

Assessment of long-term organ damage and predictors of damage accrual in Behçet's syndrome: a 10-year longitudinal study using the Behçet's Syndrome Overall Damage Index

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Abstract

Objective

To assess long-term organ damage and its accrual in a real-life cohort of Behçet's syndrome (BS) patients using the Behçet's Syndrome Overall Damage Index (BODI), identifying predictors of damage at diagnosis and factors associated with its accrual during follow-up.

Methods

This single-centre retrospective study included 155 BS patients followed for at least six months. Organ damage was assessed at diagnosis and at various timepoints. Damage was defined as a BODI score ≥ 1 and damage accrual as an increase (Δ BODI) ≥ 1 between timepoints. Multivariable logistic regressions were used to identify predictors of damage.

Results

At diagnosis, 31.1% of patients already exhibited damage. This prevalence progressively increased to 53.8% at 10-year follow-up, with 39.7% of patients experiencing damage accrual. Pre-existing damage at diagnosis was a risk factor for faster accumulation of new damage. Multivariable analysis identified non-Italian origin and older age at diagnosis as independent predictors of damage at baseline. Notably, older age also remained a significant predictor of damage accrual during the 10-year follow-up. Furthermore, the accumulation of new damage during the disease course was associated with more frequent corticosteroid treatment.

Conclusion

Organ damage in BS is associated with different factors depending on the disease stage: while demographic features, particularly non-Italian origin and older age, significantly predict the presence of damage at diagnosis, older age and corticosteroid therapy are associated with damage accrual in the long-term. These findings highlight the importance of age-targeted clinical monitoring and of steroid-sparing strategies and early intervention in high-risk demographic groups to mitigate irreversible disability.

Key words

Behçet's syndrome, follow-up studies, retrospective studies, logistic models, steroids

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Introduction

Behçet's syndrome (BS) is a rare chronic multisystemic inflammatory disease characterised by an increased risk of morbidity, disability and mortality (1-5). It is a multifactorial disease with different genetic, epigenetic, immunological and infectious factors contributing to its pathogenesis (1). It is well known that its prevalence and its disease manifestations have a high geographical variability (6). The prevalence of BS in Italy is considered low (1), but it has considerable variation across latitude, ranging from 3.8/100,000 in Northern Italy to 15.9/100,000 in the South (7-10). We have previously reported that the BS prevalence is higher in the first-generation immigrants of non-Italian origin than in the Italian-origin population (10), and that patients of non-Italian origin more frequently experience severe outcomes such as permanent ocular or neurological damage (11).

The heterogeneous clinical spectrum of BS typically follows a relapsing-remitting course (1). Since patients may accrue organ damage over time because of both disease activity and treatment-related toxicity (12), current international recommendations emphasise the need of promptly suppressing inflammatory flares and recurrences to prevent irreversible organ damage (13). To this end, the Behçet's syndrome Overall Damage Index (BODI) was developed and validated to specifically identify, describe and quantify organ damage in these patients (12, 14). Recent studies demonstrated that organ damage is indeed a major determinant of work productivity impairment and reduced quality of life in BS (15). Additionally, demographic factors, including age and geographical residence, have been shown to influence the extent and characteristics of damage (16). Despite consistent assessment of damage is crucial in daily clinical practice to apply strategies aimed at preventing its accrual in patients with BS, data regarding long-term damage accrual and its predictors remain scarce. Notably, BODI has been recently validated also for retrospective studies, thus allowing such longitudinal analysis (17). The aim of this study was therefore to assess the long-term presence and ac-

crual of organ damage in a real-life cohort of BS patients using the BODI. Furthermore, we investigated the association between BODI scores and demographic or clinical features to identify independent predictors of damage at presentation and during the disease course, as well as factors driving damage accrual during follow-up.

Methods

This was a retrospective single-centre study considering BS patients prospectively followed in an Italian Rheumatology Unit with long-term experience in BS patient management. Clinical, laboratory and demographic data were retrieved from clinical charts and collected in an *ad-hoc* database.

Inclusion criteria and patient selection

In this study, we included patients with BS followed at our Unit between 1994 and 2024 who met the following criteria: age ≥ 18 years; fulfilment of the International Criteria for Behçet's Disease (ICBD) (18); a minimum of two visits with complete clinical records over at least six months of observation. Patients without any information after a follow-up visit were considered as lost to follow-up and censored at the time of the last available visit. Consistent with previous studies conducted elsewhere (19), patients were classified as being of non-Italian origin if they or both their parents were born outside of Italy.

Organ damage

Organ damage was retrospectively assessed by reviewing clinical charts and calculating the BODI, as previously described by Piga *et al.* (12). Only visits with complete clinical records allowing BODI calculations were considered in the study. This longitudinal assessment was performed at several timepoints: baseline (T0: diagnosis), one year (T1), three years (T3), five years (T5), and ten years (T10) after diagnosis. T10 refers to the nearest available visit at 10 ± 1 years after T0. For patients with further follow-up, the last available visit was recorded as $T > 10$. In these patients, time to first damage accrual was recorded at every available visit.

Competing interests: none declared.

BODI scores range from 0 to 46, where higher values represent more severe damage. Consistent with previous literature (14), the presence of damage was defined as a BODI score ≥ 1 , while damage accrual was defined as an increase in the score (ΔBODI) ≥ 1 between two timepoints.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) and were compared using non-parametric tests (Mann-Whitney, Kruskal-Wallis or Wilcoxon, as appropriated). Categorical variables are presented as number/percentages and were compared using contingency tables; *p*-values were calculated with the Chi-Square or Fisher exact test. For the multivariable analysis, logistic regression models with an *a priori* selection of variables, chosen according to literature support and personal experience for their clinical relevance, were used. Model assumptions were verified using the Hosmer-Lemeshow goodness-of-fit test. The predictive performance of the logistic regression model was assessed by calculating the area under the receiver operating characteristic curve (AUC). Collinearity among predictors was checked by calculating the Variance Inflation Factor (VIF).

The incidence of first damage accrual after T0 was determined using Kaplan-Meier survival curves and log-rank tests.

Ethical statement

Ethics approval was obtained from the local ethics committee, and patients included in the database gave their written informed consent. The study was conducted in accordance with Helsinki Declaration principles.

Results

Of the 220 patients with BS evaluated at our centre between 1994 and 2024, 29 (13.2%) were excluded due to the lack of adequate follow-up, and 36 (16.4%) because insufficient data rendered BODI evaluation unfeasible (Supplementary Fig. S1). Consequently, 155 prospectively followed patients (70.5%) were enrolled in the study. Detailed clinical and demographic data are reported in Table I. The cohort was pre-

Table I. Demographic and clinical characteristics of the cohort.

	n=155	
Demographics		
Male sex	69/155	(44.5%)
Age at diagnosis, years	36	(26-44); n=153
Disease duration, years	9	(5-14); n=153
Diagnostic delay, years	2	(0-6); n=145
Follow-up duration, years	8	(3-14); n=155
Family history of BS	16/155	(10.3%)
Italian origin	126/155	(81.3%)
Non-Italian origin	29/155	(18.7%)
- Mediterranean Africa (Morocco, Egypt)	14/29	(48.3%)
- Eastern Europe (Albania, Kosovo, Bosnia)	8/29	(27.6%)
- Asia (Bangladesh, Pakistan, India, China, Thailand)	7/29	(24.1%)
Smokers	45/147	(30.6%)
HLA-B*51 presence	85/135	(63.0%)
Deceased	4/155	(2.6%)
Lost at follow-up	24/155	(15.5%)
Cumulative manifestations		
Oral ulcers	151/155	(97.4%)
Genital ulcers	86/155	(55.5%)
Skin manifestations	106/155	(68.4%)
Ocular manifestations	63/155	(40.7%)
Musculoskeletal manifestations	90/155	(58.1%)
Gastrointestinal manifestations	24/155	(15.5%)
Neurological manifestations	33/155	(21.3%)
Vascular manifestations	35/155	(22.6%)
Cardio-pulmonary manifestations	17/155	(11.0%)
Epididymitis	3/69	(4.35%)
Cumulative treatment		
Glucocorticoids	126/155	(81.3%)
Colchicine	116/155	(74.8%)
Apremilast	25/155	(16.1%)
cs-DMARDs	99/155	(63.9%)
b-DMARDs	56/155	(36.1%)

Continuous variables are expressed as median (1st-3rd quartile); categorical variables are expressed as n/number of available data (%).

dominantly of Italian origin (81.3%), with the remaining 18.7% being of other origins (primarily Mediterranean Africa or Eastern Europe). Females accounted for 55.5% of the population, and 63% of patients were HLA-B*51 positive. The median age at diagnosis was 36 years [IQR 26-44], with a median diagnostic delay of 2 years [IQR 0-6]. At the last visit, the median disease duration and follow-up were 9 years [IQR 5-14] and 8 years [IQR 3-14], respectively. Eighty patients were still evaluable at T10 (Suppl. Fig. S1). Their demographic and clinical characteristics, including baseline BODI scores and treatment regimens, did not significantly differ from those of patients who did not reach the 10-year follow-up (Suppl. Table S1).

Cumulative clinical manifestations over the disease course at diagnosis and at 10-years follow-up are reported in Table I, and, at other timepoints, in Sup-

plementary Table S2. Details of clinical features, treatments and damage according to patient's origin are reported in Supplementary Table S3. Interestingly, patients of non-Italian origin were more frequently male ($p=0.002$) and had a shorter diagnostic delay ($p=0.008$) than patients of Italian origin. Moreover, patients from Mediterranean Africa were more frequently male ($p=0.046$) and exhibited significantly higher damage score and frequency at T>10 years ($p=0.024$ and $p=0.021$). This group also showed greater damage accrual after diagnosis at T10 ($p=0.046$) and T>10 ($p=0.012$), as compared to Eastern European and Asian cohorts.

Prevalence of damage at different timepoints

The BODI scores observed in our cohort and the prevalence of organ damage (defined as BODI ≥ 1) at various timepoints are illustrated in Figure 1

and Figure 2a, respectively. At the time of diagnosis (T0), damage was already present in 31.1% of patients. This proportion increased progressively over time, reaching 53.8% at the 10-year follow-up ($p=0.0013$). More frequent causes of damage already present at diagnosis were due to vascular (10.6%), ocular (9.9%), and neuropsychiatric (8.6%) BODI domains, while at the last follow-up miscellaneous manifestations including diabetes, malignancy and systemic amyloidosis were also frequent (15.1%) (Suppl. Table S4).

Incidence of new damage accrual at different timepoints

BODI variations (Δ BODI) are illustrated in Figure 1 and Figure 2b. Progressive accumulation of new damage (defined as Δ BODI ≥ 1) was observed during the follow-up period. The accrual of new damage occurred in 7.4% of patients within the first year after diagnosis and increased to 39.7% of patients after 10 years (Fig. 2b). As shown in Figure 3, the number of patients who experienced new damage accrual increased rather steadily over time; notably, time-to-first-damage-accrual was shorter in patients with BODI ≥ 1 at T0 than in patients with BODI=0 at T0 (log-rank test; $p=0.0132$).

Comparisons of patients with and without damage (BODI ≥ 1 vs. BODI=0) at diagnosis

At diagnosis, patients with damage (BODI ≥ 1) were significantly older and exhibited a higher prevalence of neurological and vascular involvement compared to those without damage (Table II, Suppl. Table S5).

Comparisons based on the presence (BODI ≥ 1) and accrual (Δ BODI ≥ 1) of damage at 10-year follow-up

Patients with established damage after 10 years of follow-up were older and exhibited a higher prevalence of ocular and neurological manifestations, compared to those without damage. Furthermore, this group had a significantly higher frequency of corticosteroid treatment (Table II, Suppl. Table S5). The same findings were observed when comparing patients who experienced

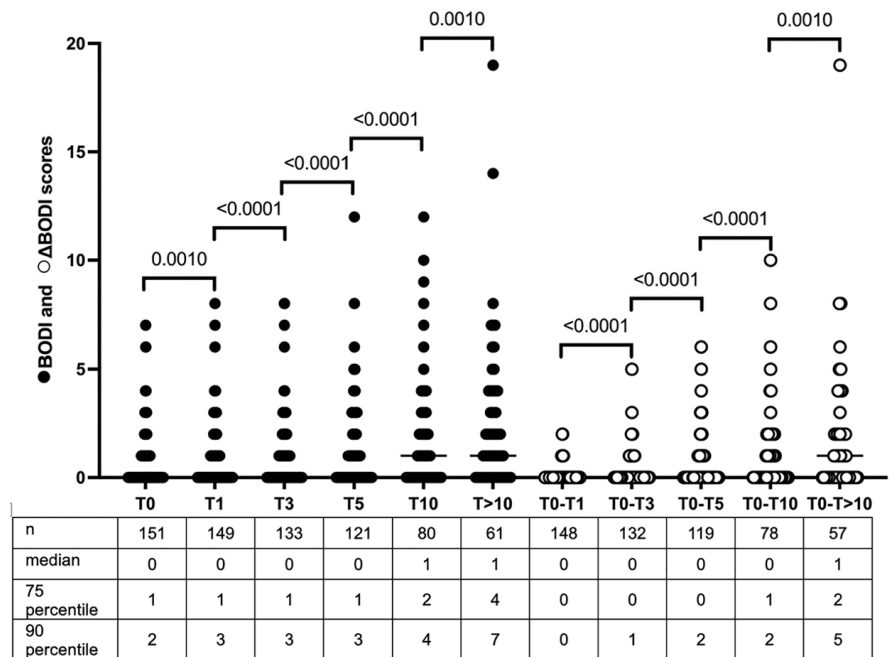


Fig. 1. BODI scores and Δ BODI scores in a cohort of BS patients.

damage accrual (Δ BODI ≥ 1) over the 10-year period with those who remained stable (Δ BODI = 0), confirming that these were the key factors associated with progression of damage.

Analysis of factors associated with damage and damage accrual during follow-up

To identify potential predictors of damage at baseline and at 10 years follow-up, as well as factors driving damage accrual over the 10-year follow-up period, we performed multivariable logistic regression analysis. Variables were a priori selected based on their clinical relevance, existing literature, and personal experience: age at diagnosis, male gender, non-Italian origin, HLA-B*51 positivity, and ever-exposure to glucocorticoids (as a binary variable) during follow-up. Model assumptions were verified by Hosmer-Lemeshow goodness-of-fit test and were found to be met. No relevant collinearity among predictors was observed, as confirmed by Variance Inflation Factor analysis (Suppl. Table S6).

Advanced age at diagnosis emerged as an independent predictor of both cross-sectional damage (at T0 and T10) and longitudinal damage accrual (Δ BODI T0-T10 ≥ 1) (Table III).

Notably, non-Italian origin was inde-

pendently associated with the presence of damage at baseline, but this association did not persist at T10 (Table III). Finally, glucocorticoid use was identified as an independent predictor of damage at T10 and of damage accrual over time (Table III).

To further validate our findings, an additional analysis was performed to identify factors associated with higher degrees of damage (BODI ≥ 2); results are presented in Supplementary Table S7 and confirm the robust association with age at diagnosis, whereas other variables (non-Italian origin at T0; glucocorticoid use at T10) did not reach statistical significance.

Discussion

Although assessing damage in chronic rheumatic disorders is crucial for both clinical trials and routine practice, damage measurement in BS was only recently introduced (12). In this study, we utilised BODI, the first disease-specific tool designed to evaluate cumulative organ damage in BS (12). Recent evidence has confirmed the reliability of BODI and its validity in distinguishing disease activity from permanent damage (20, 21). Furthermore, BODI exhibits a strong correlation with other indices previously adapted for BS despite their lack of disease-specificity, such as

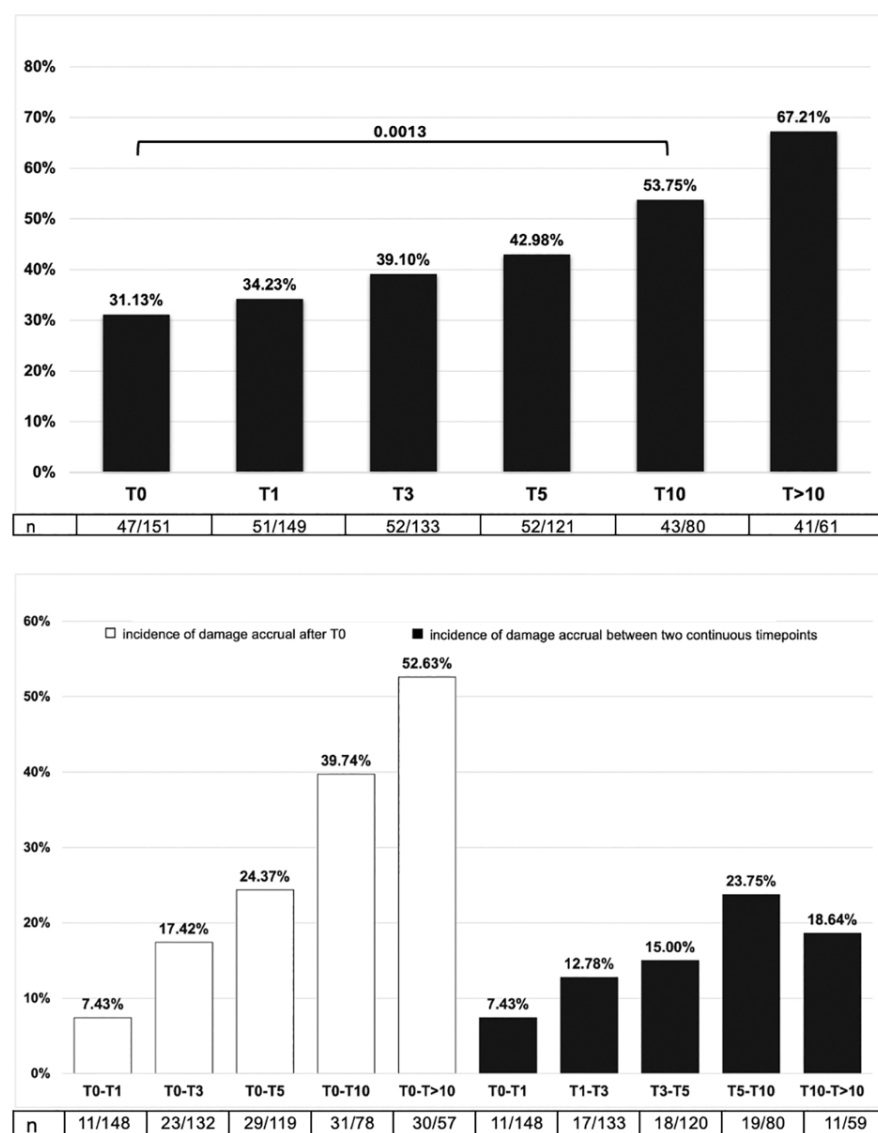


Fig. 2. A: Prevalence of organ damage (BODI ≥ 1) in a cohort of BS patients; **B:** Incidence of damage accrual ($\Delta BODI \geq 1$) in a cohort of BS patients.

Cumulative incidence of first damage accrual according to BODI score (0 vs ≥ 1) at T0

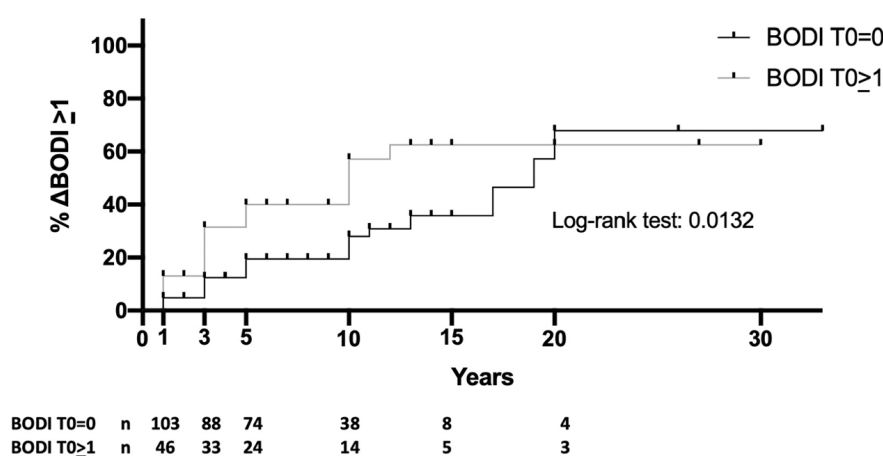


Fig. 3. Cumulative incidence of the first damage accrual in patients with BODI = 0 at T0 vs. patients with BODI ≥ 1 at T0.

the Vasculitis Damage Index (VDI) (12, 20-22), and its derivative, the Behçet's Disease Damage Index (BDI) (20, 23). Finally, its validation for retrospective research and its high clinical feasibility further support its integration into routine clinical practice (17).

In our cohort, we observed that damage, as measured by BODI, was already present in 31% of patients at the time of diagnosis. This prevalence is slightly lower than the 40% reported in a retrospective study of Turkish patients (17). While the prevalence of most clinical manifestations was comparable between the two groups, genital ulcers occurred more frequently in the Turkish cohort than in our experience. Given that approximately two-thirds of patients with genital ulcers develop permanent scarring (17), this disparity likely accounts for the observed differences in damage prevalence at diagnosis between these cohorts. Consistent with this hypothesis, lower BODI scores, similar to our findings, were observed in an Iranian cohort, which also exhibited a lower prevalence of genital aphthous ulcers compared to Turkish patients (21). Furthermore, the BODI scores observed in our cohort after a 10-year follow-up were comparable to the findings from the cross-sectional evaluation of an international cohort of patients with BS with a mean disease duration of 10.8 years at baseline enrolled in the BODI validation study (14). On the other hand, significantly higher BODI scores were reported at baseline in a cohort of Egyptian patients with a mean disease duration of eight years (20). This divergence underscores the influence of demographic and geographical factors on the extent and characteristics of damage in patients with BS (16).

In our cohort, new damage accrual was observed in 7.4% of patients during the first-year post-diagnosis, with a subsequent steady increase up to nearly 40% of patients after 10 years. Notably, the time-to-first-damage-accrual was shorter in patients with pre-existing damage at baseline, suggesting that damage at diagnosis is a risk factor for further accumulation.

While methodological differences limit direct comparisons, prior studies have

Table II. Comparisons of demographics, cumulative manifestations and treatments according to BODI score at T0 (n=151), T10 (n=80) and ΔBODI T0-10 (n=78).

	BODI T0=0 n=104	BODI T0 ≥1 n=47	p-value	BODI T10=0 n=37	BODI T10 ≥1 n=43	p-value	ΔBODI T0-T10=0 n=47	ΔBODI T0-T10 ≥1 n=31	p-value
Demographics									
Male sex	43/104 (41.3%)	23/47 (48.9%)	0.488	13/37 (35.1%)	22/43 (51.2%)	0.224	21/47 (44.7%)	12/31 (30.7%)	0.773
Age at diagnosis, years	33 [24-42]; n=103	41 [28-53]; n=46	0.002	31 [24-41]; n=36	38 [28-49]; n=42	0.050	31 [24-41]; n=46	39 [29-52]; n=30	0.018
Diagnostic delay, years	3 [0-7]; n=98	2 [0-6]; n=44	0.497	3 [0-7]; n=36	2 [0-9]; n=38	0.976	3 [0-6]; n=46	3 [0-10]; n=26	0.824
Italians	90/104 (86.5%)	34/47 (72.3%)	0.060	33/37 (89.2%)	35/43 (81.4%)	0.367	42/47 (89.5%)	25/31 (80.7%)	0.453
HLA-B*51 presence	61/95 (64.2%)	24/39 (61.5%)	0.925	20/33 (60.6%)	20/33 (60.6%)	0.654	22/40 (55.0%)	18/26 (69.2%)	0.837
Cumulative manifestations									
Ocular	38/104 (36.5%)	23/47 (48.9%)	0.208	10/37 (27.0%)	27/43 (62.8%)	0.003	12/47 (25.5%)	23/31 (74.2%)	0.001
Neurological	15/104 (14.4%)	15/47 (31.9%)	0.023	4/37 (10.8%)	14/43 (32.6%)	0.040	6/47 (12.8%)	11/31 (35.5%)	0.036
Vascular	18/104 (17.3%)	17/47 (36.2%)	0.019	6/37 (16.2%)	15/43 (34.9%)	0.102	10/47 (21.3%)	11/31 (35.5%)	0.261
Cumulative treatments									
Glucocorticoids	-	-	-	28/37 (75.7%)	41/43 (95.3%)	0.020	37/47 (78.2%)	30/31 (96.8%)	0.042

Continuous variables are expressed as median [1st-3rd quartile] and compared using Mann-Whitney test; categorical variables are expressed as n/number of available data (%) and compared using Chi-square test with Yates' correction or Fisher's exact test.

Table III. Multivariable analysis exploring potential predictors of damage and damage accrual.

	BODI ≥1 T0* n=47/151			BODI ≥1 T10** n=43/80			ΔBODI ≥1 T0-T10*** n=31/78		
	n	OR (95% CI)	p-value	n	OR (95% CI)	p-value	n	OR (95% CI)	p-value
Male sex	66/151	1.545 (0.635-3.799)	0.337	35/80	2.431 (0.718-9.125)	0.156	33/78	1.243 (0.370-4.326)	0.726
Non-Italian origin	27/151	4.371 (1.486-13.400)	0.007	12/80	1.811 (0.356-11.040)	0.479	11/78	4.348 (0.824-28.620)	0.084
HLA-B*51	85/134	1.231 (0.501-3.000)	0.648	40/66	0.760 (0.222-2.508)	0.653	40/66	0.395 (0.107-1.306)	0.130
Glucocorticoids	-	-	-	69/80	13.590 (2.071-273.200)	0.004	67/78	8.024 (1.220-161.400)	0.028
Age at diagnosis	149	1.078 (1.045-1.118)	<0.001	78	1.072 (1.025-1.134)	0.002	76	1.057 (1.015-1.109)	0.007

*AUC 0.7904 (CI 95%: 0.7054-0.8754), Hosmer-Lemeshow test: $p=0.1126$; **AUC 0.7856 (CI 95%: 0.6753-0.8959), Hosmer-Lemeshow test: $p=0.0651$; ***AUC 0.7726 (CI 95%: 0.6584 to 0.8867), Hosmer-Lemeshow test: $p=0.5762$.

evidenced a similar or slightly higher incidence of patients with new damage accrual as detected by BODI during follow-up. These findings clearly indicate that organ damage continues to accumulate in BS, even in patients with long-standing disease. Specifically, an increase in BODI scores was detected in 37% of Turkish patients over a median follow-up of 5 years (17), in 19% of Iranian patients after a median follow-up of 40 months (21), and in 19% of patients during the 2-year follow-up of the original BODI validation study (14). A notably higher rate was reported in Egyptian patients with an established diagnosis, where 27% showed damage progression over just one year (20). Furthermore, it has been observed that the rate of damage accumulation

remains constant over time throughout the observation period (14).

Since developing patient-tailored strategies to prevent damage accrual is an essential unmet need in clinical care of patients with BS, identifying associated predictors is a priority in clinical research.

In our study, older age at diagnosis emerged as an independent predictor not only of the presence of cross-sectional damage at diagnosis and at 10-year follow-up, but also of longitudinal damage accrual. Accordingly, age was previously shown to be correlated with the total BODI score in large multicentre cohorts (16, 20). Specifically, age was found to be independently associated with neuropsychiatric and "miscellaneous" BODI domains (the latter

including diabetes, malignancies and amyloidosis) (16). Since data in literature indicate that older age is generally associated with milder disease manifestations and reduced disease activity over time (24, 25), these observations suggest that the increased risk of damage in older patients might result from age-related comorbidities (e.g. diabetes, osteoporosis and cardiovascular risk factors), which were indeed increasingly prevalent during follow-up also in our experience, rather than from the primary disease itself (16).

Previous studies have established that geographic areas independently influence damage risk, likely reflecting differences in ethnic compositions of populations driven by genetic and cultural elements, as well as socioeconom-

ic status and healthcare access (16). In our study, non-Italian origin was independently associated with damage presence at diagnosis, reinforcing our previous observation of greater severity of disease in this population (11). In our experience, patients of origin from Mediterranean Africa exhibited the greatest damage accrual compared to other groups. Possible explanations of these findings might include not only a milder course of BS in Italian patients compared to other populations (7), but also more frequent late referral among non-Italian individuals. However, since we did not observe a higher diagnostic delay in this group of patients, a potential selection bias cannot be ruled out: among immigrants, those with more severe symptoms may be more likely to seek medical attention, potentially overestimating BS-related damage in this group. Notably, non-Italian origin was not associated with development of new damage during follow-up in our patients. This suggests that the disease course was not more severe in this population when adequately monitored and treated. Similarly, a large-scale French study also identified ethnic origin as a major determinant of morbidity and mortality, with patients of Sub-Saharan descent exhibiting the poorest prognosis (19). Further research is therefore warranted to better elucidate the interplay between genetic and environmental factors in the progression of BS-related damage. In this context, the possible role of epigenetic mechanisms, including microbiome alterations, has been recently suggested (1, 26, 27).

Finally, glucocorticoid use was identified as an independent predictor of both damage presence and accrual of new damage in the long-term follow-up in our cohort. These data confirm previous findings demonstrating that prolonged exposure to glucocorticoid treatment is associated with the accumulation of damage (14). Accordingly, over 40% of items defining new damage were classified as definitely or possibly related to glucocorticoid therapy (14). Although the association between glucocorticoid exposure and damage accrual is plausible and clinically important, it should be noted that in this retrospective ob-

servational setting it is highly vulnerable to confounding by indication, since patients receiving glucocorticoids are likely to have more severe disease, more relapses, or more major organ involvement. Moreover, dose, duration, or cumulative exposure, which would make the finding more informative, were unfortunately not available, and this limits the relevance of our observation.

The primary limitations of this study derive from its design: its single-centre nature potentially restricts the broader applicability of the findings. Due to the limited number of enrolled patients, the study may have lacked the statistical power to confirm the role of male gender in damage progression, as previously reported in larger international studies (28); we acknowledge that, analogously, the small sample size and low event rate might cause unstable estimates and suggest caution in the interpretation of ORs having wide confidence intervals, especially for glucocorticoid use. Therefore, these findings should be considered as exploratory only. Moreover, the retrospective nature of our study led to a significant loss of patients during follow-up. This could potentially introduce a selection bias, as patients lost to follow-up might have different disease trajectories compared to those who remained in the study. However, to mitigate this concern, we compared the demographic and clinical characteristics of patients who reached the 10-year follow-up with those who did not. Since no significant differences were found between the two groups, we believe our enrolled cohort remains representative of the overall BS population at our centre. This suggests that the attrition was likely missing at random, thereby minimising the risk of skewed results.

We could not evaluate the occurrence of disease flares during follow-up, which were identified as another predictor of damage accrual in a previous study (14). Relevant socioeconomic data as well as patient education were not routinely recorded, precluding their assessment. Finally, the results were not compared with other damage assessment instruments. While BODI has several

advantages (29), some limitations of this instrument have been noted, including the identification of items not covered, and some modifications have been proposed (17).

Despite these limitations, our study suggested the different role played by sociodemographic factors and by treatment strategies in the development of organ damage in the long-term follow-up of patients with BS. Studies of long-term damage accrual in larger, multicentre, and multinational cohorts are warranted to better clarify this highly relevant clinical issue.

In conclusion, in our study older age was a predictor of organ damage at diagnosis, and of further damage accrual over time during long-term follow-up. Non-Italian origin was identified as another predictor of damage at diagnosis, but it was not associated with development of new damage during follow-up. Finally, the use of glucocorticoids was associated with the accrual of damage in the long-term.

These findings highlight the importance of age-targeted clinical monitoring and of steroid-sparing strategies and early intervention in high-risk demographic groups, to optimise patient care, prevent irreversible disability, and improve quality of life.

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