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Serum Amyloid-A in Behçet's Disease: Relation to Clinical Manifestations and Disease Activity

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ABSTRACT

Background: Behcet's disease (BD) is an autoimmune systemic vasculitis with an unknown origin. Recent discoveries have proven the essential role of Serum Amyloid A (SAA) in the pathophysiology of inflammatory rheumatic illnesses, including its involvement in the activation of the inflammasome cascade and the recruitment of interleukin 17-producing T helper cells.

Aim of the work: This study aimed to measure the level of SAA in Behçet's disease and to examine the relation of SAA levels with disease activity and different organ involvement.

Patients and Methods: This case-control research was done on 30 Behcets' cases which were subjected to history taking, full clinical examination, and assessment of disease activity by Behcet Disease Current Activity Form (BDCAF). Investigation in the form of CBC, ESR, CRP, and SAA were assessed.

Results: Serum amyloid-A level was significantly greater in BD cases when contrasted to controls (P<0.001). Higher SAA was significantly related to the existence of oral ulcers, genital ulcers (P=0.041), eye involvement (P=0.005), and musculoskeletal manifestations (P=0.049). Skin manifestations, neurologic and large vessel involvements were not associated with SAA levels (P=0.948, P=0.077, and P=0.198 respectively). Lower SAA was significantly associated with those who received biologic therapy (P=0.045). Serum amyloid-A levels revealed significant positive relationships with disease activity (P<0.05) and higher SAA was considered a risk predictor for BD susceptibility (P=0.002), OR 1.156**.**

Conclusion: Serum amyloid-A would be a predictor for BD susceptibility and activity. SAA levels are associated with ocular manifestations and could be a predictor of eye involvement.

Keywords: Serum amyloid-A, Behçet's disease, Behçet's disease activity form (BDCAF).

INTRODUCTION

Genital ulcers, Oral aphthosis, and sight-threatening ophthalmologic symptoms are the clinical hallmarks of BD. Repeated attacks of posterior uveitis, pan uveitis, and/or retinal vasculitis can cause significant impairment to vision and need for cautious diagnosis and therapeutic therapy [1]. Moreover, major vessel disease and CNS problems may further complicate the clinical scenario of these individuals [2]**.** Skin involvement, such as pseudofolliculitis and erythema nodosum, may also be present. The assessment of disease activity is presently dependent on BDCAF, one of the most utilized clinimetric scores due to its high dependability amongst observers [3]**.**

Serum amyloid-A is a greatly preserved apolipoprotein implicated in the acute phase response, and its levels are commonly elevated in several autoinflammatory illnesses, both throughout acute inflammatory episodes and the inter-critical periods [4]**.** Interleukin-6 (IL-6), IL-1, tumor necrosis factor, interferon-γ, and transforming growth factor- (TGF-) are examples of proinflammatory cytokines that induce the production of acute-phase SAA. In situations of injury or acute inflammation, the levels of SAA may elevate dramatically to 1000-fold greater than normal in as little as 5 or 6 hours. Similar to other acute-phase reactants, the liver is the primary supplier of circulating SAA. Nevertheless, individuals with chronic disorders including Alzheimer's, cancer, obesity, insulin resistance, diabetes, metabolic syndrome, and atherosclerosis have been shown to produce extrahepatic SAA by a variety of tissues and cell types [5]**.** This research aimed to measure the level of SAA in BD and to examine the relation of SAA levels with disease activity and different organ involvement.

PATIENTS AND METHODS

This case-control research was done on Behcet's cases attending the Inpatient and outpatient clinic of the Rheumatology, Rehabilitation, and Physical Medicine Department of Benha University Hospitals. Our study population was divided into two groups; Group I included 30 BD cases and Group II (control group) included 30 subjects healthy with comparable age, sex, and social level to the patient group.

Inclusion criteria: According to the international criteria of Behçet's Disease (ICBD) [6]**.**

Exclusion criteria: Concomitant inflammatory disorders, chronic diseases**,** positive history of malignancies, ongoing infections, pregnancy, and individuals who are obese (demarcated as a body mass index > 30 kg/m^2).

Data collection: In this research, patients' data were mostly retrieved through paper-based patient files. Information from patient records was recorded for the following factors: disease duration, different organ involvements (mucocutaneous, eye, gastrointestinal, vascular, neurological, cardiovascular, and

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musculoskeletal) during their follow-up visits and prescribed medications after their diagnoses.

All patients were subjected to:
(A) History taking (B) Thorough clinical examination
(**C**) **Assessment of disease activity by BDCAF:** This instrument assessed twelve common clinical manifestations of BD (headache, oral ulcers, pustules, erythema nodosum, arthritis, genital ulcers, arthralgia, abdominal pain/nausea/vomiting, gastrointestinal bleeding, damage to CNS, ocular symptoms, and damage of major vessel) over the four weeks previous to the day of follow up visit. The produced activity index used variables varying from zero to 12 and then transformed to a 0-20 interval scale, to associate with the disease activity [7].
(D) Laboratory investigations: Complete blood count (CBC), Erythrocyte sedimentation rate (ESR), C – reactive protein (CRP), and SAA: using double ELISA technique by human serum amyloid an ELISA kit Cat. No: MBS037390.

Ethical approval: The Research Ethics Committee Faculty of Medicine Benha University approved the study protocol (study no: Ms.15.12.2021). Before they participated in the trial, the patients gave their informed permission to the researchers. Every piece of information was kept under wraps. Everyone who took part in the research was allowed to drop out of the research at any time, with no adverse effects on their care. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis
Using SPSS Statistics for Windows Version 25.0, the acquired data were edited, coded, and tabulated following being collected. The data were provided, and appropriate analysis was carried out. Both descriptive statistics and analytical statistics, such as the student T-test, the Mann-Whitney test (U test), the Chi-square test, the regression analysis, and the ROC curve were done. The P value equal to or less than 0.05 with a 95% confidence interval was deemed significant.

RESULTS

The current research was done on 30 BD cases. Their mean age was 35.6 years. They were 93.3% males and 6.7% females in addition to the 30 age- and gender-matched healthy controls. There was no significant variance among studied groups concerning age and sex (P>0.05). The mean disease duration was 7.8 years, varying from 0.33 to 25 years.

Regarding mucocutaneous manifestations, 93.3% had oral ulcers, 93.3% had genital ulcers and 33.3% had skin manifestations in the form of 3.3% pustules, 10% erythema nodosum, 16.7% pseudofolliculitis and 3.3% erythema nodosum with pseudofolliculitis.
Eye involvement was found in 80% of cases, 30% had unilateral eye involvement, and 50% had bilateral eye involvement. Uveitis was diagnosed among 73.3%; 23.3% pan uveitis, 6.7% anterior uveitis, and 43.3% posterior uveitis, while 6.7% lost their vision.
Neurologic affection was found in 36.7% of BD patients; 10% sagittal sinus thrombosis, 10% tension-type headache, 10% CNS vasculitis, and 6.7% parenchymal brain lesions. None of the studied cases had CVS affection. Among all studied cases, only a case had anal bleeding (3.3%) as GIT involvement.
Musculoskeletal manifestations were observed in 30% of cases; 16.7% arthritis and 13.3% arthralgia.
Large vessels were affected in 33.3%; 26.7% had LL DVT: 16.7% were unilateral and 10% were bilateral.
In addition, 3.3 % had superficial thrombophlebitis, 3.3% had carotid thrombosis and 3.3% had pulmonary thrombosis.

No significant variances were observed among BD cases & control group regarding haemoglobin concentration, platelets, and WBC count (P>0.05). BD cases were associated with significantly higher ESR and positive CRP (P<0.001). The mean patient index disease activity score was 2.77; ranging from 0 to 7, while transformed index disease activity score was 5.5; ranging from 0 to 11 [Table 1 & figure 1].

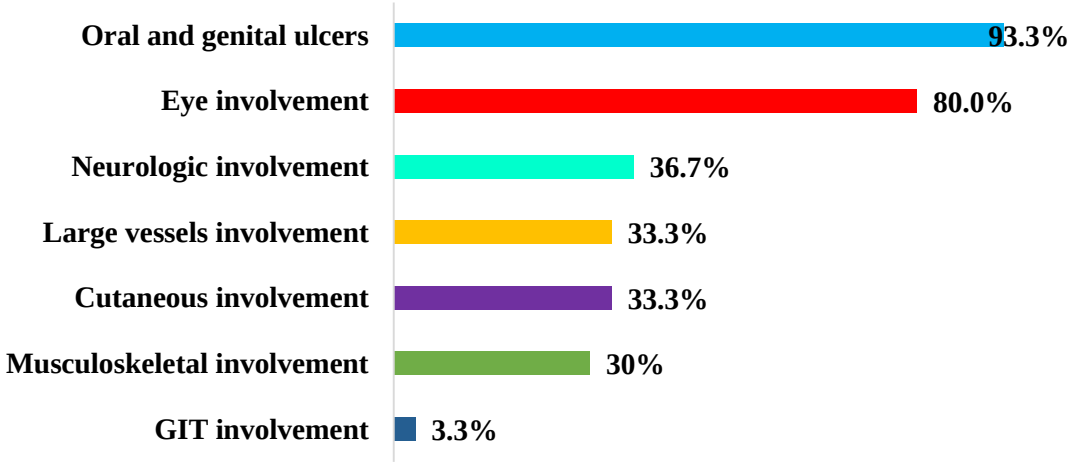

Figure (1): Clinical findings among the BD group

Table (1): Duration of disease, Behcet disease activity score (BDCAF), and laboratory data among BD group

	BD (N = 30)
Duration of disease (years)	
Mean ± SD	7.81 ± 1.08
Median (Range)	5.50 (0.33 – 25.0)
Disease activity score (patient index score)	
Mean ± SD	2.77 ± 0.39
Median (Range)	3.0 (0.0 – 7.0)
Disease activity score (transformed index score)	
Mean ± SD	5.50 ± 0.68
Median (Range)	7.0 (0.0 – 11.0)
Hemoglobin (g/dL)	
Mean ± SD	13.72 ± 2.30
Platelet ($X10^9$/L)	
Mean ± SD	237.90 ± 56.09
WBCs ($X10^9$/L)	
Mean ± SD	8.43 ± 0.58
ESR (mm/h)	
Mean ± SD	21.73 ± 3.16
CRP (mg/L)	
Negative	15 (50.0%)
Positive	15 (50.0%)

The study revealed that 96.7% of cases received DMARDS in the form of 63.3% azathioprine, 26.7% cyclosporine, 13.3% methotrexate, 3.3% leflunomide, 3.3% cyclophosphamide and 36.7% received biology in the form of 6.7% adalimumab, 30.0% infliximab, 90% steroid, 20% colchicine and 3.3% warfarin.

Serum amyloid-A level was significantly greater in BD cases when contrasted to control groups (median=18.4 versus 9.45, P<0.001) **[Figure 2].** Higher SAA was significantly associated with the presence of oral ulcers (median=19.4 versus 11.7, P=0.041), genital ulcers (median=19.4 versus 11.7, P=0041), eye involvement (median=19.8 versus 13.1, P=0.005), musculoskeletal manifestations (median=22.2 versus 16.7, P=0.049). Skin manifestation, neurologic, and large vessel involvement were not associated with SAA levels (P=0.948, P=0.077, P=0.198 respectively). Higher SAA was significantly related to positive CRP (median=19.8 versus 14.9, P=0.023).

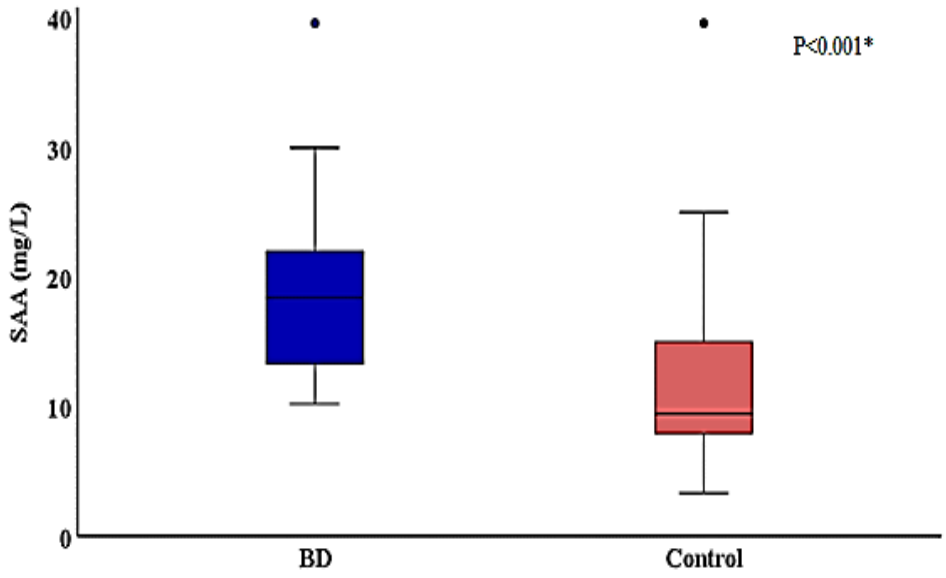

Figure (2): Boxplot for comparison of SAA among BD patients and control group.

Lower SAA was significantly associated with those who received biologic therapy (median=16.7 versus19.8, P=0.045). While, lower SAA was non-significantly associated with those received steroids (median=18.6 versus 22.4, P=0.350). No significant variances were observed concerning SAA levels who received any drug of DMARDS versus those who did not receive (P>0.05). We found that SAA level revealed significant positive relationships with ESR, and disease activity (correlation coefficient>0, P<0.05) **[Figure 3]**. While, no significant correlations were observed between SAA with age, duration, haemoglobin, platelets, and WBCs count (P>0.05).

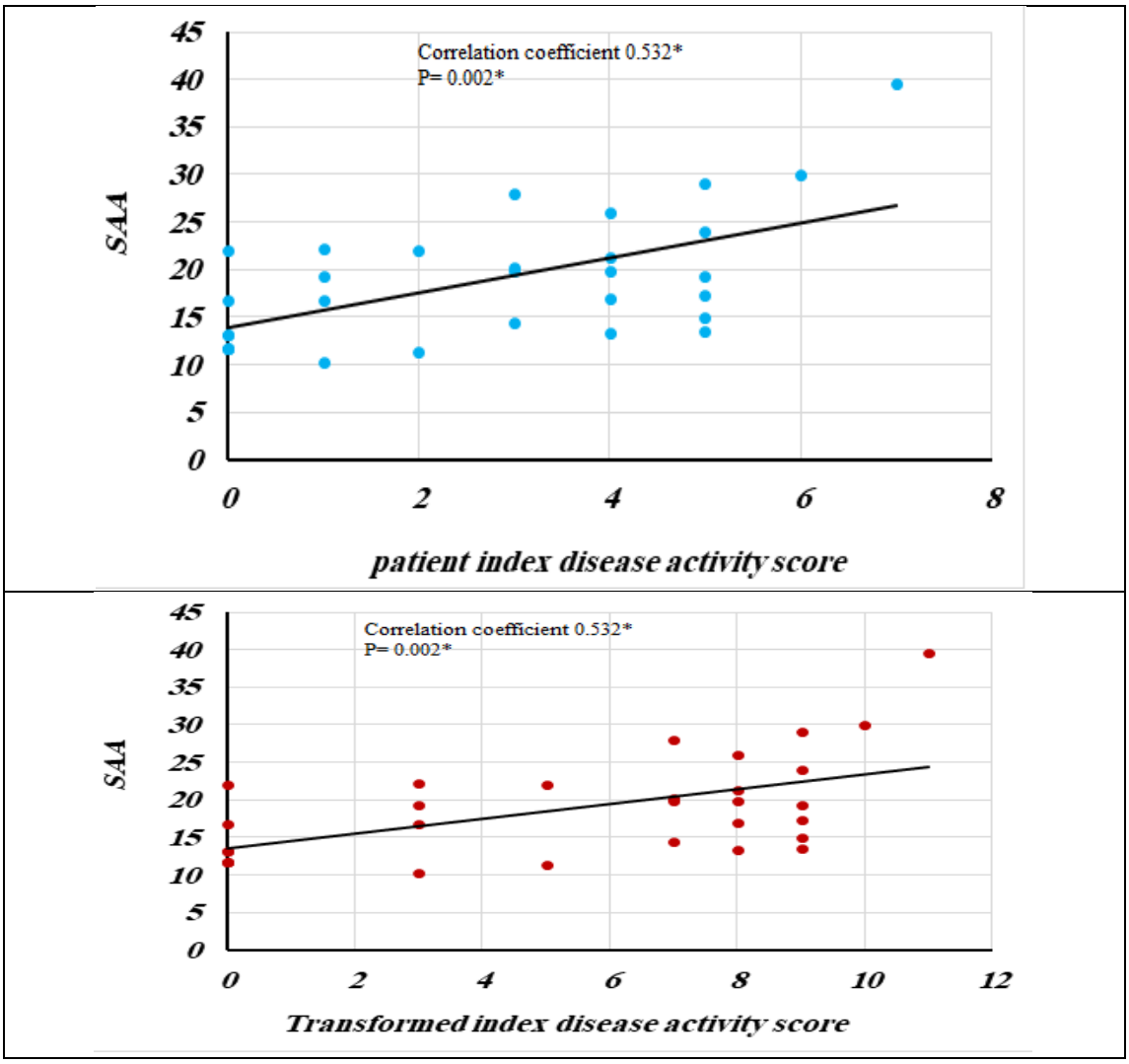

Figure (3): Correlation between SAA and disease activity score (BDCAF) among BD patients.

The receiver operating characteristic (ROC) curve of SAA was done for discrimination among BD patients & control group. Moderate accuracy AUC (AUC=0.812) was found. At the best cut-off value (>13.05), sensitivity was 83.3%, specificity was 70%, PPV was 73.5%, NPV was 80.8% and accuracy was 76.7% **[Figure 4].**

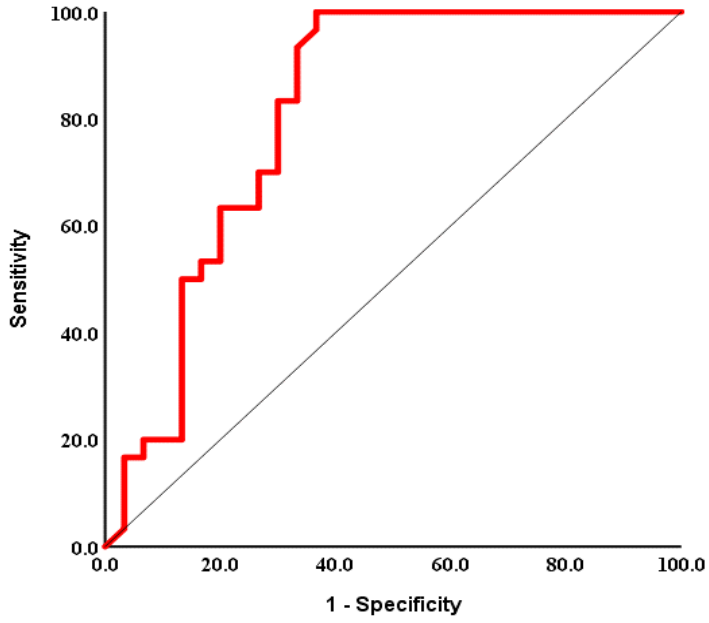

Figure (4): ROC Curve for SAA for discrimination between BD patients and control group.

Logistic regression analysis was performed for the prediction of BD susceptibility, using haemoglobin, platelets, WBCs, ESR, and SAA as covariates. Higher SAA was considered a risk predictor for BD susceptibility (P=0.002), OR 1.156**.** Linear regression analysis was conducted for the prediction of transformed index disease activity form (BDCAF) utilizing age, sex, patient index score, disease duration, CBC, ESR, CRP, biologic treatment, steroid, and SAA as covariates. Higher patient index scores, ESR, CRP, SAA and not receiving biologic treatment were significantly related to greater transformed index scores in univariable analysis. While, in multivariable analysis, higher patient index score, SAA and not receiving biological treatment were considered independent predictors for advanced transformed disease activity index score [Table 2].

Table (2): Linear regression analysis for prediction of Behcet disease activity score (Transformed index score)

	Univariate		**Multivariate**	
	β	**P**	**β**	**P**
Gender	4.286	0.117		
Age	0.056	0.570		
patient index score	1.698	**<0.001***	1.761	**<0.001***
Duration of disease	-0.140	0.240		
Hemoglobin	-0.204	0.506		
Platelet	0.005	0.677		
WBCs	0.067	0.761		
ESR	0.114	**0.003***	-0.009	0.786
CRP	3.267	**0.013***	-0.019	0.396
Biology treatment	-2.368	**0.029***	0.162	**0.032***
Steroid treatment	-0.926	0.690		
SAA	0.300	**0.002***	-0.381	**0.030***

SAA: serum amyloid A, B: unstandardized coefficients,
*: P value Significant < 0.05.

DISCUSSION

Patients suffering from inflammatory rheumatic disorders have a great deal to gain by monitoring their SAA levels. Recent findings, such as SAA's participation in inflammasome activation and recruitment of interleukin 17-producing T helper cells, have established its essential position in the pathophysiology of inflammatory rheumatic illnesses [8, 9].

Numerous prior investigations have posited that specific diseases, including rheumatoid arthritis, ankylosing spondylitis, autoinflammatory diseases such as familial Mediterranean fever and Hashimoto's thyroiditis, cardiovascular diseases, major depression, systemic lupus erythematosus, diabetes mellitus, psoriasis, inflammatory bowel diseases, acute pancreatitis, vasculitis, and epilepsy, have the potential to modify SAA levels [10]. So, this case-control study sought to measure the serum level of SAA in BD and to examine the relation of SAA levels with disease activity and different organ involvement.

In the current research, there were 93.3% males and 6.7% females. These results are consistent with a cohort study in Saudi Arabia where patients were classified as 73.6% males and 26.4% females [11]. Arab populations tend to be predominately male, whereas those of Korea, China, the United States, and even certain northern European nations tend to be predominately female [8].

As regards mucocutaneous manifestations of BD in this research, 93.3% of cases had either oral or genital ulcers, 3.3% had pustules, 10% had erythema nodosum, 16.7% had pseudofolliculitis and 3.3% had erythema nodosum with pseudofolliculitis. The current research results are in the same line with **Limtong *et al.*** [12] who revealed that oral ulcers affected 97.5% of cases, genital ulcers affected 57.9% of cases, erythema nodosum in 35.3%, papulopustular lesions affected 24.4% of cases.

Eye involvement was found in 80% of cases; 30% had unilateral eye, and 50% had bilateral eye involvement. Uveitis was diagnosed among 73.3% in the form of 23.3% pan uveitis, 6.7% anterior uveitis, and 43.3% posterior uveitis, while 6.7% lost their vision. **Paovic *et al.*** [13] found that the most frequent ocular manifestations were retinal peri-phlebitis 81.6%, peri-phlebitis and periarteritis 65%, and sero-fibrinous uveitis 63.2%. The complication of macular edema was found in 63.2% of those affected. **Limtong *et al.*** [12] discovered that ophthalmologic involvement was the most frequent result in 60.5% of patients, which were mostly pan-uveitis and retinal vasculitis (65.7% and 55.7%, respectively).

The present study revealed that neurological involvement was found in 36.7% of BD patients, 10% had sagittal sinus thrombosis, 10% had tension-type headache, 10% had CNS vasculitis and 6.7% had parenchymal brain lesions. **Limtong *et al.*** [12] also, found that neurological manifestations were found in 11 (9.2%), 9 of which involved the CNS. Four of 9 patients (44.4%) had CNS vasculitis.

None of the studied cases had cardiac manifestations and only one case had anal bleeding (3.3%) as a GIT manifestation. Also, none had cardiac involvement in **Limtong *et al.*** [12] study. They showed that 9 (7.6%) individuals were affected by gastrointestinal involvement, with gastrointestinal

ulcers being the most prevalent presenting symptom in 5 of these 9 patients (55.6%). The musculoskeletal system was affected in 30% of all studied cases, 16.7% had arthritis and 13.3% had arthralgia. **Davatchi *et al.*** [14] reported that 17.2% of patients had articular symptoms, including 7.6% with mono-arthritis, 16.8% with oligo-arthritis, and 2% with ankylosing spondylitis.

The current study showed that large vessels were affected by 33.3%. 13.3% had LL deep venous thrombosis (DVT), 16.7% were unilateral and 10% bilateral. In addition, 3.3% had superficial thrombophlebitis, 3.3% had carotid thrombosis and 3.3% had pulmonary thrombosis. **Limtong *et al.*** [12] revealed that of the 5 patients with substantial vascular involvement, 3 (60.0%) were diagnosed with DVT. A study by **Daoud *et al.*** [15] reported that vascular symptoms occurred in 31.5% of patients, with venous dysfunction occurring in 95.1% of these instances. The most common vascular manifestation was deep vein thrombosis (78%), and the most common sites of DVT were the lower extremities (84.4%), the vena cava (28.1%), the upper extremities (9.4%), pulmonary embolism (PE) (9.4%), cerebral venous thrombosis (6.2%) and Budd Chiari syndrome (3.1%).

The present study revealed no significant variances among BD cases and the control group concerning hemoglobin concentration, platelet, and WBC counts (P value >0.05). However, **Zhang *et al.*** [16] revealed that WBCs and platelets were significantly raised while the hemoglobin level was noticeably reduced in BD patients compared to healthy controls. Moreover, **Ye and his colleagues** [17] observed that BD patients frequently suffered from anemia.

Consistent with **Davatchi *et al.*** [14] and **Tezcan *et al.*** [18], this research revealed that BD individuals were significantly correlated with greater ESR (P<0.05). In line with **Hou *et al.*** [19] and **Tezcan *et al.*** [18], the present research displayed that BD cases were significantly correlated with positive CRP (P=0.023).

In the present research, the SAA level was significantly greater in BD cases when contrasted to the control group. Also, **Lopalco *et al.*** [20] showed that elevated levels of SAA in BD patients contrasted with healthy controls. Consistent with **Carbone *et al.*** [21] and **Zhen-yuan *et al.*** [22] who observed statistically significant greater SAA levels in BD cases contrasted to healthy controls.

The results agree with **Vitale *et al.*** [23] who found that high SAA levels were significantly related to an increased rate of oral aphthosis and eye involvement but they disagreed with our findings in increasing incidence of CNS involvement, which is associated with high SAA. This may be due to different sample sizes of CNS cases (9/30 cases in our study versus 19/26 in **the Vitale *et al.*** study). They also reported that severe ocular and central nervous system symptoms may be more likely to develop in those with elevated SAA levels.

In disagreement with the results, **La Regina *et al.*** [24] suggested that BD patients who had or are experiencing vascular involvement may be at a higher risk for thrombosis if their SAA levels are elevated. Also, different from the results, **Cantarini *et al.*** [25] and **Sota *et al.*** [1] found SAA levels associated with skin involvement.

The present research showed that higher SAA was significantly associated with the presence of uveitis. In accordance with **Cai and his colleagues** [26] who found that uveitis presented with higher concentrations of SAA they hypothesized that SAA might be a predictive factor for uveitis risk in BD patients, which would aid in both disease prevention and therapy. Serum amyloid-A levels were observed to be significantly greater in uveitis patients than in healthy controls, as reported by **Dai *et al.*** [27]. Also, they reported that the active state was shown to have greater SAA levels (P< 0.05). Additionally, **Sota *et al.*** [1] discovered a strong correlation between elevated SAA levels and ocular illness.

The present study revealed that SAA level showed significant positive correlations with ESR. **Lucherini *et al.*** [28] reported that patients with BD have been shown to have increased levels of some inflammatory mediators, particularly throughout periods of active illness and in those patients with high SAA, which may indicate a function for SAA in the development of inflammatory symptoms of BD. On the other hand, **Vitale *et al.*** [23] observed no associations between SAA and ESR or CRP.

The present research revealed that SAA levels showed significant positive relationships with disease activity. This is consistent with **Lopalco *et al.*** [20], who discovered that SAA was positively related to disease activity in BD patients. In addition, **Zhen-yuan *et al.*** [22] found that SAA can work as a predictor for BD activity. Although **Vitale *et al.*** [23], **Cantarini *et al.*** [25], and **Sota *et al.*** [1] revealed no significant variance of mean SAA level among cases with active disease and those with inactive disease, which relatively disagrees with our results. This may be due to different study designs. Also, **Lee *et al.*** [29] authorized a non-significant relationship between SAA and disease activity in BD cases and this may be attributed to that their study was conducted on BD cases with only intestinal involvement.

This research revealed that 96.7% of studied cases received DMARDS (63.3% on Azathioprine, 26.7% on Cyclosporine, 13.3% on Methotrexate, 3.3% on Leflunomide, 3.3% on cyclophosphamide), 6.7% on adalimumab, 30.0% on infliximab, 90% on steroid, 20% on colchicine and 3.3% on warfarin). While **Alharthy *et al.*** [11] revealed that patients who received prednisolone were 72.5%, azathioprine was 36.3%, mycophenolate mofetil was 0.75%, cyclosporine was 0.03% and colchicine was 95.6%.

The present study discovered that lower SAA was significantly associated with those who received

biological treatment, while was non-significantly associated with those who received steroids or DMARDs. This agrees with **Sota *et al.*** [1] who found that patients on biologic therapies displayed more frequently low SAA levels versus patients who were not on biologic therapies (P=0.012) and use of corticosteroids in combination with traditional DMARDs showed no additional statistically significant variations (P > 0.05).

ROC curve analysis of SAA at the best cut-off value of >13.05 for discrimination between BD patients and the control group showed that sensitivity was 83.3%, specificity was 70% and accuracy was 76.7%. These findings agree with **Aygunduz *et al.*** [30] who advocated the use of SAA as a diagnostic marker of BD since it is sensitive at 70% and specific at 96%.
The present study showed that SAA was significantly related to higher disease activity in univariable analysis. While, in multivariable analysis, higher SAA was considered an independent predictor. Consistent with the results, **Sota *et al.*** [1] reported that SAA level is not a biomarker for disease activity but may indicate the involvement of major organs.

CONCLUSION

In conclusion, the present study observed that SAA levels were greater in BD than in the control group as well as in active cases more than in inactive disease. In addition, SAA could be a predictor of BD susceptibility and activity. SAA associated with ocular manifestations could be a predictor of eye involvement.

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