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Assessment of sleep quality, anxiety, depression, and quality of life in Behçet's disease

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Abstract

Background Behçet's disease (BD) is a multi-organ disease with different systemic manifestations. While rare in the United States and Europe, it is more common in the Middle East and Asia. BD is one of the commonest encountered vasculitis in Egypt. This study aims to evaluate BD patients' sleep patterns, quality of life, and psychological aspects.

Methods Patients suffering from Behçet's disease (thirty patients) and 30 matched age and sex-healthy control participants were recruited in our study. The assessment included the entire clinical history and laboratory investigations, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Oxygen saturation level. Evaluation of sleep quality and presence of sleep-disordered breathing was done using the Pittsburgh Sleep Quality Index (PSQI), Insomnia severity index (ISI), and Epworth sleepiness scale (ESS). Hamilton's anxiety (HAM-A) and depression rating scales (HAM-D) were used for psychological assessment. The Short Form 36 Quality Of Life Scale (SF-36 QOL) assessed participants' quality of life.

Results Behçet's disease patients suffered significantly higher levels of anxiety and depression compared to the control group. The prevalence of insomnia and daytime sleepiness was significantly higher among BD patients. All components of PSQI, including the global score, were significantly higher among the BD group. Physical functioning, role limitation due to physical health, and emotional problems; also, general health indices were significantly lower for the BD group. Patients with active BD showed significantly higher levels of anxiety, depression, insomnia, day time dysfunction and significantly lower all domains of the SF-36 QOL Scale.

Conclusions BD is associated with low sleep quality and high levels of anxiety and depression.

Disease activity directly impacts anxiety, depression levels, lower sleep quality, and lower quality of life among BD patients.

Trial registration ClinicalTrials.gov. NCT05142995. Registered November 20, 2021.

Keywords Behcet disease, Sleep quality, Quality of life, Anxiety, Depression, Vasculitis Damage Index

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Background

Behçet's disease (BD) is a multisystem, autoimmune disease representing a form of systemic vasculitis. The clinical picture associated with BD is diverse and complex, including various symptoms affecting almost all body systems [1]. These diverse manifestations proceed in a cycle of remissions and exacerbations, reframing quality

of life (QOL) in those patients and representing a massive concern for them and their families.

Sleep quality is an essential component of QOL. Sleep disturbance is described in the literature in relation to various rheumatic diseases, including BD [2–4]. Neurological involvement in BD is variable, which ranges between 2–50% among studies [5, 6]. Even without neurological involvement, neuropsychiatric symptoms, including anxiety and depression, are commonly described in BD. An incidence of 86% of psychiatric illness was reported after the first manifestations of the disease [7].

Several aspects impact sleep quality in BD patients, including disease duration, disease activity, treatment, and psychological disorders. All these factors affect QOL in BD patients.

This study aims to; evaluate sleep quality and efficiency, psychological aspects, and the impact of such factors on health status and quality of life for BD patients and their relation to disease activity.

Patients and methods

Study participants and ethical approval this prospective case–control study was performed on 30 BD patients in the age group of 18–60 years diagnosed via International Criteria for Behçet's disease; point score system: scoring ⩾4 indicates Behçet's disease [8] and 30 healthy matched control participants. Patients were recruited from outpatient clinics and wards of physical medicine, rheumatology, rehabilitation department, and Assiut university hospitals from October 2021 to October 2022.

Informed written consent was obtained from participants. Exclusion criteria were evidence of end-organ failures such as heart failure, a liver cell or renal failure, history of psychological disturbance or medications, and inability to obtain written informed consent. The Faculty of Medicine, Assiut University's ethical committee approved the study protocol under the Declaration of Helsinki.

Demographic, clinical, and laboratory data history taking, full clinical examination, and comorbidities such as Diabetes, Hypertension, and BD medication were assessed. ESR, CRP, and oxygen saturation level (SpO2) were obtained for all participants.

Behçet's disease assessment

Behçet's Disease Current Activity Form (BDCAF)

Patients were further categorized according to disease activity into active BD group and inactive BD group according to BDCAF. BDCAF is a tool to assess disease activity through data in the last four weeks before recruitment on a scale from 0 to 12, with scores > 4 considered an active disease [9].

Krause's Behçet's disease activity assessment

Total clinical severity score for BD was calculated as the sum of 1 point for each of the mild symptoms (Mouth ulcers, Genital ulcers, Skin lesions, Arthralgia, Recurrent headaches, Epididymitis, Mild gastrointestinal symptoms, Pleuritic pain, Superficial vein thrombosis), 2 points for each of the moderate symptoms (Arthritis, Deep vein thrombosis of the leg, Anterior uveitis and Gastrointestinal bleeding) and 3 points for each of the severe disease manifestations (Posterior/pan uveitis, retinal vasculitis, Arterial thrombosis or aneurysm, Neuro-Behçet and Intestinal perforation) [10].

Vasculitis damage index (VDI)

The VDI is comprised of 64 items of damage (grouped into 11 organ-based systems) defined by a consensus of experts to represent forms of damage in patients with systemic vasculitis. Behçet's disease is considered a systemic vascular disease. We aimed to study the relationship between VDI and the psychological impact on BD, sleep quality, and QOL [11, 12].

Assessment of anxiety and depression

Hamilton Anxiety Rating Scale (HAM-A)

Consists of 14 items and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where a score ≤ 17 indicates mild anxiety, 18–24 mild to moderate severity, and more than 24 moderate to severe anxiety [13].

Hamilton Depression Rating Scale (HAM-D)

The original HAM-D has 21 items, but scoring is based only on the first 17. Scores less than or equal to 7 indicates normal response, 8–13 mild depression, 14–18 Moderate, 19–22 severe, and more than 22 very severe depression [14, 15].

Assessment of sleep quality

Insomnia severity index (ISI)

The version intended to be completed by a clinician for subjective assessment of the patient's symptoms and consequences of insomnia. ISI contains seven domains assessing sleep-onset difficulties, sleep maintenance, sleep satisfaction, effect on daily functioning, impairment attributed to sleep problems, and distress associated with insomnia. Each item is rated on a 0–4 scale, and the total

score ranges from 0 to 28. A higher score suggests more severe insomnia [16, 17].

Epworth sleepiness scale (ESS)

Self-administered questionnaire assessing the likelihood of daytime sleepiness. Subjects describe how often they fall asleep or doze in specific situations on a scale of 0–3, with total scores ranging from 0 to 24. An ESS score ≥ 10 is indicative of subjective excessive daytime sleepiness. [18, 19].

Pittsburgh Sleep Quality Index (PSQI)

Self-reported questionnaire consists of a combination of Likert-type and open-ended questions to indicate how frequently participants experienced sleep difficulties over the past month. Scores for each question range from 0 to 3, with higher scores indicating more acute sleep disturbances. Consisting of 19 items, the PSQI measures several aspects of sleep, offering seven component scores and one composite score. The global PSQI score is then calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21 [20, 21].

Assessment of Health status and QoL

SF-36 QOL Scale was used to assess the quality of life among participants. SF-36 includes eight domains; physical functioning, social functioning, role limitations due to physical impairment, role limitations due to emotional problems, mental health, vitality, pain, and general health. The scale was assessed regarding the last four weeks. Scores of each category ranged from 0 to 100, where 0 represented the lowest QOL and 100 the highest QOL [22, 23].

Statistical analysis

SPSS program (version 20, IBM and Armonk, New York) used for data management. Mann–Whitney test was used for continuous data while Chi2-test compared nominal data. Different correlations of continuous variables in the study were assessed with spearman's correlation. The sample size was estimated by Open Epi V.3.01 computer program.

Results

In the current study, 80% of BD patients were males with a mean age of 34.7 ± 8.8. Demographic and baseline data for the BD and control groups showed no significant difference (Table 1). The BD group had significantly higher ESR and CRP compared to the control with significantly lower SpO2 readings. Anxiety and depression levels; were significantly higher among BD patients than in the control group (Table 2).

Table 1 Demographic data of Behçet's Disease patients and control group ($n = 60$)

	Behçet's Disease $N = 30$	Control Group $N = 30$	*P*-value
Gender			
Male	24 (80%)	25 (83.3%)	0.739
Female	6 (20%)	5 (16.7%)	
Age (years)			
Mean ± SD	34.7 ± 8.8	35.6 ± 8.1	0.683
Smoking			
Smoker	24 (80%)	23 (76.7%)	0.754
Non-smoker	6 (20%)	7 (23.3%)	
Education			
Literate	24 (80%)	26 (86.7%)	0.731
Illiterate	6 (20%)	4 (13.3%)	
Residence			
Urban	21 (70%)	20 (66.7%)	0.781
Rural	9 (30%)	10 (33.3%)	

Data expressed as frequency (percentage) and mean (SD). The *P*-value was significant if < 0.05

Table 2 Laboratory data, HAM-A, HAM-D, ISI, and ESS of Behçet's Disease patients and control group ($n = 60$)

	Behçet's disease $N = 30$	Control Group $N = 30$	*P*-value
CRP	17.27 ± 8.35	4.77 ± 2.22	< 0.001*
ESR	25.8 ± 10.54	11.4 ± 3.92	< 0.001*
SpO_2	97.33 ± 1.8	98.7 ± 0.52	< 0.001*
HAM-A	29.13 ± 14.13	6.83 ± 10.22	0.001*
HAM-D	27.67 ± 17.89	5.03 ± 3.76	< 0.001*
ISI	10.9 ± 7.27	3.03 ± 4.17	< 0.001*
ESS	8.20 ± 6.29	1.2 ± 2.73	< 0.001*

Data expressed as frequency (percentage), mean, and (SD). The *P*-value was significant if < 0.05. *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *SpO2* Saturation of peripheral oxygen, *HAMA-A* Hamilton anxiety scale, *HAMA-D* Hamilton depression rating scale, *ISI* insomnia severity index. *ESS* Epworth sleepiness scale

The BD group was associated with high level of sleep disturbance, including a high level of insomnia ($p < 0.001$) and daytime sleepiness ($p < 0.001$) compared to the control group (Table 2). All domains of PSQI were significantly higher for the BD group, with PSQI global score significantly higher compared to the control group (9.17 ± 4.31 vs. 1.77 ± 1.97; $p < 0.001$) (Table 3).

Patients with BD showed lower values regarding health status and QOL versus control with significantly lower values for physical functioning, Role-physical, Role-emotional, and general health ($p = 0.007$, $p = 0.008$, $p = 0.03$, and $p = 0.004$; respectively) (Table 4).

Table 3 Pittsburgh Sleep Quality Index for Behçet's Disease patients and control group ($n=60$)

PSQI	Behçet's disease $N=30$	Control Group $N=30$	*P*-value
Sleep Quality	1.77 ± 1.073	0.33 ± 0.479	< 0.001*
Sleep onset latency	1.97 ± 1.299	0.3 ± 0.702	< 0.001*
Sleep duration	1.63 ± 1.098	0.5 ± 0.731	0.001*
Sleep efficiency	1.7 ± 0.837	0.37 ± 0.049	0.010*
Sleep disturbance	1.13 ± 0.819	0.13 ± 0.346	< 0.001*
Sleep medications	0.2 ± 0.551	0.0 ± 0.0	< 0.001*
Daytime dysfunction	1.1 ± 0.759	0.13 ± 0.346	< 0.001*
PSQI global score	9.17 ± 4.31	1.77 ± 1.97	< 0.001*

Data expressed as frequency (percentage), mean, and (SD). *P* value was significant if < 0.05

PSQI Pittsburgh Sleep Quality Index

Table 4 Health status and quality of life assessment for Behçet's Disease patients and control group ($n=60$)

SF-36	Behçet's disease $N=30$	Control Group $N=30$	*P*-value
Physical functioning	70.67 ± 10.23	91.6 ± 3.7	0.007*
Role-physical	65.73 ± 10.37	90.73 ± 3.5	0.008*
Role-emotional	59.97 ± 8.18	89.97 ± 3.97	0.030*
Energy/ fatigue	57.77 ± 9.03	89.43 ± 3.59	0.156
Emotional wellbeing	58.53 ± 11.57	86.23 ± 7.3	0.317
Social functioning	57.2 ± 8.91	87.33 ± 6.05	0.136
Pain	57.33 ± 10.77	85.73 ± 8.01	0.315
General Health	56.5 ± 13.18	83.93 ± 8.91	0.004*

Data expressed as frequency (percentage), mean, (SD). The *P*-value was significant if < 0.05

SF-36 The Short Form (36) Health Survey, *Role-physical* Role limitations due to physical health, *Role-emotional* Role limitations due to emotional problems

Table 5 Demographic data of Behçet's Disease patients according to disease activity ($n=30$)

	Active BD $N=13$	Inactive BD $N=17$	*P*-value
Gender			
Male	11 (84.6%)	13 (76.5%)	0.672
Female	2 (15.4%)	4 (23.5%)	
Age (years)			
Mean ± SD	32.85 ± 7.95	36.12 ± 9.38	0.304
Smoking			
Smoker	13 (100%)	11 (64.7%)	0.024*
Non-smoker	0 (0%)	6 (35.3%)	
Education			
Literate	10 (76.9%)	14 (82.4%)	0.531
Illiterate	3 (23.1%)	3 (17.6%)	
Residence			
Urban	9 (69.2%)	12 (70.6%)	0.623
Rural	4 (30.8%)	5 (29.4%)	

Data expressed as frequency (percentage), mean, and (SD). *P* value was significant if < 0.05. *BD* Behçet's Disease, Active/inactive: using BDCAF (Behçet's Disease Current Activity Form)

Regarding clinical characteristics, active BD patients showed insignificant differences regarding age and gender (Table 5), with a significantly higher frequency of fever, fatigue, skin lesions, and pulmonary manifestations than the inactive group. Disease duration was longer among active BD (8.34 ± 5.1 vs. 5.85 ± 2.73; $p=0.029$) than the inactive group. All disease assessment scales were significantly higher among active BD patients, including BDCAF score, Krause's severity score, and VDI ($p<0.001$, $p<0.001$, and $p=0.002$, respectively) (Table 6).

Regarding anxiety and depression levels, they were significantly higher among active BD patients than in the inactive BD group. BD activity was associated with a high level of sleep disturbance, including a high level of insomnia ($p=0.008$) and daytime sleepiness ($p=0.007$) (Table 7). Domains significantly higher for the active BD group included sleep onset latency, sleep efficiency, and disturbed sleep ($p=0.017$, $p=0.033$, and $p=0.033$, respectively (Table 8). Behçet's disease

Table 6 Clinical characteristics and treatment of Behçet's Disease according to disease activity ($n=30$)

	Active BD $N=13$	Inactive BD $N=17$	*P*-value
Clinical data			
Fever	9 (69%)	1 (5%)	< 0.001*
Fatigue	11 (84%)	2 (11%)	< 0.001*
Weight loss	3 (23%)	1 (5%)	0.029*
Oral ulcer	5 (38%)	6 (35%)	0.579
Genital ulcer	5 (38%)	6 (35%)	0.579
.Skin lesion	1 (7%)	3 (17%)	0.041*
Arthritis/arthralgia	2 (15%)	1 (5%)	0.397
Ophthalmic	3 (23%)	3 (17%)	0.531
Vascular	3 (23%)	0 (0%)	0.070
GIT	1 (7%)	1 (5%)	0.068
Pulmonary	5 (38%)	1 (5%)	0.04*
Disease Duration	8.34 ± 5.18	5.85 ± 2.73	0.029*
BDCAF	4.15 ± 1.28	1.05 ± 0.66	< 0.001*
Clinical Severity score	5.62 ± 1.26	0.18 ± 0.39	< 0.001*
VDI	4.08 ± 2.13	0.53 ± 0.62	0.002*
Treatment			
Colchicine	3 (23%)	0 (0%)	0.07
Steroid	8 (61%)	5 (29%)	0.082
Azathioprine	8 (61%)	6 (35%)	0.145
Anti-TNF	1 (7%)	0 (0%)	0.433
Cyclophosphamide	1 (7%)	0 (0%)	0.433
No Medication	0 (0%)	6 (35%)	0.021*

Data expressed as frequency (percentage), mean, and (SD). *P* value was significant if < 0.05. BD: Behçet's Disease, Active/inactive: using BDCAF (Behçet's Disease Current Activity Form), *GIT* gastrointestinal tract, *BDCAF* Behçet's Disease Current Activity Form, *Clinical Severity score* Krause's Behçet's disease activity assessment, *VDI* Vasculitis damage index, *Anti-TNF* Anti-tumor necrosis factor

*Significant difference in *P*-value

Table 7 Laboratory data, HAM-A, HAM-D, ISI, and ESS of Behçet's Disease patients according to disease activity ($n=30$)

	Active BD $N=13$	Inactive BD $N=17$	P-value
CRP	25.15 ± 4.52	11.24 ± 4.68	< 0.001*
ESR	35.46 ± 6.66	18.41 ± 5.85	< 0.001*
SpO2	96.08 ± 2.02	98.29 ± 0.77	0.002*
HAM-A	42.69 ± 6.56	18.76 ± 8.15	< 0.001*
HAM-D	45.69 ± 6.04	13.88 ± 9.32	< 0.001*
ISI	12.92 ± 5.85	9.35 ± 8.02	0.008*
ESS	11 ± 3.83	6.06 ± 7.05	0.007*

Data expressed as frequency (percentage), mean, and (SD). *P* value was significant if < 0.05. *BD* Behçet's Disease, Active/inactive: using BDCAF (Behçet's Disease Current Activity Form), *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *SpO2* Saturation of peripheral oxygen, *HAMA-A* Hamilton anxiety scale, *HAMA-D* Hamilton depression rating scale, *ISI* insomnia severity index, *ESS* Epworth sleepiness scale

*Significant difference in *P*-value

Table 8 Pittsburgh Sleep Quality Index for Behçet's Disease patients according to disease activity ($n=30$)

PSQI	Active BD $N=13$	Inactive BD $N=17$	*P*-value
Sleep Quality	2.08 ± 1.03	1.53 ± 1.06	0.075
Sleep onset latency	2.23 ± 1.16	1.76 ± 1.39	0.017*
Sleep duration	1.77 ± 1.09	1.53 ± 1.12	0.097
Sleep efficiency	1.92 ± 0.76	1.53 ± 0.87	0.033*
Sleep disturbance	1.38 ± 0.87	0.94 ± 0.74	0.033*
Sleep medications	0.23 ± 0.59	0.18 ± 0.52	0.062
Daytime dysfunction	1.23 ± 0.72	1 ± 0.79	0.098
PSQI score	10.46 ± 3.97	8.18 ± 4.41	0.064

Data expressed as frequency (percentage), mean, and (SD). *P* value was significant if < 0.05. *BD* Behçet's Disease, Active/inactive: using BDCAF (Behçet's Disease Current Activity Form), *PSQI* Pittsburgh Sleep Quality Index

*Significant difference in *P*-value

Table 9 Health status and quality of life assessment for Behçet's Disease patients according to disease activity ($n=30$)

SF-36	Active BD $N=13$	Inactive BD $N=17$	*P*-value
Physical functioning	63.08 ± 10.88	76.47 ± 4.30	0.001*
Role-physical	58.77 ± 10.07	71.06 ± 6.3	0.002*
Role-emotional	56.31 ± 7.57	62.76 ± 7.69	0.030*
Energy/ fatigue	51.31 ± 8.41	62.71 ± 5.91	< 0.001*
Emotional wellbeing	48.46 ± 6.57	66.24 ± 8.06	< 0.001*
Social functioning	50.15 ± 5.11	62.59 ± 7.30	< 0.001*
Pain	50.08 ± 9.44	62.88 ± 8.24	0.001*
General Health	46.46 ± 5.30	64.18 ± 12.21	< 0.001*

Data expressed as frequency (percentage), mean, and (SD). The *P*-value was significant if < 0.05. *BD* Behçet's Disease, Active/inactive: using BDCAF (Behçet's Disease Current Activity Form), *SF-36* The Short Form (36) Health Survey. *Role-physical* Role limitations due to physical health, *Role-emotional* Role limitations due to emotional problems

*Significant difference in *P*-value

activity was associated with significantly lower values regarding the SF-36 QOL scale (Table 9).

In this study, Krause's BD activity assessment, referred to as clinical severity score, showed a significantly positive correlation with anxiety, depression, VDI, and BDCAF ($P<0.001$) (Table 10), an insignificant correlation with PSQI (Table 11) while showing significantly negative correlation with SF-36 QOL domains (Table 12).

The VDI was associated with a significantly positive correlation with anxiety, depression, disease severity, and BDCAF ($P=0.001$, $p=0.002$, $P<0.001$ and $P<0.001$; respectively) (Table 10), insignificant correlation with PSQI (Table 11) while showed significantly negative correlation with almost all SF-36 QOL domains (Table 12).

BDCAF was associated with a significantly positive correlation with anxiety, depression, disease severity, VDI ($P<0.001$), and ESS ($p=0.048$) (Table 10), with an insignificant correlation with PSQI (Table 11) while showing

Table 10 Correlation of disease duration, disease severity, VDI, and BDCAF with other parameters for Behçet's Disease group ($n=30$)

	Disease Duration		Clinical Severity Score		VDI		BDCAF	
	r	*P*	r	*P*	r	*P*	R	*P*
Age	0.461	0.010*	-0.087	0.649	-0.019	0.922	-0.118	0.053
ESR	0.236	0.209	0.817	< 0.001*	0.708	< 0.001*	0.831	< 0.001*
CRP	0.396	0.030*	0.807	< 0.001*	0.633	< 0.001*	0.845	< 0.001*
SpO2	-0.484	0.007*	-0.540	0.002*	-0.353	0.070	-0.571	0.001*
HAM-A	0.255	0.137	0.791	< 0.001*	0.574	0.001*	0.828	< 0.001*
HAM-D	0.236	0.210	0.740	< 0.001*	0.546	0.002*	0.819	< 0.001*
ISI	0.017	0.929	0.174	0.250	0.273	0.144	0.214	0.256
ESS	0.030	0.876	0.359	0.182	0.164	0.368	0.364	0.048*
Disease duration	––	––	0.267	0.153	0.233	0.214	0.288	0.122
Clinical severity	0.267	0.153	––	––	0.768	< 0.001*	0.935	< 0.001*
VDI	0.233	0.214	0.786	< 0.001*	––	––	0.816	< 0.001*
BDCAF	0.288	0.122	0.935	< 0.001*	0.816	< 0.001*	––	––

Correlation for variables in the study was determined with spearman's correlation. r: Correlation coefficient rho. *P*-value: was significant if < 0.05. *ESR*: erythrocyte sedimentation rate, *CRP* C-reactive protein, SpO_2 Oxygen saturation, *MMSE*: Mini-Mental state examination, *HAM-A* Hamilton anxiety rating scale, *HAM-D* Hamilton depression rating scale, *ISI* insomnia severity index, *ESS* Epworth sleepiness scale, *Clinical Severity score* Krause's Behçet's disease activity assessment, *VDI* Vasculitis damage index, *BDCAF* Behçet's Disease Current Activity Form

*Significant difference in *P*-value

Table 11 Correlation of disease duration, disease severity, VDI, and BDCAF with PSQI components for Behçet's Disease group ($n=30$)

	Disease duration		Clinical Severity Score		VDI		BDCAF	
	r	*P*	R	*P*	r	*P*	r	*P*
Sleep Quality	0.112	0.557	0.212	0.261	0.193	0.307	0.266	0.155
Sleep onset latency	0.162	0.393	0.191	0.311	0.261	0.163	0.211	0.263
Sleep duration	0.065	0.733	0.043	0.822	0.163	0.389	0.102	0.593
Sleep efficiency	-0.007	0.972	0.118	0.534	0.177	0.349	0.166	0.380
Sleep disturbance	0.092	0.629	0.240	0.200	0.200	0.290	0.252	0.178
Sleep medications	-0.061	0.774	-0.003	0.978	0.031	0.871	0.090	0.635
Daytime dysfunction	-0.036	0.849	0.171	0.365	0.128	0.500	0.179	0.343
PSQI score	0.141	0.459	0.180	0.340	0.278	0.137	0.245	0.192

Correlation for variables in the study was determined with spearman's correlation. *r* Correlation coefficient rho. *P*-value: was significant if < 0.05. *Clinical Severity score* Krause's Behçet's disease activity assessment, *VDI* Vasculitis damage index, *BDCAF* Behçet's Disease Current Activity Form, *PSQI* Pittsburgh Sleep Quality Index

Table 12 Correlation of disease duration, disease severity, VDI, and BDCAF with SF-36 domains for Behçet's Disease group ($n=30$)

	Disease Duration		Clinical Severity Score		VDI		BDCAF	
	r	*P*	R	*P*	r	*P*	r	*P*
Physical functioning	-0.184	0.436	-0.704	< 0.001*	-0.534	0.002*	-0.735	< 0.001*
Role-physical	-0.224	0.235	-0.546	0.002*	-0.427	0.019*	-0.633	< 0.001*
Role-emotional	0.070	0.712	-0.277	0.139	-0.238	0.206	-0.387	0.035*
Energy/ fatigue	-0.262	0.162	-0.547	0.002*	-0.527	0.003*	-0.603	< 0.001*
Emotional wellbeing	-0.229	0.223	-0.729	< 0.001*	-0.687	< 0.001*	-0.753	< 0.001*
Social functioning	-0.015	0.938	-0.618	< 0.001*	-0.550	0.002*	-0.718	< 0.001*
Pain	-0.333	0.072	-0.549	0.002*	-0.414	0.023*	-0.655	< 0.001*
General Health	-0.172	0.364	-0.746	< 0.001*	-0.655	< 0.001*	-0.759	< 0.001*

Correlation for variables in the study was determined with spearman's correlation. *r* Correlation coefficient rho. *P*-value: was significant if < 0.05. *Clinical Severity score* Krause's Behçet's disease activity assessment, *VDI* Vasculitis damage index, BDCAF: Behçet's Disease Current Activity Form, *SF-36* The Short Form (36) Health Survey. *Role-physical* Role limitations due to physical health, *Role-emotional* Role limitations due to emotional problem

a significantly negative correlation with all SF-36 QOL domains (Table 12).

Discussion

Worldwide the prevalence of BD is estimated to be 5.2/per 100,000 population [24]. BD is common in Asia and the Mediterranean Sea region and is considered the most common vascular disease in Egypt [25]. Sex predominance is still a matter of debate in the literature. Still, it has been reported in many studies that the course of the disease is more aggressive in the male gender [26]. The disease is expected in the third and fourth decades with rare occurrence in children and adults over 50 years [27].

Behçet's disease is a chronic multisystem disorder with different systemic manifestations. Oral and genital ulcers represent the most common clinical manifestations of BD; reported in 50 -85% of patients [28, 29]. Arthritis and arthralgia are common in up to 50% of BD patients [30]. Ophthalmic affection is common in about 70% in males and 30% in females [31]. Neurological affection is common in 5–10% of BD patients with male predominance and a recognized latency period of about five years from initial diagnosis [32].

Gastrointestinal (GIT) manifestation is common in East Asia; about 50% of patients in Japan have GIT symptoms, while in the Mediterranean region, GIT involvement is infrequent [33]. Zhang et al. (2015) enrolled 119 patients with BD, and 14% had pulmonary involvement. All patients had venous thromboembolism; a pulmonary artery aneurysm was detected in 6 patients; 5 had pulmonary parenchymal affection, and 3 had isolated pulmonary embolism [34].

In the current study, we observed a male predominance of 80% with a mean age of 34.7 ± 8.8; the most commonly observed symptoms were fatigue (43%), fever (33%), and oral and genital ulceration (36%). The mean duration of the disease was 8.34 ± 5.18 in the active BD vs. 5.85 ± 2.73 in the inactive group, with mean BDCAF 4.15 ± 1.28 vs. 1.05 ± 0.66. The severity index of the active BD group was 5.62 ± 1.26 compared to 0.18 ± 0.39 and VDI 4.08 ± 2.13 versus 0.53 ± 0.62 for the inactive BD group.

Regarding VDI, Elgengehy et al. (2021) studied the impact of VDI on the course and severity of BD in relation to clinical manifestations and comorbidities. They observed a mean VDI of 3.5 ± 1.8, which was significantly associated with total thrombosis, neurological manifestation, and impaired vision this was correlated to the use of immunosuppressive treatment, especially cyclophosphamide, and anti-TNF and was significantly correlated with age and disease duration [12].

BD pathophysiology is complex, with genetic and altered immune system responses behind the different systemic manifestations observed during BD. Family history is common in up to 10% of patients [35].

Vascular involvement is the key factor for the systemic manifestation of Behçet's disease, with venous involvement predominance over arterial involvement. The arterial aneurysm is also a common presentation [36].

HLA-B51/B5 carriers are at more risk of developing BD than others; the role of HLA-B51/B5 in the development of BD manifestations is through the presentation of CD8 + T cells and Killer immunoglobulin-like receptors of NK cells [37]. In other studies, there was a significant reduction in interleukin 10 (IL10) in BD patients, another polymorphism in the IL-23R gene is detected, and among possible etiological mechanisms are the association of BD with CCR1 and KLRC4 Chemoreceptors which regulate the release of IL-12 and IL-23 [38].

The heterogenicity of the immunological profile and the difference in clinical manifestation is associated with the emergence of 4 phenotypes of BD; mucocutaneous, superficial and deep venous thrombosis, ophthalmic, and articular type.

Anxiety and depression are among the most common neuropsychiatric manifestations of BD, occurring in around 86% of patients [7]. The pathogenesis of anxiety and depression in BD is unclear and may be related to disease progression, functional decline, CNS affection, and use of corticosteroid drugs [39]. However, a combined interaction between acute stress in the course of the disease and alteration in the immune system could be an acceptable explanation.

In our study, we observed high levels of anxiety and depression among BD patients compared to healthy controls. Also, levels of anxiety and depression were significantly higher among the active disease group.

In concomitant with our results, Taner and colleagues (2007) compared anxiety and depression in 2 groups of BD; they enrolled 112 BD patients and 95 BD patients with psoriasis using Beck's depression & anxiety inventory test. More than 50% of patients of both groups had anxiety and depression, with an increased risk of 12 folds in BD patients with a disease course of more than three years [40]. Also, Monastero et l., (2004) enrolled 26 BD patients finding that depression and anxiety were more in the diseased group than the control group [39].

In agreement with our study, Çalıkoglu et al. enrolled 23 BD patients with psoriasis finding depression and anxiety were more in the diseased group than the control group [41]. In a study of 155 BD patients (86 males, 69 females with a median age of 37) compared to 107 control using Hospital Anxiety and Depression (HADS) scale; 76.7% had active disease, 43.2% of patients exhibited anxiety, and 40.6% suffered from depression, anxiety, and depression were significantly higher among active

disease patients with positive correlation with ESR [42]. Also, anxiety and depression were higher in patients with high Multidimensional Assessment of Fatigue (MAF) scores, and there was no significant correlation with different symptoms.

Yazmalar et al. (2017), studying 112 BD patients and 67 control participants using HADS, revealed that anxiety and depression were higher in BD patients than in controls. PSQI with all components and Global score was significantly higher in BD patients than in control (7.91 ± 4.65 vs. 4.58 ± 2.78, $p = 0.001$) [4].

Disturbance of sleep patterns in patients with BD is related to variable systemic affection, anxiety, depression, limitation of activity, and medical treatment. Many sleep disorders have been reported in BD patients, including obstructive sleep apnea syndrome (OSAS), concerning the increased serum level of leptin, adiponectin, and resistin [43]. Also, Tascilar et al. (2012) reported restless leg syndrome in patients with BD [44].

Some BD manifestations as genital ulceration, were reported to be associated with difficulty in initiating sleep in BD patients and increasing rapid eye movement (REM) sleep. Arthralgia was reported to be negatively correlated with REM sleep latency [45]. Total sleep time and time in bed were negatively correlated with ophthalmic manifestations of BD [46].

We observed that patients self-reported a high degree of insomnia and daytime dysfunction among BD patients compared to control participants ($p < 0.001$). All domains of PSQI, including sleep quality, duration, efficiency, disturbance, drugs, sleep onset latency, and daytime dysfunction, were significantly higher among the BD group. Active disease assessed using BDCAF was associated with higher scores of ISI, ESS, and selective domains of PSQI, including sleep efficiency, disturbance, and sleep onset latency.

Tascilar et al. assessed the relationship between sleep disorders in Behçet's disease in relation to fatigue and QOL; they enrolled 51 BD patients and 21 healthy controls, reporting a mean HAM-D score of 10.7 ± 8.6 and mean HAM-A score of 14.98 ± 11.9 in patients with BD which was significantly higher than control, respectively. Regarding sleep disturbance, insomnia was the most common presentation in 50.9% of patients, RLS in 35.3%, and there was a significant difference in all components of PSQI [44].

Koca et al. (2015) studied the relationship between BD activity, depression, and sleep quality; enrolled 40 BD patients and 30 healthy controls, revealing a significant positive correlation between Beck's depression inventory (BDI) and BDCAF ($r = 0.559$, $p = 0.001$), and also significant positive correlation BDI and PSQI ($r = 0.617$, $p = 0.001$). The study also revealed a significant difference between the BD group and control regarding BDI score (12.4 ± 7.62 vs. 5.1 ± 1.42, $p = 0.012$) and regarding PSQI global score (6.4 ± 4.44 vs. 3.1 ± 1.33, $p = 0.02$) [47].

Lee et al. (2017), studying the association of sleep quality in BD patients with disease activity, depression, and QOL, enrolled 100 BD patients; according to PSQI using cut off value of 9; patients were grouped into good sleepers (58 patients) and poor sleepers (42 patients). Poor sleep was observed in patients with higher BDI scores and BDCAF. Among the 7 PSQI components, daytime dysfunction was higher in patients with high disease activity ($p = 0.03$). Total PSQI scores were strongly correlated with BDCAF, BDI-2, Behçet's disease quality of life measure (BD QOL), and pain VAS score ($p = 0.02$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively) [48].

Many etiological factors have been reported to decrease quality of life (QoL) in patients with BD; the chronicity of the disease and its relapsing course with deterioration of physical and mental functions can explain that finding [49].

In a study of 123 BD patients vs. 123 healthy controls to assess QOL in patients of BD in relation to symptoms and disease activity using BDCAF and VDI to assess severity, the SF-36 QOL scale was lower in all domains among the BD group with a significant difference in general health, vitality, and physical health domains. Also, BDCAF was associated with a significant negative correlation with all domains of the SF-36 QOL scale [50].

Zulfiqar et al. (2020) studied the correlation between the disease activity of BD and the psychological condition of patients; they enrolled 102 patients; oral ulceration was found in the initial assessment in 69% of patients, genital ulcers in 29% of patients, arthralgia in 53%. They assessed for each unit increase in Behçet's Disease Activity Index (BDAI); the decline or increase in; the European Quality of Life Five Dimensions Five Level scale (EQ-5D-5L) was −0.01, Work and Social Adjustment Scale (WSAS) was −0.02, Patient Health Questionnaire-9 (PHQ-9) was 0.14, General Anxiety Disorder-7 (GAD-7) was 0.41, Warwickshire-Edinburgh Mental Wellbeing Scale (WEMWBS) was −0.53 [51].

Ertam et al. enrolled 195 patients and 195 control SF-36 and WHO QOL-100 scale scores. The overall SF-36 and WHOQOL-100 scale scores, as well as their domains, were significantly lower in BD patients. General health and role-physical domains of SF-36 showed significantly negative linear correlations with Krause's clinical severity score [52].

Conclusion

Based on the evaluation of HAM-A, HAM-D, and SF-36 scores, levels of anxiety and depression are high in BD patients; quality of life is impaired in BD, and these

impairments are related to disease activity and severity. Sleep quality also is markedly affected in BD, with some domains affected more than others. These results highlight the importance of managing psychological comorbidities experienced by patients and taking measures to improve sleep quality and quality of life.

Limitations of the study

Limited sample of selected patients was recruited in a single-center stud. Also, the need for specific diagnostic tools, including sleep study evaluation of the study population, may limit the generalization of the results.

Abbreviations

BD	Behçet's disease
BDAI	Behçet's Disease Activity Index
BDCAF	Behçet's Disease Current Activity Form
BDI-II	Beck Depression Inventory II
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
ESS	Epworth sleepiness scale
GIT	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton's anxiety rating scale
HAM-D	Hamilton's depression rating scale
IL	Interleukin
ISI	Insomnia severity index
MAF	Multidimensional Assessment of Fatigue score
OSAS	Obstructive sleep apnea syndrome
PSQI	Pittsburgh Sleep Quality Index
QOL	Quality of life
REM	Rapid eye movement
SF-36 QOL	Short Form 36 Quality Of Life Scale
SpO2	Saturation of peripheral oxygen
VDI	Vasculitis damage index
WHOQOL	World Health Organization Quality of Life

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Authors' contributions

AMS, EAT and WGE conception and design. SMS, EAT, SF and NMG: data collection. AMS and WGE: statistical analysis. AMS, AARMH, SF and WGE: medical writing. All authors revised the manuscript. The author(s) read and approved the final manuscript.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board and ethical committee of Faculty of Medicine- Assiut University in compliance with the Helsinki Declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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