

Neutrophil-to-lymphocyte ratio: relation to disease activity and carotid intima-media thickness in Behçet's disease

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Background

Behçet's disease (BD) is an autoinflammatory disorder. Disease activity could be detected by changes in peripheral blood cell components. The aim of this study was to assess the relationship between neutrophil-to-lymphocyte ratio (NLR) with disease activity and carotid intima-media thickness (cIMT) in patients with BD.

Patients and methods

This study was conducted on 20 adult patients with BD (group I). This group was subdivided according to cIMT into group Ia, which included patients with increased cIMT, and group Ib, which included patients with cIMT within normal ranges. Moreover, 20 age-matched and sex-matched apparently healthy volunteers were included as a control group (group II). Patients with BD were subjected to full history taking, thorough clinical examination, and assessment of disease activity according to Behçet's Disease Current Activity Form score. The white blood cell count, neutrophil count, and lymphocytes count were recorded, and NLR was calculated. cIMT assessment was done for all participants.

Results

There were statistically significant differences ($P < 0.05$) regarding lymphocytes count and NLR and highly statistically significant difference ($P < 0.001$) regarding neutrophil count, being higher in patients with BD. There was a statistically highly significant difference ($P < 0.001$) regarding cIMT, being higher in group Ia patients (0.82 ± 0.03) than group Ib patients (0.50 ± 0.04) and healthy control group (0.47 ± 0.04). There was a statistically significance positive correlation ($R=639$, $P=0.005$) between NLR and Behçet's Disease Current Activity Form score. In conclusion, higher NLR values were recorded in patients with BD. Furthermore, patients with active BD had higher NLR values than inactive, and NLR is higher in patients with increased cIMT; thus, NLR may be an important bio-index for detecting BD activity and the presence of vascular affection.

Keywords:

Behcet's disease, carotid intima media thickness, disease activity, neutrophil to lymphocyte ratio

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Introduction

Behçet's disease (BD) is a relapsing systemic inflammatory disease characterized by recurrent oral ulcers, genital ulcers, and ocular inflammation. The predominant histopathology of BD is mainly vasculitis, which is present within the vessel wall and the perivascular tissues infiltrated with lymphoid cells, monocytes, plasma cells, and neutrophils [1].

In BD, arteries, veins, and capillaries are affected. Aortic and peripheral artery aneurysms, pulmonary artery occlusion and aneurysms, coronary artery aneurysms, deep vein thrombosis, and cerebral venous thrombosis have been described [2].

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are markers that are most extensively used for measuring acute-phase response. Although they are affected by age, sex, and hemoglobin level,

which are factors not related to inflammation, neutrophil-to-lymphocyte ratio (NLR) is not affected [3].

NLR is a simple index calculated from routine blood test. As a traditional inflammatory index, it has been proved to be associated with disease activity and prognosis of various inflammation-related diseases, such as sepsis, autoimmune disease, and cancer [4].

Color Doppler ultrasound (US) is considered as an important modality for the evaluation of vascular pathology to provide flow information in addition to vascular morphology. The most important advantages

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are that it is technically easily applicable, cheap, and noninvasive. Doppler US can provide the earliest signs of vasculitis [5].

Recent studies have shown the numbers and ratios of white blood cell (WBC) subgroups in inflammatory rheumatic diseases [3,6,7]. However, the relationship between hematologic indices and rheumatologic diseases is still controversial [8–10].

The aim of this study was to assess the relationship between NLR with disease activity and carotid intima-media thickness (cIMT) in patients with BD.

Patients and methods

This study was conducted on 20 adult patients with BD (group I) diagnosed according to the International Study Group Criteria of BD [11].

This group was subdivided according to cIMT as follows:

Group Ia: patients with increased cIMT.

Group Ib: patients with cIMT within normal ranges.

Moreover, 20 age-matched and sex-matched apparently healthy volunteers were also included as a control group (group II).

These patients were selected randomly from the inpatients' and the outpatients' clinics of rheumatology, rehabilitation and physical medicine, ophthalmology, and dermatology and andrology departments of Benha University Hospitals.

Exclusion criteria

Patients were excluded from this study if their age was less than 18 years, had other illnesses that may affect the results of this study such as evidence of infections, had diabetes mellitus, pregnancy, alcoholics, smokers, family history of atherosclerosis, chronic systemic disease, patients with advanced hepatic and renal diseases, previous surgery such as stent or coronary bypass, cerebrovascular events, or on statin therapy as well as those receiving antiplatelet medications such as aspirin and patients with other rheumatologic autoimmune diseases.

Study approval

The study was approved by the Ethical Committee of Benha University. All participants gave written informed consent before participation in this study.

All BD patients were subjected to the following: full history taking, thorough clinical examination, skin pathergy test as described by Altac *et al.* [12], and assessment of disease activity according to Behcet's Disease Current Activity Form (BDCAF) score [13], in which scoring depends on the symptoms present over the 4 weeks before assessment.

Laboratory procedures included the following:

- (1) ESR by the Westergren method, recorded in mm/first hour.
- (2) Complete blood count, including hemoglobin, RBCs, WBCs, and platelets count. The WBC count, neutrophil count, and lymphocytes count were also recorded, and the NLR was calculated from these parameters.
- (3) CRP by quantitative nephelometry.
- (4) Fasting blood sugar level.
- (5) Lipid profile: it was performed on blood samples obtained from the patients after overnight fasting. It included total cholesterol and triglycerides measured in plasma by the colorimetric method using commercial assays, high-density lipoprotein-cholesterol (HDL-C) using the direct HDL method (BS-300 Chemistry analyzer, USA), and low-density lipoprotein-cholesterol (LDL-C).

Radiological examination

Patients underwent high-resolution Doppler US examination for common carotid arteries assessment. The ultrasonographic scan protocol was performed on the last 2 cm of both common carotid arteries, before their bifurcation to detect increase in the cIMT or presence of atheromatous plaques. The patients and controls were scanned with Toshiba Xario (USA) using 7.5 MHz probe. The intima-media thickness measurements on each side were taken.

Statistical analysis

All data were calculated, tabulated, and statistically analyzed using statistical package for the social sciences, version 20, software (SPSS Inc., Chicago, Illinois, USA). Categorical data were presented as number and percentages whereas quantitative data were expressed as mean±SD and range. Mann-Whitney *U* test and Spearman's correlation coefficient were used as test of significance.

The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant).

Results

This study included 20 patients with BD, with 17 (85%) males and three (15%) females. Their ages ranged between 19 and 51 years, with a mean of 32.3 ± 9.9 years and mean disease duration of 9.65 ± 6.03 years. This group was subdivided according to cIMT into the following:

Group Ia: nine (45%) patients with BD with increased cIMT.

Group Ib: 11 (55%) patients with BD with cIMT within normal ranges.

Moreover, 20 healthy volunteers [15 (75%) males and five (25%) females] were included in this study as a control group (group II). Their ages ranged between 25 and 55 years, with a mean of 36.8 ± 9.4 years.

All patients with BD had oral aphthous ulcers (100%), 85% had genital ulcers, 70% were positive to skin pethargy test, 35% had acneiform lesions, 45% had erythema nodosum, 15% had arthritis, 75% had ocular lesions (10 patients with red eye, eight patients had painful eye, and five patients had reduced visual acuity), and 10% had nervous system manifestations (two patients with blackouts and loss of balance). Cardiovascular manifestations were detected in 15 (75%) patients with BD [12 (60%) patients had hypertension and three (15%) patients had deep venous thrombosis in the deep veins of the leg] and 10% had gastrointestinal manifestations (abdominal pain and diarrhea).

Table 1 shows that there are statistically insignificant differences ($P > 0.05$) regarding hemoglobin level, RBCs count, hematocrit level, platelet count, and WBCs count; statistically significant differences ($P < 0.05$) regarding ESR level, lymphocytes count, and NLR; and highly statistically significant difference ($P < 0.001$) regarding CRP level and neutrophil count, being higher in patients with BD than healthy control group.

Regarding lipid profile, there were statistically significant differences ($P < 0.05$) regarding triglyceride and HDL levels and statistically highly significant differences ($P < 0.001$) regarding cholesterol and LDL levels.

Table 2 shows that regarding BDCAF, nine patients with active BD had a mean score of 5.67 ± 1.3 and 11 patients with inactive BD had a mean score of 2.45 ± 1.2 . There was a statistically significant difference

Table 1 Comparison between laboratory parameters in Behçet's disease and healthy controls

Variables	BD (N=20) (mean±SD)	Control group (N=20) (mean±SD)	P value
Hemoglobin (g/dl)	11.2±2.1	13.4±1.6	>0.05
RBCs (10^6 cell/ μ l)	4.44±0.44	4.91±0.42	>0.05
Hematocrit (%)	32.2±4.3	35.3±2.3	>0.05
Platelets (10^3 / μ l)	269.2±42.56	259.34±50.2	>0.05
WBCs (10^3 / μ l)	7.892±1.253	6.953±1.230	>0.05
Neutrophil (10^3 / μ l)	5.03±1.5	3.9±0.9	<0.001
Lymphocyte (10^3 / μ l)	2.14±0.54	2.23±1.8	<0.05
NLR	2.5±1.3	1.42±1.8	<0.05*
ESR (mm/1st h)	23.2±17.98	8.3±6.3	<0.01*
CRP (mg/l)	2.7±2.97	0.17±0.84	<0.001**
Triglyceride (mmol/l)	145±37.5	113.32±18.4	<0.01*
Cholesterol (mmol/l)	196.6±52.8	138.3±25.25	<0.001**
LDL (mmol/l)	112.15±25.6	86.1±9.9	<0.001**
HDL (mmol/l)	49.9±7.2	55.4±2.8	<0.01*

BD, Behçet's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NLR, neutrophil-to-lymphocyte ratio; RBC, red blood cell; WBC, white blood cell. *P* value less than 0.05 is significant, *P* value less than 0.001 is highly significant, and *P* value more than 0.05 is not significant. *Significant. **Highly significant.

Table 2 Comparison between neutrophil-to-lymphocyte ratio in Behçet's disease regarding disease activity parameters

Variables	Active BD (N=9)	Inactive BD (N=11)	P value
BDCAF	5.67±1.3	2.45±1.2	<0.001**
ESR (mm/1st h)	28.44±8.03	18.9±22.8	<0.05*
CRP (mg/l)	3.03±1.98	0.8±0.96	<0.001**
NLR	2.8±0.9	2.1±0.9	<0.01*

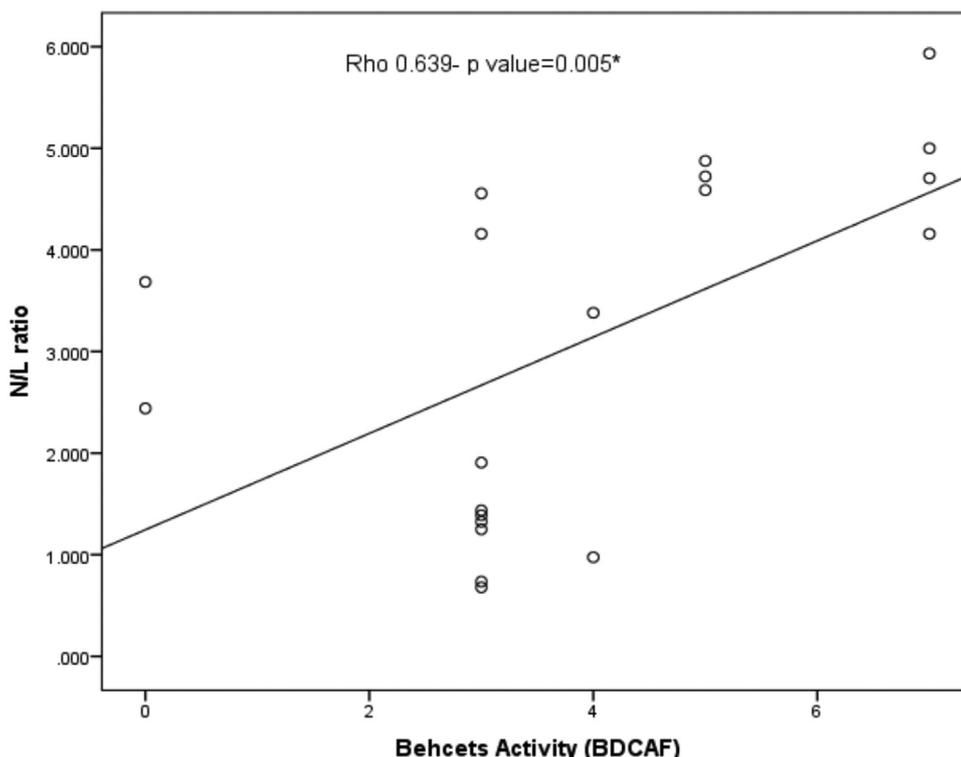
BD, Behçet's disease; BDCAF, Behçet's Disease Current Activity Form; CRP, C-reactive protein; ESR, erythrocytes sedimentation rate; NLR, neutrophil-to-lymphocyte ratio. *Significant. **Highly significant.

($P < 0.05$) regarding ESR and NLR levels, being higher in patients with active BD than those with inactive BD (28.44 ± 8.03 vs. 18.9 ± 22.8 and 2.8 ± 0.9 vs. 2.1 ± 0.6 , respectively). Regarding CRP level, there was a statistically highly significant difference ($P < 0.001$), being higher in patients with active BD (3.03 ± 1.98) than those with inactive BD (0.8 ± 0.96).

Figure 1 shows there was a statistically significance positive correlation ($R=639$, $P=0.005$) between NLR and BDCAF score.

Table 3 shows there was a statistically highly significant difference ($P < 0.001$) regarding cIMT, being higher in group Ia patients (0.82 ± 0.03) than group Ib patients (0.50 ± 0.04) and healthy control group (0.47 ± 0.04).

Figure 1



Correlation between BDCAF and mean NLR. BDCAF, Behcet’s Disease Current Activity Form; NLR, neutrophil-to-lymphocyte ratio.

Table 3 Comparison between carotid intima-media thickness in Behçet’s disease and healthy controls

Carotid intima-media thickness (mm)	BD (group I) (N=20) (mean±SD)	Control group (group II) (N=20) (mean±SD)	P value
Group Ia (N=9)	0.82±0.03	0.47±0.04	<0.001**
Group Ib (N=11)	0.50±0.04		

BD, Behçet’s disease. **Highly significant.

Table 4 shows there were highly statistically significance differences ($P < 0.001$) regarding ESR and CRP levels, neutrophils count [3.2 ± 0.5 vs. 4.6 ± 1.2 ($10^3/\mu\text{l}$)], lymphocytes count [1.9 ± 0.41 vs. 2.03 ± 0.32 ($10^3/\mu\text{l}$)], NLR [1.8 ± 0.9 vs. 2.4 ± 0.5 ($10^3/\mu\text{l}$)], and BDCAF, being higher in group Ia patients than group Ib patients.

There were highly statistically significant differences in patients with BD ($P=0.001$) regarding cholesterol level, triglycerides level, and LDL level, being higher in group Ia cases than group Ib cases (242 ± 23 , 174.6 ± 33 , and 135.9 ± 16 vs. 159 ± 37 , 120.8 ± 19 , and 92.7 ± 9.7 , respectively) and also a highly significance difference regarding HDL level, being lower in group Ia cases than group Ib cases (43.3 ± 4.6 vs. 55.3 ± 3).

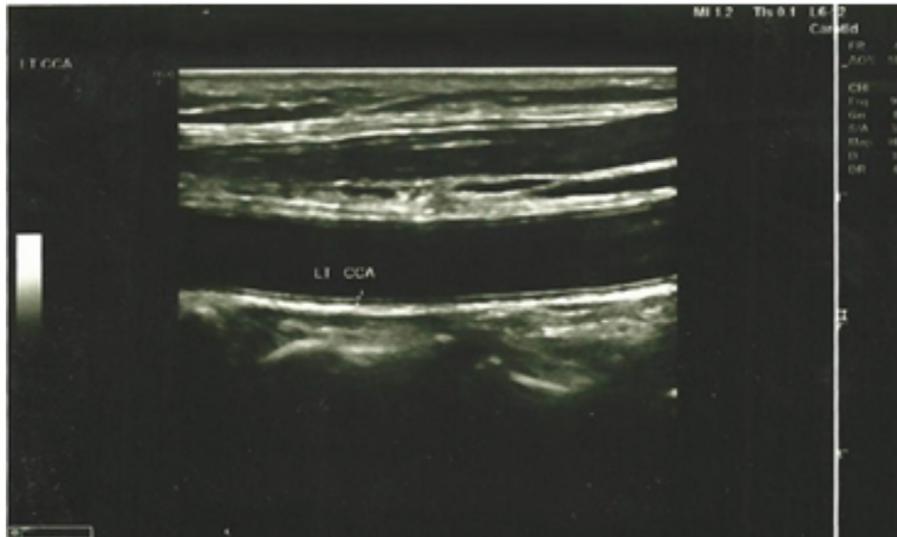
Table 4 Relation between inflammatory parameters, neutrophil-to-lymphocyte ratio, lipid profile, and Behçet disease activity regarding carotid intima-media thickness

	Group Ia (N=9) (mean ±SD)	Group Ib (N=11) (mean ±SD)	Mann–Whitney U test (Z)	P value
ESR (mm/1st h)	27.7±6.5	11.4±7	3.7	0.000**
CRP (mg/l)	2±2.9	0.7±0.6	3.5	0.001**
Neutrophils ($10^3/\mu\text{l}$)	4.6±1.2	3.2±0.5	3.8	0.000**
Lymphocytes ($10^3/\mu\text{l}$)	2.03 ±0.32	1.9±0.41	3.7	0.000**
NLR	2.4±0.5	1.8±0.9	3.8	0.000**
Cholesterol (mmol/l)	242±23	159±37	3.5	0.000**
Triglycerides (mmol/l)	174.6 ±33	120.8±19	3.3	0.001**
LDL (mmol/l)	135.9 ±16	92.7±9.7	3.8	0.000**
HDL (mmol/l)	43.3±4.6	55.3±3	3.8	0.000**
BDCAF score	5±1.7	2.6±1.4	3	0.0002**

BDCAF, Behçet’s Disease Current Activity Form; CRP, C-reactive protein; ESR, erythrocytes sedimentation rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NLR, neutrophil-to-lymphocyte ratio. **Highly significant.

Figure 2 shows the US examination of the right common carotid artery in a 60-year-old male patients with BD, which revealed calcified atherosclerotic plaque.

Figure 2



Ultrasound examination of the right common carotid artery in a 60-year-old male patient with BD, which revealed calcified atherosclerotic plaque. BD, Behcet's disease.

Figure 3 shows increased cIMT (0.85 mm) in a 51-year-old male patient with BD, as detected by ultrasonography.

Discussion

BD is a chronic, immuno-inflammatory disease. In early lesions of BD, the major infiltrating cell is the neutrophil. Neutrophils are one of the main players of the innate immunity system. Neutrophil chemotaxis abnormalities have been extensively reported in BD. The NLR and cIMT are markers of inflammation and vascular risk, respectively [14].

The aim of this study was to assess the relationship between NLR with disease activity, clinical manifestations, and cIMT in patients with BD.

In this study, cardiovascular manifestations were detected in 75% of cases, where 12 (60%) patients had hypertension and three (15%) patients had deep venous thrombosis. These results were nearly similar to the study by El-Gazzar *et al.* [15], where deep venous thrombosis was detected in 31% of cases. The discrepancy in the occurrence of cardiovascular manifestations may be related to larger sample size (38 cases).

In our study, there were statistically insignificant differences ($P > 0.05$) regarding WBCs, statistically significant differences ($P < 0.05$) regarding lymphocytes count and NLR, and a highly statistically significant difference ($P < 0.001$) regarding neutrophil count, being higher in patients with BD than

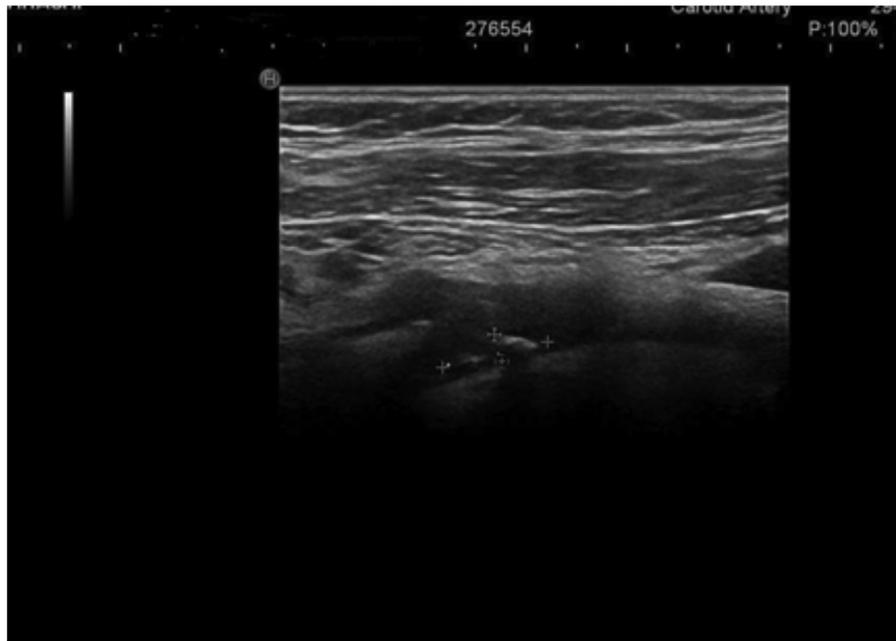
healthy control group. These results go hand in hand with the studies by Ozturk *et al.* [14] and Pancar and Kalkan [16]. They concluded that higher NLR may be related to endothelial dysfunction (ED) and may reflect disease activity in patients with BD. However, in the study by Yolpas *et al.* [17], the NLR was similar in the BD and HC group ($P=0.863$).

This was explained by Macey *et al.* [18], who assessed the histopathologic features of BD lesions, which are characterized by vasculitis and perivascular infiltration of lymphocytes, monocytes, and neutrophils, and surrounding tissue necrosis.

Noninvasive markers of inflammation, such as CRP and ESR, are widely used. In this work, there was a statistically significant difference ($P < 0.01$) regarding mean ESR level (23.2 ± 17.98 vs. 8.3 ± 6.3) and a statistically highly significant difference ($P < 0.001$) regarding mean CRP level (2.7 ± 2.97 vs. 0.17 ± 0.84), being higher in patients with BD than the healthy control group. These results were similar to the studies by Pancar and Kalkan [16] and Ozturk *et al.* [14].

Regarding lipid profile in patients with BD in the current study, there were statistically significant differences ($P < 0.05$) regarding triglyceride and HDL levels and statistically highly significant differences ($P < 0.001$) regarding cholesterol and LDL levels. This is similar to the results of Pancar and Kalkan [16]. However, Yolpas *et al.* [17] found no statistically significant difference ($P < 0.05$).

Figure 3



Increased cIMT (0.85 mm) in a 51-year-old male patient with BD, as detected by ultrasonography. BD, Behcet's disease; cIMT, carotid intima-media thickness.

In the present study, according to BDCAF, nine patients with active BD had a mean score of 5.67 ± 1.3 and 11 patients with inactive BD had a mean score of 2.45 ± 1.2 , with a statistically highly significant difference between the two groups ($P=0.001$). There were statistically significant differences ($P<0.05$) regarding ESR and NLR, being higher in patients with active BD than those with inactive BD (28.44 ± 8.03 vs. 18.9 ± 22.8 and 2.8 ± 0.9 vs. 2.1 ± 0.6 , respectively). Regarding CRP level, there was a statistically highly significant difference ($P<0.001$), being higher in patients with active BD (5.03 ± 2.98) than patients with inactive BD (0.8 ± 0.96). Moreover, there was a statistically significant positive correlation ($R=0.639$, $P=0.01$) between NLR and BDCAF score.

These findings were in agreement with Ricart *et al.* [19], who found that the CRP levels were higher among the patients with active BD compared with those with inactive BD and control group. Similarly, in the studies by Ozturk *et al.* [14] and Yolpas *et al.* [17], the NLR was significantly higher in active patients than in inactive patients (3.15 ± 1.03 vs. 1.75 ± 0.49 , $P<0.001$, and 2.7 ± 1.1 vs. 2 ± 0.7 , $P=0.008$, respectively). Moreover, Yolpas *et al.* [17] also reported that NLR was significantly higher in the patients with neuro-BD and active genital ulcers than in those without ($P<0.05$). In addition, there was a positive correlation between the NLR and the ESR and Behcet's syndrome activity score (BSAS) in the BD

group. In BD, cIMT represents a key event in atherosclerosis and may enlighten the increased development of cardiovascular diseases. The intima-media thickness may be a useful parameter in defining BD progression and identifying those at high risk [20]. Regarding cIMT, the results of this study revealed a statistically highly significant difference ($P<0.001$), being higher in group A (0.82 ± 0.03) than group B (0.50 ± 0.04) and healthy controls (0.47 ± 0.04). In agreement with our results, the studies by Ozturk *et al.* [21] and Yuksel *et al.* [22] revealed that cIMT was greater in patients with BD than in control participants (0.55 ± 0.07 vs. 0.48 ± 0.05 , $P<0.001$, and 0.523 ± 0.090 vs. 0.417 ± 0.035 mm, $P<0.001$, respectively).

Increase in cIMT is a sign of structural arterial remodeling which was shown to be related with ED, which is another characteristic of BD, and can be observed even in patients without clinical vascular involvement [23].

Previous studies showed elevated levels of soluble thrombomodulin concentration [24]. E-selectin [25,26] and vascular endothelial growth factor play roles in ED.

Recent studies have shown that cIMT and arterial stiffness were significantly increased in patient with BD [27].

The present study revealed that there was a statistically significance difference ($P < 0.05$) regarding BDCAF and highly statistically significance difference regarding ESR and CRP levels, being higher in group Ia than group Ib (5 ± 1.7 vs. 2.6 ± 1.4 , 27.7 ± 6.5 vs. 11.4 ± 7 , and 5 ± 2.9 vs. 0.7 ± 0.6 , respectively). These results go hand in hand with El-Gazzar *et al.* [15].

In our study, there were statistically highly significant differences ($P < 0.000$) regarding neutrophils count [4.6 ± 1.2 vs. 3.2 ± 0.5 ($10^3/\mu\text{l}$)], lymphocytes count [7.9 ± 0.41 vs. 2.03 ± 0.32 ($10^3/\mu\text{l}$)], and NLR [2.4 ± 0.5 vs. 1.8 ± 0.9 ($10^3/\mu\text{l}$)], being higher in group Ia cases than group Ib cases. These results go hand in hand with Oz *et al.* [28], who found a positive correlation between cIMT and NLR in patients with BD.

Conclusion

In conclusion, higher NLR values were recorded in patients with BD. Furthermore, patients with active BD had higher NLR values than inactive and NLR is higher in patients with increased cIMT; thus, NLR may be an important bio-index for detecting BD activity and the presence of vascular affection.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Nair JR, Moots RJ. Behcet's disease. *Clin Med (Lond)* 2017; 17:71–77.
- Emmi G, Silvestri E, Squatrito D, Amedei A, Niccolai E, Milco D'Elios M, *et al.* Thrombosis in vasculitis: from pathogenesis to treatment. *Thromb J* 2015; 13:15.
- Mercan R, Bitik B, Tufan A, Bozbulut UB, Atas N, Ozturk MA, *et al.* The association between neutrophil/lymphocyte ratio and disease activity in rheumatoid arthritis and ankylosing spondylitis. *J Clin Lab Anal* 2015; 30:597–601.
- Yang Z, Liang Y, Xi W, Li C, Zhong R. Association of increased serum IL-33 levels with clinical and laboratory characteristics of systemic lupus erythematosus in Chinese population. *Clin Exp Med* 2011; 11:75–80.
- Yuksel M, Yildiz A, Oylumlu M, Mehmet B, Bilik M, Ekinci A, *et al.* Novel markers of endothelial dysfunction and inflammation in Behçet's disease patients with ocular involvement: epicardial fat thickness, carotid intima media thickness, serum ADMA level, and neutrophil-to-lymphocyte ratio. *Clin Rheumatol* 2016; 35:701–708.
- Safak S, Uslu AU, Serdal K, *et al.* Association between mean platelet volume levels and inflammation in SLE patients presented with arthritis. *Afr Health Sci* 2014; 14:919–924.
- Rifaioğlu EN, Bulbulşen B, Ekiz O, *et al.* Neutrophil to lymphocyte ratio in Behçet's disease as a marker of disease activity. *Acta Dermatovenereol Alp Pannonica Adriat* 2014; 23:65–67.
- Qin B, Ma N, Tang Q, *et al.* Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. *Mod Rheumatol* 2016; 26:372–376.
- Azab B, Torbey E, Singh J, *et al.* Mean platelet volume/platelet count ratio as a predictor of long-term mortality after non-ST-elevation myocardial infarction. *Platelets* 2011; 22:557–566.
- Yazici S, Yazici M, Erer B, *et al.* The platelet functions in patients with ankylosing spondylitis: anti-TNF- α therapy decreases the mean platelet volume and platelet mass. *Platelets* 2010; 21:126–131.
- Davatchi F, Assaad-Khalil S, Calamia KT, Crook J, Sadeghi-Abdollahi B, Schirmer M, *et al.* International study group for Behçet's disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335:1078–1080.
- Altac M, Tu Y, Yurdakul S, Binyildiz P, Yazici H. The validity of the pathergy test (non-specific skin hyperreactivity) in Behçet's disease: a double-blind study by independent observers. *Acta Derm Venereol* 1982; 62:158–159.
- Suzuki N, Nara K, Suzuki T. Skewed Th1 responses caused by excessive expression of Txx, a member of the Tec family of tyrosine kinases, in patients with Behçet's disease. *Clin Med Res* 2006; 4:147–151.
- Ozturk C, Balta S, Balta I, Demirkol S, Celik T, Turker T, Iyisoy A. Neutrophil lymphocyte ratio and carotid-intima media thickness in patients with Behçet disease without cardiovascular involvement. *Angiology* 2015; 66:291–296.
- El-Gazzar I, El-Dakrony A, Sayed S, *et al.* Clinical significance of metabolic syndrome and carotid intima media thickness in Behçet's disease patients: relation to disease activity. *Egypt Rheumatol* 2017; 3:171–174.
- Pancar GS, Kalkan G. Diagnostic value of Hb A1c level in Behçet's disease and evaluation of neutrophil-lymphocyte ratio, mean platelet volume and body mass index. *J Hematol* 2015; 4:219–222.
- Yolpas S, Yildirim A, Gozel N, Koca S. Hematological indices may be useful in diagnosis of systemic lupus erythematosus and in determining disease activity in Behçet's disease. *Med Princ Pract* 2016; 25:510–516.
- Macey M, Hagi-Pavii E, Stewart J, Wallace GR, Stanford M, Shirlaw P, *et al.* Age, gender and disease-related platelet and neutrophil activation ex vivo in whole blood samples from patients with Behçet's disease. *Rheumatology (Oxford)* 2011; 50:1849–1859.
- Ricart JM, Espana F, Navarro S, Vayá A. Mean platelet volume does not seem to relate to thrombosis or posterior uveitis in Behçet's disease. *Clin Hemorheol Microcirc* 2013; 54:51–57.
- Oylumlu M, Dogan A, Oylumlu M, *et al.* Relationship between platelet to lymphocyte ratio and coronary slow flow. *Anatol J Cardiol* 2015; 15:391–395.
- Ozturk C, Balta S, Balta I, *et al.* Neutrophillymphocyte ratio and carotid-intima media thickness in patients with Behçet disease without cardiovascular involvement. *Angiology* 2015; 66:291–296.
- Yüksel S, Kucukazman SO, Karataş GS, Ozturk M, Prombhul S, Hirankarn N. Methylation status of Alu and Line 1 interspersed repetitive sequences in Behçet's disease patients. *Bio Med Res* 2016; 2016:1393089.
- Onur E, Kabaroglu C, Inanir I, Var A, Guvenc Y, Gunay O, *et al.* Oxidative stress impairs endothelial nitric oxide levels in Behçet's disease. *Cutan Ocul Toxicol* 2011; 30:217–220.
- Kiraz S, Ertenli I, Ozturk MA, Haznedaroglu IC, Celik I, Calguneri M. Pathological haemostasis and 'prothrombotic state' in Behçet's disease. *Thromb Res* 2002; 105:125–133.
- Haznedaroglu S, Karaaslan Y, Buyukasik Y, Ozcebe A, Haznedaroglu A, Kirazli S, Dundar S. Selectin adhesion molecules in Behçet's disease. *Ann Rheum Dis* 2000; 59:61–63.
- Kosar A, Haznedaroglu S, Karaaslan Y, *et al.* Effects of interferon-alpha2a treatment on serum levels of tumor necrosis factor-alpha, tumor necrosis factor-alpha2 receptor, interleukin-2, interleukin-2 receptor, and E-selectin in Behçet's disease. *Rheumatol Int* 1999; 19:11–14.
- Balta I, Balta S, Koryurek OM, *et al.* Mean platelet volume is associated with aortic arterial stiffness in patients with Behçet's disease without significant cardiovascular involvement. *J Eur Acad Dermatol Venereol* 2014; 28:1388–1393.
- Ozturk C, Sevket B, Ilknur B, Sait D, Turgay C, Turker T, *et al.* Carotid-intima media thickness in patients with Behçet disease without cardiovascular involvement. *Angiology* 2015; 66:291–296.