Review

Assessing quality of life in Behçet's disease: a systematic review

M.V. Mastrolia[1], D. Marinello[2], F. Di Cianni[2], R. Talarico[2], G. Simonini[3]

[1]Rheumatology Unit, Meyer Children's University Hospital, Firenze;
[2]Rheumatology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa;
[3]Rheumatology Unit, Meyer Children's University Hospital, NEUROFARBA Department, University of Florence, Italy.

Maria Vincenza Mastrolia, MD
Diana Marinello
Federica Di Cianni, MD
Rosaria Talarico, MD, PhD*
Gabriele Simonini, MD*

*These authors contributed equally.

Please address correspondence to:
Maria Vincenza Mastrolia,
Rheumatology Unit,
Meyer Children's University Hospital,
Viale Gaetano Pieraccini 24,
50139 Firenze, Italy.
E-mail: maria.mastrolia@unifi.it

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ABSTRACT

Objective. *The assessment of quality of life (QoL) in Behçet's disease (BD) patients has been a surrogate of disease outcomes, but a wider impact on the patient's lifestyle has not been considered. This systematic review aims to provide an overview of the existing tools specifically adopted to explore the QoL in BD patients.*

Methods. *A systematic literature review was conducted using 2 electronic databases, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. A combination of BD and QoL-related search terms were used. All articles were screened by 3 independent reviewers for title, abstract and full text level. Studies investigating QoL in BD patients were included.*

Results. *64 papers of 497 records were retained. Data about 7,449 patients with a BD diagnosis and QoL evaluation were collected. 47 different tools to evaluate QoL were detected. The mean number of tools adopted in each study was 2.14±1.34. General QoL and psychological and social impact were investigated in 68.75% and 54.69% respectively. The correlation with disease activity was investigated in 71.86%.*

Conclusion. *The assessment of QoL in BD patients may provide a fundamental measurement for health to evaluate the outcome of interventions for BD patients. The adoption of a single validated QoL tool, developed including the BD patient's perspective, may provide an accurate and effective assessment, ensure the comparison within different cohorts, and set standardised values to define QoL level in BD patients.*

Introduction

Behçet's disease (BD) is a chronic inflammatory disorder of unknown aetiology affecting small to medium size vessels and characterised by a relapsing and remitting course. Clinical hallmarks of the disease are recurrent skin lesions and mucosal ulcers along with ocular inflammatory manifestations. Musculoskeletal, gastrointestinal, central nervous system and vascular involvement may also encompass the disease with different prevalence according to the ethnic background. Currently, a body of literature evidences that fatigue, sleep disorders and psychiatric disorders, strongly correlated with disease activity, more frequently occur in BD patients than in general population (1).

By definition, the term quality of life (QoL) points out the individual ability to satisfy own basic needs, to be satisfied with own life, to sustain adequate level of social, interpersonal and working interactions, and, eventually, to achieve emotional and physical well-being (2).

In this setting, several variables, including the chronic natural history of the disease, delayed diagnosis, and life-threatening manifestations, significantly affect QoL of these patients, thus impairing their physical and mental health. As previously reported (3-7), due to the organ involvement and/or to the disease activity, comparing to other group of patients, BD strikes the QoL.

For many years, the assessment of QoL in BD patients has mainly been a surrogate of disease outcomes, but a wider impact of the disease on the patient's lifestyle has not been considered. Generic outcome measures of global health status such as the Nottingham Health Profile (NHP) and the Medical Outcomes Study Short-Form 36 (SF-36) are appreciated tools to measure the global influence of the disease, as they take in consideration multiple domains (8, 9). At the opposite, QoL measures offer a more comprehensive approach to the evaluation of disease outcome, as
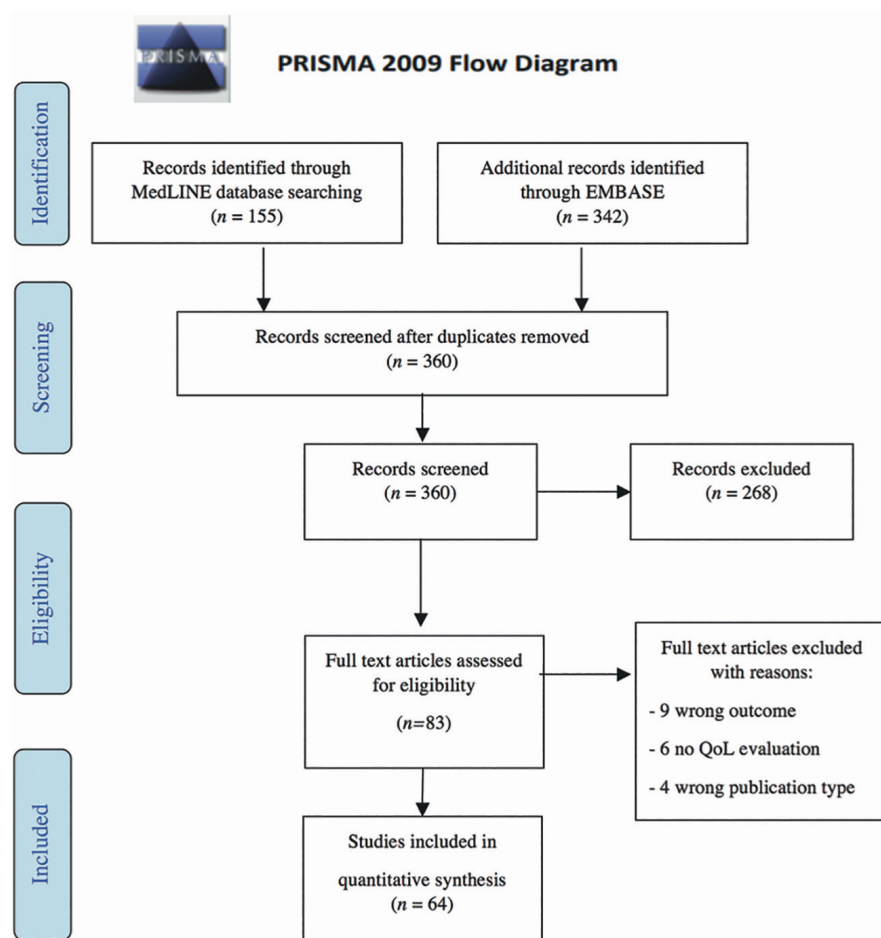
Fig. 1. PRISMA 2009 flow diagram.

they assess the impact of disease and the effectiveness of interventions from the patient's perspective, beyond the simple information about the level of impairment and activity limitations (10).

Therefore, over the last few years, QoL assessment has also become routine in clinical research, showing the growing awareness of the non-inferiority of QoL measures as measure of outcome.

In this regard, the OMERACT Vasculitis Working Group reported that the BDQoL is the only one specific outcome measure adopted in few randomised clinical trials (RCTs) and observational studies for BD (10). Generic measures are the most adopted tools to assess QoL in BD, and among these, only the oral health-related QoL (OHRQOL) is specifically validated for BD (11).

Likewise, our work aimed to perform the first systematic review of the existing tools, specifically adopted to explore the QoL in BD patients. The effect size of these tools and the over-all identification of variables affecting QoL in patients suffering from BD have been also measured.

Methods

A systematic literature review was conducted to detect the tools currently used to investigate QoL in BD patients.

Search strategy

A search was performed in MEDLINE via PubMed and in EMBASE to identify publications about QoL and BD that were published between the databases inception (MEDLINE 1950, EMBASE 1974) until September 1st 2021, using the following terms ["quality of life" OR "QoL" OR "BD-QoL" OR "SF-36" OR "Short form 36 " OR " World Health Organisation Quality of Life" OR " WHOQOL-BREF " OR " WHOQOL-100 AND Behçet disease"] in all fields. Three independent reviewers have also performed a hand search of the references listed in the retrieved

articles to identify eventual additional publications.

Study selection, inclusion and exclusion criteria

Inclusion and exclusion criteria were defined a priori. Publications were considered eligible if they explored QoL of BD patients and if the language of the publication was English. We included retrospective cohort, prospective cohort studies, case series with at least two cases, experimental and quasi experimental studies including clinical trials and open label studies.

The exclusion criteria included animal studies, conference abstract and review articles, articles not in English, articles not assessing QoL in BD.

Participants/population

Studies were included if they explored QoL in patients with a confirmed diagnosis of BD according to the International Criteria for Behçet's disease (12) or according to a clinical diagnosis of BD. Studies were excluded if they involved patients without a confirmed diagnosis of BD.

Data extraction

Title and abstracts of the articles selected were assessed by three reviewers (MVM, DM, FDC) to verify the compliance with the inclusion and exclusion criteria and eliminate duplicates. Full-text screening of the retrieved publications was independently performed by the 3 reviewers and an on-line consensus meeting was held to agree on the final list of publications to be selected. Any disagreement was solved through consensus among the three reviewers and in case of unresolved disagreements, senior researchers (RT, GS) were invited to participate in the discussion and take the final decision.

A data extraction form into a predesigned Excel sheet was used to collect the following variables from the studies selected: year of publication, study setting (country), type of study, study aim(s), number of patients involved in the study and their gender/age, number and names of the tools used, validation of the tool, explored domains (general QoL, organ involvement-related QoL,
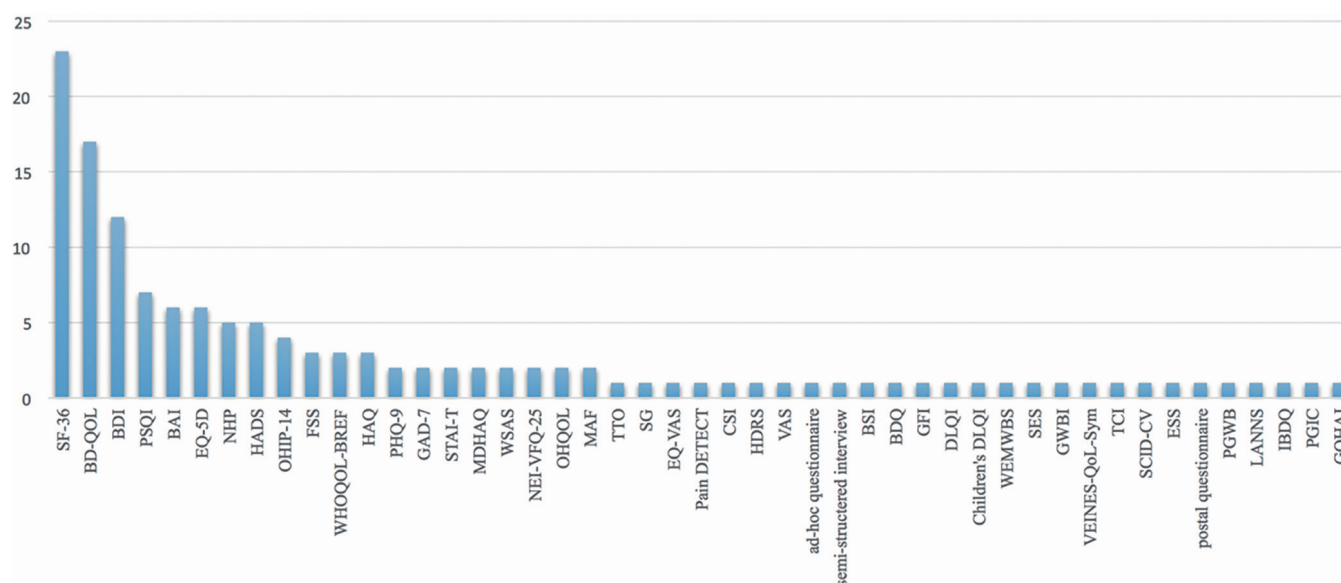
Fig. 2. Type and frequency of QoL tools.
DLQI: Dermatology Life Quality Index; IBDQ: inflammatory bowel disease questionnaire; BDI: Beck inventory scale; BAI: Beck anxiety inventory; SF-36: Short Form-36; BD-QoL: Behçet's disease quality of life; HAQ: health assessment questionnaire; GWBI: general wee-being index; NHP: Nottingham Health Profile; BSI: brief symptoms inventory; BDQ: brief disability questionnaire; OHQOL: oral health quality of life; OHIP-14: oral health impact profile-14; STAI-T: state trait anxiety inventory; WHOQOL-BREF: World Health Organisation QoL assessment brief; MD-HAQ: multidimensional health assessment questionnaire; PGIC: patient global impression of change; NEI-VFQ-25: National Eye Institute visual function questionnaire-25; EQ-5D: Euro Quality of life 5D; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh sleep quality index; FSS: fatigue severity scale; PGWB: psychological general well-being; LANSS: Leeds assessment of neuropaths symptoms and signs; GOHAI: General Oral Health Assessment Index; TCI: temperament and character inventory; SCID-CV: structured clinical interview for diagnostic and statistical manual of mental disorders; HADS: hospital anxiety and depression scale; VEINES-QoL/Sym: venous insufficiency epidemiological and economic study quality of life/symptoms; MAF: multidimensional assessment of fatigue; HAQ: health assessment questionnaire; VAS: visual analogue scale; GFI: global fatigue index; WSAS: work and social adjustment scale; SES: social economic status; CSI: questionnaires and the central sensitisation inventory; PHQ-9: patient health questionnaire-9; GAD-7: general anxiety disorder; WEM-WBS: Warwick-Edinburgh Mental Wellbeing scale; TTO: Time Trade off; SG: standard gamble; EQ-VAS: Euro QoL Visual Analogue scale.
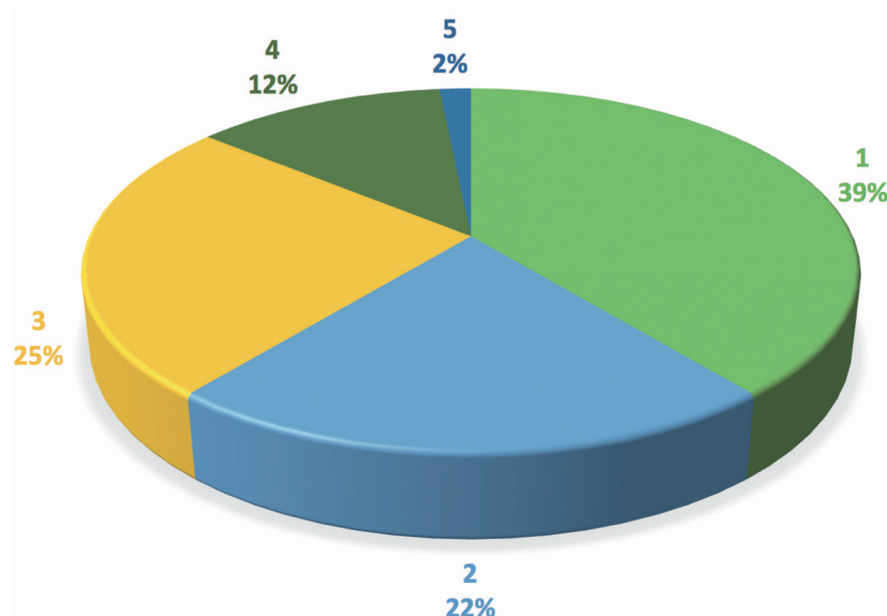

Fig. 3. Number of explored domains per study.

pain and fatigue, psychological and social impact, sleep, physical functioning and workability), correlation with disease activity, type of tool(s) used to explore disease activity, results obtained.

Results
The search of literature produced 497 records (Embase: 342, PubMED: 155). After deduplication removal, 360 papers have been screened for title and abstract evaluation and 83 papers have been included for full text evaluation. After full text screening 64 papers have been used in our systematic review (1-3, 5, 7, 10, 13-69). Figure 1. represents the flow diagram demonstrating the process of study selection.
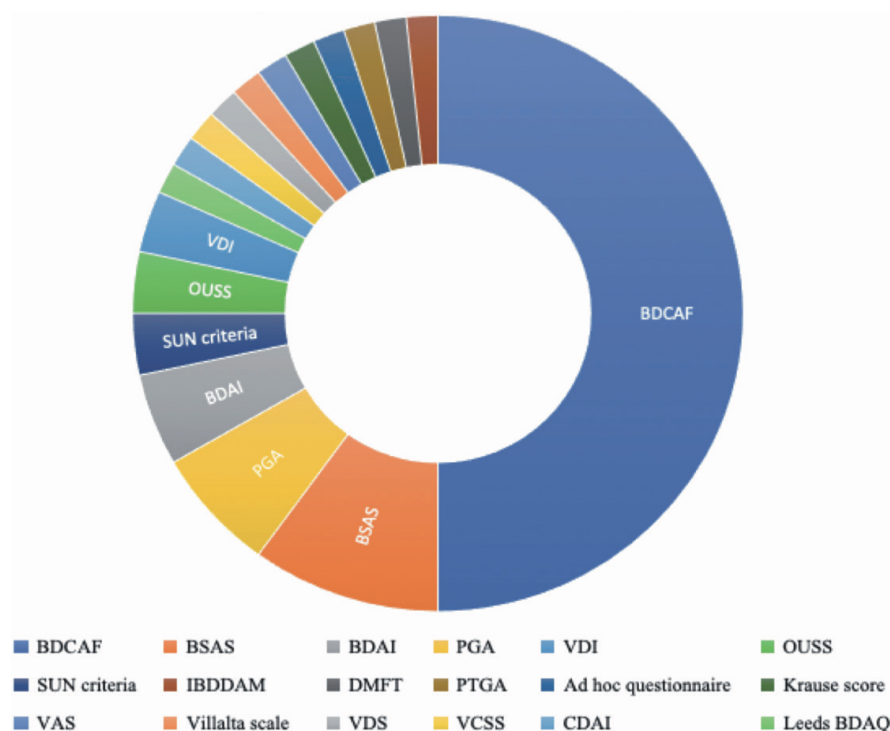
Considering the study types: 44 were cross-sectional studies (1, 3, 6, 7, 13, 15-17, 19-21, 23-27, 29-37, 40, 49-56, 58, 60-62, 64-66, 68, 69), 7 were case-control studies (5, 18, 39, 43, 46, 47, 57), 6 were clinical trials (38, 42, 45, 48, 59, 63), 6 were validation studies 810, 14, 22, 28, 41, 44) of QoL tools in different ethnic groups and 1 was a retrospective study (67). The detailed features of studies and BD patients included in this systematic review are reported in Supplementary Table S1.

We collected data about 7,449 patients with a BD diagnosis (3,491 females 51,71%, and 3,260 males 48,29% data available in 6,751 patients) (1-3, 5-7, 10, 13-36, 38-54, 56-63, 65-67, 69).

As regards age (data available in 3,867/7,449 patients) the reported adult

Table I. Percentage of each explored domain in the reported studies.

Explored domain	Number (%)
General QoL	44/64 (68.75)
Organ involvement related to QoL	11/64 (17.19)
Pain and fatigue	9/64 (14.06)
Psychological and social impact	35/64 (54.69)
Sleep	8/64 (12.50)
Physical functioning and workability	27/64 (42.19)

Legend:
■ BDCAF ■ BSAS ■ BDAI ■ PGA ■ VDI ■ OUSS
■ SUN criteria ■ IBDDAM ■ DMFT ■ PTGA ■ Ad hoc questionnaire ■ Krause score
■ VAS ■ Villalta scale ■ VDS ■ VCSS ■ CDAI ■ Leeds BDAQ

Fig. 4. Frequency of disease activity tools.
BDCAF: Behçet's disease current activity form; BSAS: Behçet's syndrome activity scale; BDAI: Behçet's disease activity index; PGA: physician's global assessment; VDI: venous disease index; OUSS: oral ulcer severity score; SUN: standardisation of uveitis nomenclature; IBDDAM: Iranian Behçet's disease dynamic activity measure; PTGA: patient's global assessment; VAS: visual analogue scale; VDS: venous disability score; VCSS: venous clinical severity score; CDAI: Crohn's disease activity index; BDAQ: Behçet's disease acticity questionnaire.

age range was 18–87 years (1, 3, 13, 15, 18, 22, 32-36, 44, 47-53, 57, 60, 61, 65-69). Only six studies included paediatric population: 3 studies enrolled BD patients from 17 years old (33, 61, 68), one included BD adolescents from 16 years old (32), one from 15 years old (69), and an additional one reported data about BD patients from 12 years old (22). The exact number of paediatric BD patients included in these cohorts was not available except for Blackford *et al*. that enrolled 10 BD children between 8 and 15 years of age (13).

We detected 47 different tools to evaluate QoL in BD patients (1-3, 5, 7, 10, 13-69). The mean number of tools adopted in each study was 2.14±1.34.

Figure 2 summarises the frequency of use of each tool in the studies included in the review. SF-36, BDQoL and Beck inventory scale (BDI) were the most explored tools, respectively in 23/64, 17/64 and 12/64 of the included studies. Considering the aforementioned 6 subdomains: general QoL and psychological and social impact were investigated in more than one half of studies, 68.75% and 54.69% respectively (Table I). None of the included studies explored all the 6 subdomains: 25 out of 64 studied (39%) investigated only one domain, represented by general QoL in 13/25 (52%). Figure 3 reports the percentage of studies based on the number of simultaneously explored domains.

The correlation with disease activity was investigated in 46/64 studies corresponding to 71.86 % (1, 3, 5-7, 14, 16, 17, 22, 23, 25-27, 30-33, 36-43, 46, 48, 50, 52-56, 58-69). The most frequent adopted tools to evaluate disease activity were Behçet's disease current activity form (BDCAF) in 46.88% of cases (30/54) (1, 6, 7, 16, 22, 27, 30-33, 36, 37, 39-43, 48, 50, 53, 55, 56, 58-60, 63-67, 69), Behçet's syndrome activity scale (BSAS) in 9.38% of included studies (6/64) (37, 46, 48, 54, 59, 61), and physician's global assessment (PGA) in 6.25% (4/64) (1, 5, 54, 65) (Fig. 4).

Discussion
The measurement of QoL is a summary of the level of impairment or activity limitation experienced by the patient because of his condition, together with his emotional response to these restrictions and the effect of the treatment. The concept of QoL is based on the "needs-based" model proposed by Hunt and McKenna, which postulates that individuals are motivated or driven by their needs and that life gains its quality from the ability and capacity of the individual to satisfy certain human needs (70).

In our systematic review, 47 different tools that were used to evaluate QoL in BD patients were identified. The lack of homogeneity in the adoption of a single, specific tool to evaluate QoL in BD reflects the complexity of measuring such a multi-dimensional domain. Furthermore, to date, only one tool is specifically designed for the BD population, that is the BD-QoL (10). The most frequently used questionnaire was the SF-36, that is a generic health status and outcomes measure of patients. Even though the SF-36 was originally designed for the general population, it was subsequently used in outpatient settings and adopted for measuring health-related QoL of individuals with several chronic health conditions, including BD. The SF-36 can be considered a very valuable tool as it estimates both the physical and the mental status of the patient; however, for BD patients (similarly to other relapsing-remitting conditions), it is necessary

also to explore QoL adopting a more comprehensive approach, collecting more information on additional dimensions related to the health-related QoL. Moreover, being a non-disease-specific tool, SF-36 does not allow to explore disease-specific outcomes. At this regard, an attempt to concentrate BD patients' needs within a single score is represented by the development of the Leeds BD-QoL questionnaire 810), currently validated in different studies and ethnic groups (14, 22, 28, 41, 44). Furthermore, except for the BD-QoL questionnaire, none of the available tools have been developed in collaboration with BD patients, in order to select the more appropriate explored domains and emphasise what their health mostly prevents them from doing.

In this perspective, BD paediatric population deserves a special consideration. Only a small number of BD children and adolescents have been involved in studies investigating QoL. Furthermore, none of the available tools are *ad-hoc* designed for the BD paediatric population. Therefore, the inadequacy is represented by the lack of specific tools taking into account the characteristic needs of subjects in developing age. In this context, a pivotal role in the QoL assessment should be assigned to the parents that represent the caregivers in charge of the therapeutical management and facing the daily limitations deriving from their child's disease.

In addition, the need to us more than one QoL questionnaire in most of the included studies additionally underlines the lack of a specific tool that can capture and assess at the same time the whole complexity of QoL in BD. Finally, the fragmentation of the tools adopted in BD does not allow to compare the different data available from the different cohorts and therefore, to appropriately quantify the impact of BD in the QoL of patients.

In conclusion, the assessment of QoL in BD patients may provide a fundamental measurement for health to evaluate the outcome of interventions for this condition characterised by complex patterns of impairment. The adoption of a single validated QoL tool, developed including the BD patient's perspective, may provide an accurate and effective assessment, ensure the comparison within different cohorts and set standardised values to define QoL level in BD patients. On this regard, it is crucial that patients and caregivers are actively involved in the process of implementation of existing tools thanks to an appropriate co-design approach ensuring that all the dimensions that have an impact on their life are measured and quantified. In this regard, the role of caregivers and their QoL should also be considered, considering also the burden caused by BD on their life and promoting their participation in the co-design process of QoL tools (71, 72).

Take home messages

- This is the first systematic review that summarises the existing tools, specifically adopted to explore the QoL in BD patients. The effect size of these tools and the overall identification of variables affecting QoL in patients suffering from BD have been also measured.
- QoL assessment has become routine in clinical research, showing the growing awareness of the non-inferiority of QoL measures as measure of outcome.
- For many years, the assessment of QoL in BD patients has mainly been a surrogate of disease outcomes, but a wider impact of the disease on the patient's lifestyle has not been considered.

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