCT values in BD (26, 31, 32). RDW is another recommended parameter related to inflammatory processes. In several recent studies, a significant increase has been reported in RDW in patients with a history of BD, independent of disease activity and involvement characteristics (7, 15). Masoumi et al. (28) determined significantly higher RDW in BD patients with ocular and oral symptoms, independent of disease activity. In a study by Aksoy et al. (15), RDW was significantly higher in BD patients than in a control group and those with active disease compared with inactive disease and the control group. Elevated RDW has also been shown to be an important marker of oxidative stress and inflammation. Several studies have demonstrated an oxidative response in patients with BD; because of the exposure to oxidative stress, the lifetime of erythrocytes decreases, reticulocyte production increases and RDW increases in peripheral blood. RDW, MPV, and PCT are different in BD patients from the control group despite treatment, regardless of whether they changed significantly with colchicine. Although NLR, ESR, CRP, neutrophil count, and SII were different from the pre-treatment healthy control, they were at

the same level as the healthy control post-treatment. SII and NLR were found to be lower in patients with BD after a three-month colchicine treatment as compared with their levels before treatment. We also observed a decrease in inflammatory predictors such as CRP and ESR. A decrease in these parameters supported the anti-inflammatory effect of colchicine. Moreover, any other medicine which affected these parameters was not added to treatment. Therefore it is appropriate to follow up these parameters in patients receiving colchicine.

Several limitations of our study need to be addressed. The sample size was relatively small, and only BD patients wıth mucocutaneous involvement were included in the study. Although the results have provided some evidence of the applicability of NLR and SII, further research is needed to validate these parameters and assess their value as tools for follow-up and evaluate the effect of colchicine on mucocutaneous involvement in BD.

## CONCLUSION

SII, CRP, ESR, and NLR are useful parameters to evaluate the colchicine response of patients with mucocutaneous BD.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** This study was approved by the Selçuk University Faculty of Medicine Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 2021/295).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

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

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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