PROBE

PROSPECTIVE VALIDATION OF THE BODI

PROspective multiethnic validation of the BEhçet's syndrome Overall Damage Index (BODI): the PROBE study

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ADMINISTRATIVE INFORMATION

TITLE:

PROspective multiethnic validation of the BEhçet's syndrome Overall Damage Index (BODI): the PROBE study

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CONFIDENTIALITY STATEMENT

LIST OF THE INVOLVED RESEARCH CENTRES AND ROLES AND RESPONSIBILITIES OF INVESTIGATORS

Research Centres	Investigators' name and role
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BACKGROUND

Behçet's syndrome (BS) is a multisystem inflammatory disease of unknown etiology, characterized by strong genetic background, distinctive geographic distribution, and wide variability in clinical presentation [1]. Disease activity related to BS as well as chronic exposure to medications may lead to the development and accrual of irreversible organ damage resulting in impairment of quality of life, disability, and increased mortality [2]. For these reasons, organ damage was included in the OMERACT outcome core set for BS [3].

The Behçet's syndrome Overall Damage Index (BODI) is a recently developed tool to identify and measure organ damage in BS [2]. The BODI is grounded in a solid evidence-based and consensus-based methodology, and its preliminary validation on a multicenter cohort of Southern European patients showed highly promising performance in terms of comprehensiveness, specificity, reliability, sensitivity to change, and feasibility [2].

Nevertheless, a prospective validation with a wider and ethnically heterogeneous cohort of BS patients is needed to generally evaluate the impact of those BODI items seldom recorded or absent in the preliminary validation cohort and to weigh the damage items depending on their relevance for predicting major outcomes.

OBJECTIVES

General objectives

The general objectives of the PROBE study are to further test the comprehensiveness of the BODI (content validity) in a wide and ethnically heterogeneous cohort of BS patients, and investigate how damage assessed by the BODI correlates with other major long-term disease outcomes (criterion validity), with the ultimate goal of drafting a weighing system for each BODI item.

Specific Objectives

1. To test the comprehensiveness of the instrument in a wide and ethnically heterogeneous cohort of BS patients, evaluating the prevalence of those BODI items seldom recorded or absent in the preliminary validation cohort
2. To describe possible differences in the entity and type of damage accrual in BS patients from different geographical areas.
3. To identify the factors independently associated with damage development and accrual.

4. To investigate the association between the results of the baseline BODI measurement (BODI ≥1, BODI score, and BODI ranking) and the 5-years mortality rate.
5. To investigate the association between the results of the baseline BODI measurement (BODI ≥1, BODI score, and BODI ranking)and the 5-years hospitalization rate.
6. To weigh each item of damage depending on their relevance in predicting mortality.

METHODS

Study design

PROBE is an observational multicenter cohort study, consisting of a cross-sectional and a 5-years prospective phase, designed to target the major study objectives, such as testing the content and criterion validity of the BODI and drafting a weighing system for each BODI items.

During the study, patients will undergo a routine clinical assessment, as scheduled in their follow-up program. No further clinical, laboratory or instrumental investigations are required in addition to those provided according to good clinical practice. Treatment prescription will be evaluated by each investigator independently from the study and according to the international and local guidelines and the good clinical practice.

Patients

The study population will consist of consecutive BS patients diagnosed according to the ICBD or ISG classification criteria [4,5] recruited in Centers with expertise for BS.

Inclusion criteria:

- Diagnosis of BS according to ICBD or ISG criteria;

Exclusion criteria:

- subjects unable or unwilling to make themselves available for the duration of the study and/or are unwilling to follow interval visits.

Any effort should be addressed by investigators to minimize the rate of lost to follow-up and guarantee the completeness of the database.

Data collection

Data will be collected at the time of recruitment (baseline, T0) and then annually (± 1 month) for 5 years. Overall, 6 visits are planned to be recorded (T0, T1, T2, T3, T4, T5). Details on the data required at each visit are reported in table 1.

A query management system (QMS) will manually track data queries so they can be adequately individualized and resolved. QMS substantially minimizes and even eliminates the risk of invalid data being unnoticed. Collected data will be checked annually and data queries (e.g., data issue) will be forwarded to Investigators. Data queries will only be resolved in the following ways:

- by correcting the error, in other words entering a new value that is valid;
- by marking the data in conflict as correct.

Table 1. Data collection at each scheduled visit

Months	T0 Baseline	T1 12 (±1)	T2 24 (±1)	T3 36 (±1)	T4 48 (±1)	T5 60 (±1)
Demographics	P					
Comorbidities	P					
Cumulative disease manifestations	P					
Active manifestations between visits		P	P	P	P	P
BD current activity form (BDCAF)	P	P	P	P	P	P
BODI score	P	P	P	P	P	P
Physician global assessment (PGA)	P	P	P	P	P	P
Patient's global assessment (PtGA)	P	P	P	P	P	P
Patient's damage assessment (PtDA)	P	P	P	P	P	P
Ongoing treatment	P	P	P	P	P	P
N of relapses (between visits)	Last 5 yrs	P	P	P	P	P
N of hospitalizations (between visits)	Last 5 yrs	P	P	P	P	P
Death		P	P	P	P	P

Variables

Details on the variables that are requested to be recorded are reported below:

- **Demographics:**
  - Gender (male/female)
  - Date of birth
  - Date of onset:
    - a) first disease manifestation including oral aphtosis;
    - b) first disease manifestation excluding oral aphtosis
  - Date of diagnosis
  - Date of enrolment
  - Smoking:
    - never smoker,
    - current smoker,
    - past smoker
  - Country of origin
  - Country of residence
  - Ethnicity:
    - Caucasian;
    - Asian;
    - Hispanic;
    - Afro-American;
    - Arab;
    - Other (please specify)
  - Education level:
    - Illiterate
    - Primary school
    - Secondary School
    - College/University
  - **Comorbidities:**
    - Fibromyalgia
    - Blood hypertension

- Dyslipidemia
- Obesity (BMI>30)
- Chronic Kidney disease
- Diabetes (diagnosed before onset of BS)
- Other (please specify)

- **Cumulative clinical manifestations:** any disease manifestation occurred from the disease onset to the enrolment visit (even no longer present at the enrolment visit). The following disease manifestations have to be recorded:
    - Oral aphtosis (yes/no)
    - Genital aphtosis (yes/no)
    - Skin lesions (yes/no, if yes specify which type)
    - Ocular (yes/no, if yes specify which type)
    - Vascular (yes/no, if yes specify which type)
    - Neurologic (yes/no, if yes specify which type)
    - Musculoskeletal (yes/no, if yes specify which type)
    - Gastrointestinal yes/no, (if yes specify which type)
    - Pathergy test (yes/no)
    - Others yes/no, (if yes specify which type)

- **Active clinical manifestations between visits:** manifestations that are present at the time of the visit or have occurred since last visit. The following disease manifestations have to be recorded:
    - Oral aphtosis (yes/no)
    - Genital aphtosis (yes/no)
    - Skin lesions (yes/no, if yes specify which type)
    - Ocular (yes/no, if yes specify which type)
    - Vascular (yes/no, if yes specify which type)
    - Neurologic (yes/no, if yes specify which type)
    - Musculoskeletal (yes/no, if yes specify which type)
    - Gastrointestinal yes/no, (if yes specify which type)
    - Pathergy test (yes/no)
    - Others yes/no, (if yes specify which type)

- **Behçet's disease current activity form (BDCAF) score:** BDCAF is a disease activity assessment tool for BS. It depends on an accurate evaluation of clinical features present during the month before the date of assessment. The presence/absence of 9 somatic symptoms from a list may be recorded, together with eye involvement, nervous system involvement, major vessel involvement, as well as the clinician's overall perception of disease activity**.** The transformed index score on an interval scale will be used for analysis in the present study. [6]
- **Behçet's syndrome overall damage index (BODI).** It is a tool recently developed to identify and measure organ damage in BS. BODI consists of 4 overarching principles and 34 items with 12 subitems, categorized into 9 organ/system domains: mucocutaneous, musculoskeletal, ocular, vascular, cardiovascular, neuropsychiatric, gastrointestinal, reproductive system, and miscellaneous. Each item and subitem scores 1 point. The total score ranges from 0 to 46 [2]. In order to score the BODI, each investigator will be provided with a user manual and a video tutorial (https://vimeo.com/264992929).
- **Physician's global assessment of disease activity (PGA).** It will be assessed through a single question ("How active is the patient's BS?") on an anchored 10-cm visual analogic scale (0.5-cm graded), where 0 corresponded to "no disease activity" and 10 to "the highest disease activity." [7]
- **Patient's global assessment of disease activity (PtGA).** It will be assessed through a single question ("How active was your BS during the last week?") on an anchored 10-cm visual analogic (0.5-cm graded), where 0 corresponded to "no disease activity" and 10 to "the highest disease activity." [7]
- **Patient's damage assessment (PtDA).** It will be assessed through a single question ("How much irreversible (non-healing) damage have you developed since the diagnosis of BS?") on an anchored 10-cm visual analogic (0.5-cm graded), where 0 corresponded to "no damage" and 10 to "the highest amount of damage".
- **Ongoing treatment:** medications that are ongoing at the time of each visit will be classified as**:**
    - Colchicine (yes/no)

  - Glucocorticoids (yes/no, if yes specify the current dosage in mg/day of prednisone ore equivalents)
  - Conventional immunosuppressant (yes/no, if yes which agent; i.e., azathioprine, cyclosporine, cyclophosphamide, thalidomide, methotrexate, sulphasalazine; others)
  - Apremilast (yes/no)
  - Biologic immunosuppressant (yes/no, if yes which agent; i.e. anti-TNFalpha agents)
  - Other (yes/no, if yes specify)

- **Number of relapses.** Relapse is defined as the onset of a new BS manifestation or recurrence/worsening of a pre-existing clinical manifestation resulting in significant treatment modifications. Significant treatment modifications will be defined as the starting or increasing dosage of corticosteroids, colchicine, apremilast, conventional or biologic immunosuppressant. For each relapse, the clinical manifestation inducing the treatment modification will be recorded.

- **Number of hospitalizations.** Hospitalization will be defined as any admission to the hospital (duration at least one day including emergency room) for any reason both related to BS (i.e. treatment, management of complications, diagnosis of new manifestations, etc.) and unrelated to BS (i.e. surgery, cardiovascular disease, malignancy, etc.). Primary reasons and numbers of days of hospitalization will be recorded.

- **Death** (yes/no, date of death, cause of death). In this regard, it is of extreme importance to make every possible effort to ensure that patients resulting lost to follow-up have not deceased.

Statistical analysis

Descriptive statistics will be performed to report on the prevalence and amount of damage, as assessed by the BODI. In the whole study cohort and different geographical sub-groups, the damage will be described as:

- prevalence of any damage (BODI ≥1);
- prevalence of any damage in the different BODI domains;
- mean (SD) or median (IQR) BODI score;

- ranking of the BODI score will be developed, using a multistate model, depending on the distribution of damage in the whole population.

Univariate and multivariate regression models will be implemented to investigate the significant difference between ethnic/geographic groups in terms of prevalence and amount of damage accrual. Similarly, univariate and multivariate regression models will be implemented to investigate independent factors associated with the development or accrual of damage, as assessed by the BODI.

Multivariate Cox proportional hazards regression models will be created to assess the effect of damage (BODI score, BODI ≥1, BODI ranking) on subsequent risk of death with adjustment for covariates, including gender, age, disease duration at enrollment, history of major organ involvement, disease activity at enrolment, comorbidities (onset before BS diagnosis). Results will be presented as hazard ratios with their corresponding 95% confidence intervals. Statistical significance will be defined as a P-value <0.05. Finally, adjusted survival estimates obtained from these Cox regression models were plotted as survival curves.

Sample size

According to the results of previous studies, 95% overall 5-year survival is expected [8]. Assuming 99% and 95% of survival rate in BS patients with and without BODI damage, respectively, and assuming 50% prevalence of damage (BODI ≥1) in the study cohort, we estimated a required sample size of at least 801 BS patients (alpha type I error = 0.05; beta type II error 0.20) to identify damage as a predictor of mortality. Under the assumption of 25%maximum attrition (5% every year), the sample size will be increased to 1040 patients.

STUDY TIMELINE

March 2021 – June 2021: Investigators involvement and Ethic Approval (if locally required)

April 2021 – December 2021: Enrollment window

January 2022 – December 2026: Prospective follow-up window

Publication plan:

- **End of 2022 :** Publication of Cross-sectional results *(content validity)*
- **End of 2025:** Publication of mid-term results (factors associated to damage accrual)

- **End of 2028:** publication of prospective results *(construct validity)*

PUBLICATION RULES

Baseline data will be published in a peer-reviewed scientific journal within 1 year from the end of recruitment. The full results of the prospective validation will be published in a peer-reviewed scientific journal following the completion of the 5-year study. Partial or preliminary results can be published beforehand.

The main publication is the responsibility of the Principal Investigator. Authorship in the main publications, as well as in ancillary papers, will be offered to all Investigators who achieve the minimum target of 30 patients with complete clinical data after 5 years of follow-up. All the other Investigators not reaching these criteria will be included in the collaborator's list according to the table below. Any exception could be evaluated, depending on the number of enrolled patients with complete data, by taking into account the national epidemiological distribution of BS. Investigators will be listed in authorship according to the number (from highest to lowest) of enrolled patients.

Number of patients	*Investigator*	*Local co-investigator*
>100	Author	Author
30-100	Author	Collaborator
<30	Collaborator	Collaborator

A list of ancillary publications will be discussed; the study proponent will be granted to access the entire data-set and will lead the ancillary publication. Authorship of ancillary papers will be the same as the main publications.

ETHIC AND REGULATORY ISSUES

Ethical Committee Approval

Ethical Committee Approval will be obtained by the Proposing and Coordinating Centre (Rheumatology Unit, AOU of Cagliari, Italy) and in the other Research Centres in accordance with the policy of the Institutions and local legislation for this kind of study.

Any future change to the protocol or informed consent needed over the study must be approved by Ethical Committee.

Data Collection

Demographic, clinical and therapeutic data will be collected during the enrolment visit and annually for 5 years during the routinary follow-up visits for each patient, by reviewing medical records and clinical files. No further clinical, laboratory or instrumental investigations will be performed in addition to those provide by the good clinical practice. No experimental drugs will be administrated. Any possible drug administration will be evaluated independently to the study and according to the good clinical practice and the observational nature of the study.

Data entry and security

The collected data from each Research Centre will be anonymously recorded in an electronic spreadsheet. Anonymous data form each Research Centre will be subsequently entered into a single password-protected database managed and guarded by the Coordinating Research Centre (Rheumatology Unit, AOU of Cagliari, Italy). To guarantee anonymity, an alphanumeric code will be attributed to each patient by the recruiting physician. The correspondence between the alphanumeric code and the patient's identity will be reported in a sperate document, accessible only to the recruiting physician. Access to patient final database will be restricted to the Chief Investigator and Collaborators above.

Informed consent

The recruiting physician must inform patients on every aspect of the study, including his right to withdraw at any time. The decision of participating to the study must be voluntary.
In accordance with the policy of the Institutions and local legislation of each Research Centre for this kind of study, a signed informed consent will be obtained at the enrolment and a copy of will be provided to the recruited patient also. The informed consent will be signed by the recruiting physician also.

Study withdrawal

Every recruited patient can withdrawal from the study at any time for any reason. If his data yet entered in the database and not published, they will be removed.

Data publication and privacy

Following completion of the study, the full results will be published in a peer-reviewed scientific journal. The data anonymity will be guaranteed in accordance with the personal data protect laws.

Insurance cover

For the purely observational nature of the study, no further insurance coverage should be requested in addition to that provided for the standard clinical practice by each Research Centre.

Funding

No specific funding is provided for the study

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