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ORIGINAL ARTICLE

Behçet's Syndrome Overall Damage Index performance and validation in an adult Egyptian cohort

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ABSTRACT

Objectives: This study aimed to evaluate the performance of the Behçet's Syndrome Overall Damage Index (BODI) in an adult Egyptian cohort.

Patients and methods: This longitudinal retrospective cohort study included 282 adult patients (233 males, 49 females; mean age: 35.3±8.7 years; range, 16 to 66 years) with Behçet's disease (BD) between January 1980 and December 2022. BODI was assessed regarding construct validity, sensitivity to change, and intra- and inter-rater reliability. The ability of BODI to discriminate between activity and damage was evaluated. Its performance in another vasculitis syndrome was assessed in 12 patients with antineutrophil cytoplasmic antibody-associated vasculitis.

Results: BODI captured more damage items compared to the Vasculitis Damage Index (VDI). BODI scores were not correlated with disease activity and had poor performance in other vasculitides. BODI had a trend of progressive increment over time. It showed consistence when reassessed by the same rater and by different raters. Some damage items in the study cohort were lacking in BODI.

Conclusion: BODI is more comprehensive compared to VDI. It shows good face, construct, and discriminant validity. It is sensitive to change and has good intra- and inter-rater reliability. Newer versions of BODI are recommended to increase score comprehensiveness.

Keywords: Behçet's disease, Behçet's Syndrome Overall Damage Index, damage assessment, outcome assessment, validation.

Vasculitides encompass a heterogeneous group of immune-mediated disorders characterized by inflammation of the blood vessel wall with subsequent destruction, thrombosis, stenosis, and aneurysm formation.[1] Despite sharing a common pathology, different types of vasculitides could be differentiated based on epidemiological, clinical, laboratory, imaging, and pathological features.[2]

Behçet's disease (BD) is a unique disorder that shares features with vasculitides and spondyloarthropathies.[3] Moreover, it stands halfway between the autoimmune and the autoinflammatory syndromes.[4] The highest prevalence of BD is observed along the Silk Road.[5] In Egypt, it is considered the most common type of primary vasculitis in adults.[6] The underlying disease pathogenesis includes blood vessel inflammation and neutrophil hyperactivity;[7] hence, organ system involvement could be attributed to vascular or parenchymal insult.[8] BD has specific tropism to the mucocutaneous, musculoskeletal, ocular, neurological, and cardiovascular systems.[9]

With advances in treatment, the prognosis of vasculitides has improved significantly. However, although this improvement allows patients to survive longer, damage accrual and considerable morbidity frequently ensue.[10]

In patients with rheumatic diseases, damage is defined as any irreversible structural or functional abnormality of an organ system that could be induced by the disease or its treatment.[11] Damage is common in vasculitides, as these are life- or organ-threatening relapsing diseases. Being the cornerstone of treatment of vasculitis, glucocorticoids and immunosuppressive drugs could add to the patient's damage owing to their high-risk profile.[12] Assessment of damage allows the prediction of the patient's prognosis, guides the assessment of drug efficacy in clinical

trials, and helps avoidance of unnecessary and potentially harmful treatment.[11] According to the OMERACT (Outcome Measures in Rheumatology) recommendations, assessment of damage should be a part of the core set measures for the assessment of patients with rheumatic diseases.[13]

The Vasculitis Damage Index (VDI) was developed to longitudinally assess systemic vasculitis-associated damage.[14] A controversy was raised among experts as to whether VDI could apply to all types of vasculitides or if disease-specific assessment tools should be used instead.[15] It is noteworthy that the population used for the development and validation of the VDI did not adequately represent BD;[14] hence, VDI lacks several damage items that are characteristic of BD. Based on the aforementioned observations, VDI is expected to underestimate damage in BD patients. Therefore, the development of a disease-specific damage index appears to satisfy an urgent need.

The Behçet's Syndrome Overall Damage Index (BODI) was recently developed as a damage assessment tool specific for BD. Most of the patients involved in the cohort used for BODI development and validation were of European origin.[16] As phenotypic expression of BD shows ethnic variability,[17-22] the performance and validity of BODI should be assessed in different populations. Hence, this study aimed to evaluate the performance and validity of BODI in a cohort of adult Egyptian patients.

PATIENTS AND METHODS

In this longitudinal retrospective cohort study, patients were recruited from the archive of the outpatient clinic of the Rheumatology and Rehabilitation Department at the Kasr Al-Ainy Hospital, Cairo University. All available files were reviewed spanning the period between January 1980 and December 2022. Patients were classified/reclassified according to the 2006 International Study Group Criteria for BD.[23] Patients with a follow-up duration of less than six months were excluded. The study included 282 patients (233 males, 49 females; mean age: 35.3±8.7 years; range, 16 to 66 years), while 378 were excluded due to a short follow-up duration. Among the included patients, 180 were drawn from an Egyptian vasculitis cohort.[6] Medical files were reviewed, and data were retrospectively collected. The study protocol was approved by the Cairo University Hospitals, Faculty of Medicine Ethics Committee (date 24.12.2022, no: N-114-2022). Written informed consent was obtained from all interviewed participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

In the study cohort, both VDI and BODI were calculated at baseline and last visits, as well as during the follow-up period (every three months for VDI and every six months for BODI). Moreover, the score given to each domain of BODI and VDI at the last visit was calculated.

BODI was evaluated regarding the face validity, feasibility, and construct validity. The face validity of the BODI was assessed regarding the comprehensiveness, conciseness, and applicability. The feasibility, easiness, and time required to fill in the index were considered as well. The scores of the different domains of BODI were compared to their corresponding scores of VDI to demonstrate the organ systems that were best represented in BODI.

For the assessment of discriminant validity, the BODI score at the last visit was compared with the 2006 Behçet's Disease Current Activity Form (BDCAF) score,[24] an activity assessment tool developed from the 12 items of the original BDCAF[25] using dichotomous variables. Moreover, BODI and VDI scores were calculated at the last visit in a group of patients (n=12) with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, classified using the 1990 American College of Rheumatology classification criteria[26,27] and the Chapel Hill Consensus Conference definitions,[1] to evaluate its performance in another vasculitis syndrome.

The sensitivity to change was assessed. The BODI at the last visit was recalculated in a subgroup of patients with BD by the same rater to assess the intra-observer reliability and by a different rater to assess the inter-observer reliability.

Furthermore, the relationship between the Arabic version of the Health Assessment Questionnaire-Disability Index (HAQ-DI),[28] the 36-item Short-Form Survey (SF-36),[29] BODI, and VDI at the last visit in 45 patients was assessed to determine whether these indices could reflect damage related to physical impairment and poor quality of life.

Sample size calculation

Sample size calculation was conducted using the calculator developed by Naing et al. using Microsfot Excel.[30] In the original study of BODI development and validation, 56% of patients had a BODI score ≥1.[16] Using an expected proportion of 50%, a 95% confidence interval, an estimated population size of 228 and, precision (d) of 0.05, the required sample size was calculated as 143 patients using the finite population correction.

Statistical analysis

Data were analyzed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequency and percentage. Numerical variables were presented as mean ± standard deviation (SD). A paired sample t-test was used for comparing paired numerical data. Correlations were done using Spearman's rank correlation coefficient. The intraclass correlation coefficient was calculated to assess the intra- and inter-rater reliability. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

The demographic characteristics and clinical phenotypes of the study cohort are shown in Table 1. The mean follow-up duration was 2.5±3.5 years (range, 0.5 to 18 years).

Table 1. Demographic characteristics and clinical phenotypes of BD patients (n=282)

Characteristics	n	%	Mean±SD
Age at onset (year)			25.2±7.4
Disease duration (year)			8.3±6.7
Follow-up duration (year)			2.5±3.5
Sex			
Male	233	82.6	
Female	49	17.4	
Constitutional	45	16.1	
Mucocutaneous	276	98.6	
Musculoskeletal	60	21.4	
Ocular	187	66.8	
Peripheral venous disease	76	27.1	
Peripheral arterial disease	15	5.4	
Aortic involvement	6	2.1	
Vena caval thrombosis	18	6.4	
Cardiac	9	3.2	
Pulmonary	27	9.6	
Neurological	65	23.2	
Gastrointestinal	8	2.9	
Renal	0	0	

SD: Standard deviation.

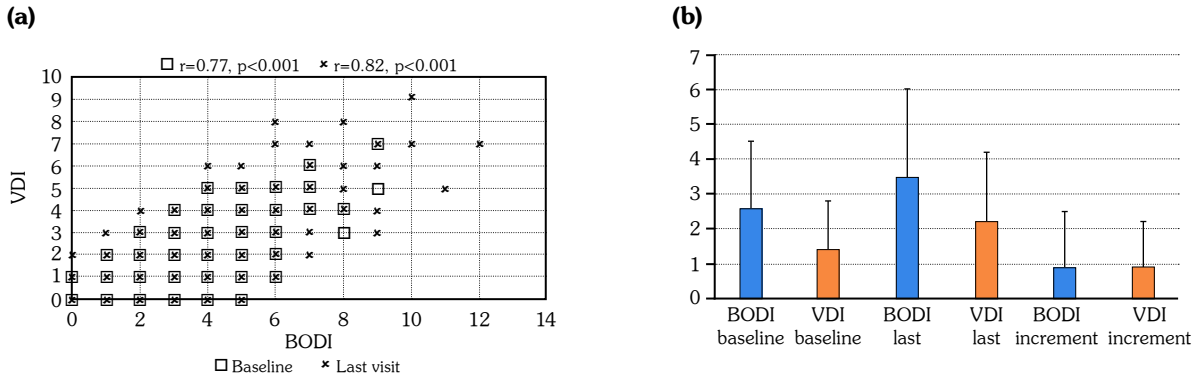

Figure 1. **(a)** Correlation between BODI and VDI scores at baseline and last visit. Spearman's rank correlation coefficient was used. **(b)** Comparison between BODI and VDI scores at baseline and the last visit, as well as between their values of increment. A paired sample t-test was used.

VDI: Vasculitis Damage Index; BODI: Behçet's Syndrome Overall Damage Index.

Construct validity

BODI scores at baseline and the last visit were significantly correlated with the corresponding VDI scores (r=0.77, p<0.0001 at baseline; r=0.82, p<0.0001 at the last visit; Figure 1a). The BODI score was significantly higher than the corresponding VDI value at the first and last visits (p<0.001 at baseline and last visits); however, the values of the increment of both scores were comparable (Figure 1b). At baseline, 178 (63.1%) patients had a VDI value >1 as opposed to 266 (94.3%) patients with a BODI value ≥1 (p<0.001). At the last visit, 213 (75.5%) patients had a VDI value ≥1 versus 271 (96.1%) patients with a BODI value >1 (p<0.001). The frequencies of the different values of BODI and VDI scores at the last visit are shown in Figure 2a, while the frequencies of the different values of increment of both indices are illustrated in Figure 2b.

To determine the organ systems that were best represented in BODI, the scores of the different domains of BODI at the last visit were compared with the corresponding ones of VDI. BODI had significantly higher scores for the mucocutaneous, ocular, neurological, and vascular domains than VDI (Figure 3).

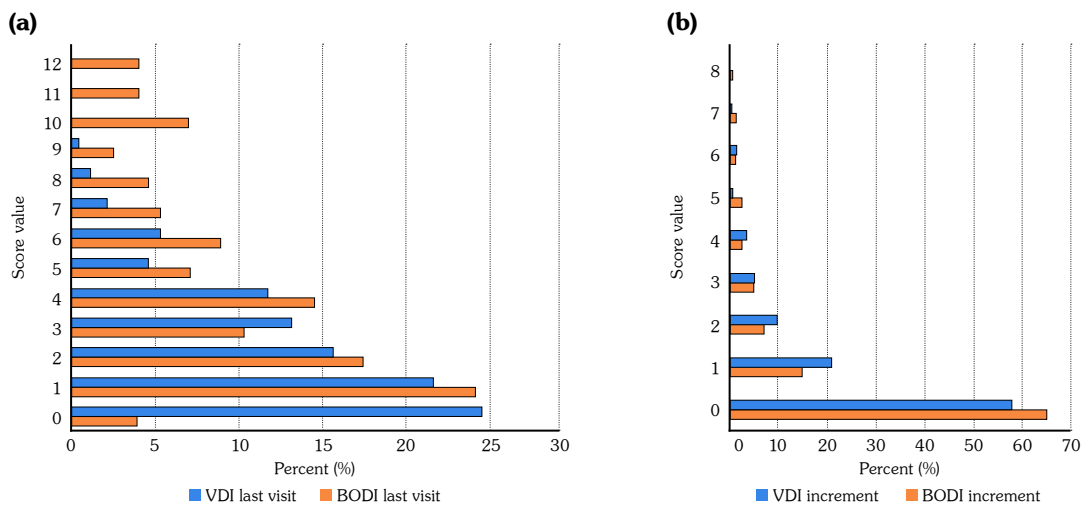

Figure 2. **(a)** Frequency of the different values of BODI and VDI scores at the last visit, and **(b)** the different values of increment of both indices.

VDI: Vasculitis Damage Index; BODI: Behçet's Syndrome Overall Damage Index.

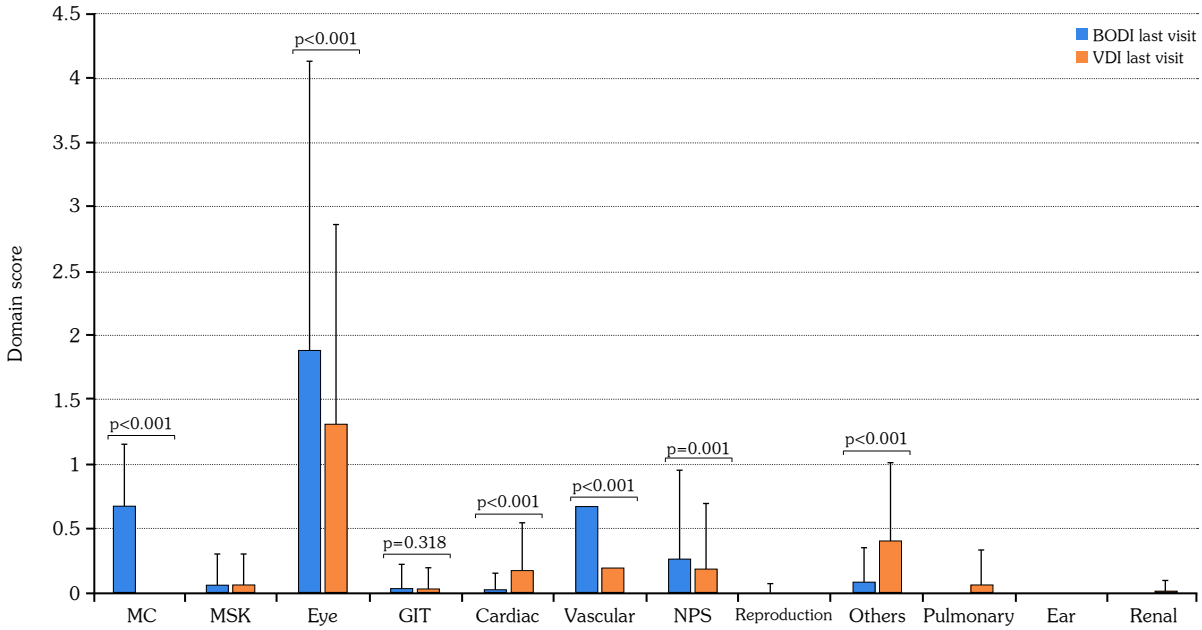

Figure 3. The comparison between the scores of the different domains of BODI and VDI at the last visit. A paired sample t-test was used.

VDI: Vasculitis Damage Index; BODI: Behçet's Syndrome Overall Damage Index.

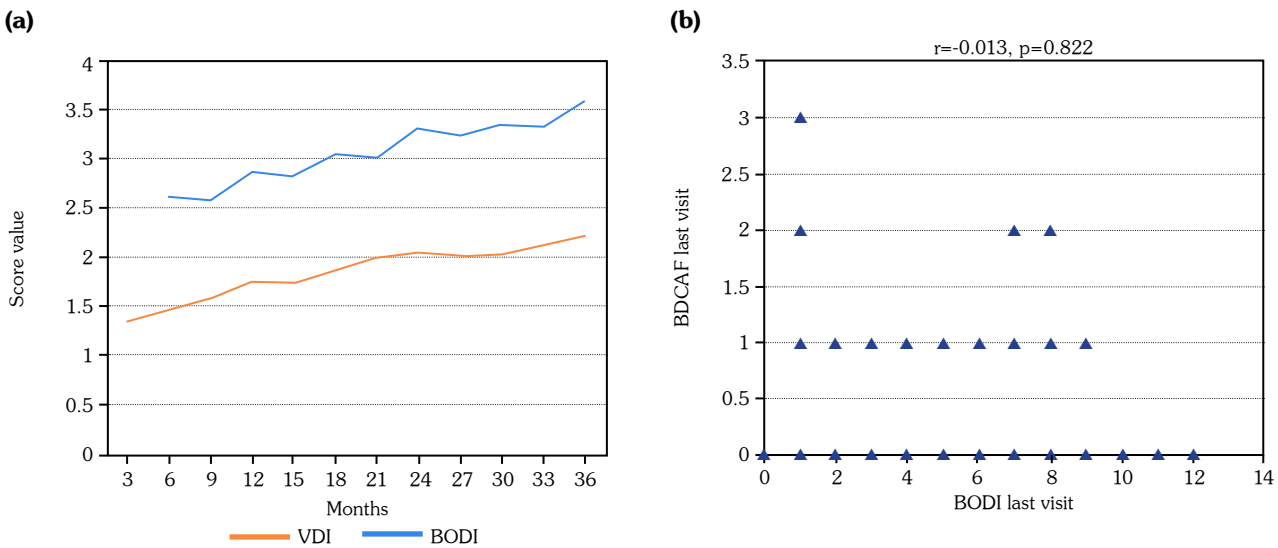

Figure 4. **(a)** The trend of change of BODI and VDI scores. **(b)** Correlation between BODI and the 2006 BDCAF at the last visit. Spearman's rank correlation coefficient was used.

VDI: Vasculitis Damage Index; BODI: Behçet's Syndrome Overall Damage Index.

Trend of change

The trend of change of both scores during the follow-up period is shown in Figure 4a. During the follow-up period, 199 (70.6%) patients showed a progressive increment of VDI by ≥1 point as opposed to 99 (35%) patients for BODI (p=0.001).

Discriminant validity

There was no correlation between BODI and BDCAF scores at the last visit (Figure 4b).

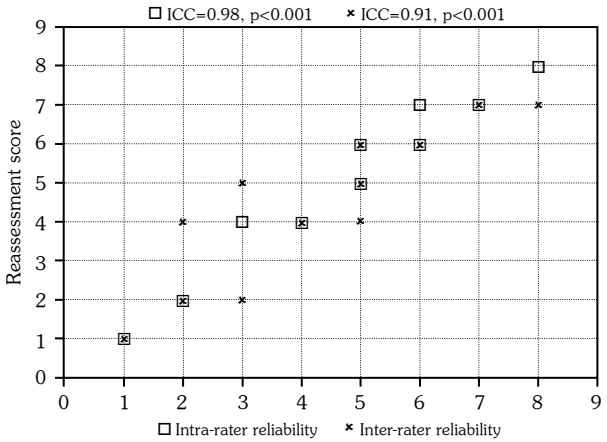

Figure 5. Intraclass correlation coefficient for intra- and inter-rater reliability of BODI at the last visit (n=20).

ICC: Intra-class correlation coefficient; BODI: Behçet's Syndrome Overall Damage Index.

When 12 patients with ANCA-associated vasculitis were assessed at the last visit using BODI and VDI, the mean BODI (1.3±1.8) was significantly lower than that of VDI (2.8±1.6), with a p-value of 0.007.

Intra- and inter-rater reliability

Intra- and inter-rater reliability of BODI was assessed in 20 patients with BD. The results are presented in Figure 5.

Correlation with HAQ-DI and SF-36

HAQ-DI and SF-36 were not correlated with BODI (p=0.242 and p=0.751, respectively) or VDI (p=0.125 and p=0.698, respectively) at the last visit. However, HAQ-DI was correlated with the BDCAF (p=0.044, r=–0.302), but there was no correlation between BDCAF and SF-36 (p=0.185).

DISCUSSION

Concerning BODI construct validity, there was a strong positive correlation between BODI and VDI scores at baseline and the last visit. However, the mean BODI scores at baseline and the last visit were significantly higher than the corresponding VDI scores. When the scores of the different domains of BODI at the last visit were compared with their corresponding scores of VDI, BODI had significantly higher scores in the mucocutaneous, ocular, neurological, and vascular systems domains, reflecting the greater sensitivity of BODI in determining damage related to organ systems commonly affected in BD.

In the original validation cohort of BODI, the VDI score for the mucocutaneous domain was higher than that of BODI. The authors explained this finding by noting that mucosal ulcers were scored in VDI but not in BODI, resulting in higher VDI scores.[16] On the contrary, the score for the mucocutaneous domain, in the current study, was higher with BODI compared to VDI. This could be explained by the high frequency of scarring genital ulcers in the study cohort. Notably, the presence of oral ulcers in the study cohort was scored using BDCAF but not BODI or VDI, as oral ulcers are a self-limited manifestation of disease activity rather than damage, tending to heal without significant scarring.[31]

Uveitis is one of the most common manifestations of BD, with blindness eventually developing in 16 to 25% of patients, making it a leading cause of disease morbidity.[32,33] Although individual items in BODI are not weighted, linking the item "blindness" to "visual impairment" increases the weight given to "blindness" as a reflection of end organ damage. The protean abnormalities of the anterior and posterior eye segments reported in BD are included in BODI but not in VDI, adding to the weight of the ocular domain in BODI. Moreover, unlike VDI, BODI considers legal blindness[34] for scoring the item "blindness" rather than complete loss of vision (no perception of light) as in VDI.

Although the neurological components in BODI and VDI are almost similar, the addition of the item "motor/sensory disturbance" to BODI captures the various presentations of motor/sensory disturbances associated with parenchymal involvement characteristic of BD, including cerebellar and brainstem manifestations.[35] This results in a higher score for the neurological domain in BODI.

A unique feature of BD among other vasculitides is that it can affect vessels of any size and type. Venous involvement is more common than arterial involvement, and peculiar sites such as dural sinuses, vena cava, hepatic veins, aorta, and pulmonary artery could be

affected. Aneurysms carry a worse prognosis and are more common than arterial stenosis and thrombosis.[36] Arterial stenosis and thrombosis are well represented in VDI. Aneurysms, however, are not included, and venous involvement is represented by only one item that does not take into consideration recurrence and peculiar sites of involvement in BD. On the other hand, the vascular domain of BODI is well adapted to the peculiar vascular involvement of the disease.

The cardiovascular domain of BODI was inferior to its counterpart in VDI. This could be explained by the lack of an item for "systemic hypertension," a common complication in our study cohort, in BODI. Moreover, this could explain the lower amplitude of increment of BODI during the follow-up period compared to VDI.

The gastrointestinal manifestations were not adequately represented in our study cohort being more prevalent in certain ethnicities, such as Far Eastern individuals.[37] Assessing the validity of BODI in other ethnicities will help evaluate the performance of domains not adequately represented in our cohort.

Regarding discriminant validity, the lack of a correlation between the mean BODI and BCDAF scores at the last visit signifies the ability of BODI to differentiate damage from activity. In this context, a study addressed BDCAF as a predictor of the development or recurrence of inflammatory major organ events, with the hope of establishing a treat-to-target approach focusing on reducing BDCAF.[38] The results showed that a high BDCAF at baseline is associated with the development of inflammatory major organ events in the near future. Accordingly, they suggested a treatment target of BDCAF approaching a value of zero. Notably, most patients with a high baseline BDCAF had a preexisting major organ event. Moreover, patients with a low BDCAF were receiving tumor necrosis factor inhibitors with adequate disease activity control. The authors could not address the association between BDCAF and damage accrual due to the short duration of the study.

Additionally, the mean VDI at the last visit was higher than that of BODI in patients with ANCA-associated vasculitis, confirming the superiority of VDI performance and the lower specificity of BODI in this population.

Regarding the sensitivity to change, BODI had the same trend of change as VDI. Concerning the intra- and inter-rater reliability of BODI, the high intraclass correlation coefficients of 0.98 and 0.91, respectively, confirmed the reproducibility of BODI. Training and adherence to the guidance provided by the glossary can help improve the inter-rater reliability.

Of note, the pulmonary domain of VDI has been merged with the vascular domain in BODI since pulmonary involvement in BD is almost always vascular, rather than parenchymal. Similarly, the ENT (ear, nose, throat) domain of VDI has been merged with the neuropsychiatric domain in BODI since the characteristic ENT involvement in BD is due to a neurological insult. The renal domain was omitted in BODI as renal involvement in BD is rare, keeping the conciseness of the score without compromising its comprehensiveness.[39]

The following limitations of BODI were observed in our study. First, some items that were experienced by the study cohort were lacking in BODI, including eye surgery, systemic hypertension, pulmonary infarction, pulmonary hypertension, heart failure, erectile dysfunction, and portal hypertension. Second, BODI lacked the item "others" that could encompass other manifestations of damage experienced by our cohort, such as surgery for avascular necrosis, lobectomy for pulmonary aneurysm, inferior vena cava filter insertion for recurrent pulmonary embolism, lung mycetoma, and incisional hernia development following bowel resection. Third, an event had to be persistent for a minimum period of six months to be scored in BODI; this also applied to inevitably irreversible events such as bowel resection and amputation. Fourth, BODI did not consider cumulative events for paired organs/parts, such as bilateral chronic venous thrombosis of limbs, and thrombosis of the superior and inferior vena cava, as well as avascular necrosis affecting more than one joint. Fifth, BODI did not consider repeated events unless the second occurred six months after the first, even if the second event affected a different anatomical site, such as arterial aneurysm of the aorta and a peripheral artery. Finally, thrombosis

of dural venous sinuses, hepatic veins, and vena cava was given a score of 1 instead of being separate items for these different anatomical sites.

In agreement with this study, a recent study including Turkish patients proved the validity and reliability of BODI for use in retrospective studies.[40] The authors reported that the main damage items not captured by BODI were systemic hypertension, liver cell failure, lung parenchymal disease, glaucoma, and lymphedema. They recommended modifying BODI by adding additional damage items to enhance its comprehensiveness. Similarly, an Iranian study reported acceptable validity and reliability of BODI in Iranian patients compared to VDI; however, the authors stated that the low frequency of certain damage items in their population did not allow adequate comparisons of some BODI and VDI subclasses.[41]

In another study comparing the performance of VDI, BODI, and Behçet's Disease Damage Index (BDI), a newly proposed damage index, in 102 Egyptian patients, the authors stated the superiority of BDI over BODI due to better consistency of the former with VDI.[42] However, VDI should not be used as a reference to assess the sensitivity, specificity, or negative and positive predictive values of either BODI or BDI as VDI is not considered a gold standard damage assessment tool in BD. This unfair judgment led to a falsely low sensitivity of BODI, keeping in mind that one item, oral ulcers, is stated as a damage item in the VDI. However, oral ulcers are almost always a manifestation of active BD that should not be included in the damage score. Similarly, the lack of multiple items in VDI led to a falsely low specificity of BODI.

This study was limited by its retrospective design. Although the retrospective design may have resulted in missing some damage items, the findings confirmed the superiority of BODI over VDI. Moreover, a Turkish study proved the validity and reliability of BODI for use in retrospective studies.[40] Nevertheles, the relatively larger sample size, the heterogeneous disease characteristics of the study population, and the patients being recruited from a tertiary center, where relatively uncommon and complex presentations are managed, can be considered the strengths of the study. The performance of BODI should be assessed in other races where the phenotypic expression of the diseases is different from that of the Mediterranean race.[37]

In conclusion, BODI is a comprehensive yet concise tool that allows a thorough evaluation of damage in adult Egyptian patients with BD. It is feasible and easy to use in clinical practice and research settings. New versions of BODI could be developed to address its limitations in different populations.

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Author Contributions: Idea/concept, design, control/supervision, materials, other, references and fundings, literature review: D.A.; Data collection and/or processing, analysis and/or interpretation, writing the article, critical review: D.A., L.M.

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