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Measuring fatigue: A Meta-Review

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ABSTRACT

There is a lack of validated tools to measure fatigue in patients with inflammatory skin, neuropsychiatric and medical disorders. The use of non-validated tool may compromise the quality of data. The purpose of this meta-review was to evaluate existing fatigue scales commonly used to assess fatigue in other inflammatory conditions and to identify if there are scales that have been validated in dermatologic conditions. The PubMed/MEDLINE and SCOPUS databases were systematically searched from inception through March 10th, 2020 in accordance with the PRISMA statement. Validated tools were identified and assessed according to their main measurement properties. The literature search identified 403 references, and eight studies were eligible and assessed in this review. The unidimensional fatigue scales included were the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), Brief Fatigue Inventory, Fatigue Severity Scale, Numerical Rating Scale – Fatigue, and Visual Analog Scale – Fatigue. The multidimensional fatigue scales found were the Checklist Individual Strength, Chalder Fatigue Scale, Multidimensional Assessment of Fatigue, Multidimensional Fatigue Inventory Scale, and Piper Fatigue Scale. To measure fatigue, a brief scale with the ability to detect change is needed as there is a growing interest in evaluating this dimension of treatment response. In addition, a good content validity is also needed. From this systematic review, none of the selected scales have had content validation, even though the FACIT was validated in patients with Psoriatic Arthritis. Validation studies in specific disorders are urgently warranted.

INTRODUCTION

Fatigue, defined as an overwhelming sense of tiredness, lack of energy, and a feeling of exhaustion,(1) has been described in patients suffering a range of inflammatory conditions, including psoriatic arthritis (PsA), cutaneous psoriasis,(2-4) hidradenitis suppurativa (HS),(5-7) and rheumatoid arthritis (RA).(8) There is a broad array of pathways that may underpin fatigue occurring in systemic and neuroinflammatory disorders. This range of abnormalities includes increased levels of pro-inflammatory cytokines, e.g., interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF) α and interferon (IFN) α; that are often augmented in these disorders. (9-12)

Even though there is a wide array of inflammatory skin, neuropsychiatric and medical conditions that has been associated with fatigue, the questionnaires adopted to measure this phenomenon are validated in other medical conditions. For instance, in a study by Tarazi *et al*. (2018) the short-form 36 (SF-36) vitality scale was applied to assess fatigue in patients with cutaneous lupus erythematosus, amyopathic dermatomyositis, and autoimmune blistering diseases, in which it was evidenced higher levels of fatigue in these patients when compared to healthy controls.(13) Studies

which assesses fatigue in patients with HS face the same challenge, as fatigue questionnaires of other medical conditions are often adopted. For example, in a cross-sectional study on 54 Polish patients diagnosed with HS, 40% of patients experienced clinically significant fatigue measured by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Scale.(5) Finally, Riis et al. (2017) recently conducted a pilot study investigating fatigue in Danish patients with HS using the Multidimensional Fatigue Instrument 20 (MFI-20), and found out that those patients reported higher levels of fatigue when compared with the general population.(7)

The lack of validated tool may compromise the quality of data, as validation assessment assures whether the content is suitable or not for a group of patients,(14) and it is clearly an unmet need in the field. The purpose of this meta-review, which is a method of systematically appraising the results of existing reviews (15), was to evaluate existing fatigue scales commonly used to assess fatigue in other inflammatory conditions and to identify if there are scales that have been validated in dermatologic conditions.

METHODS

Protocol and registration

The protocol for this meta-review was defined *a priori* and registered online in the International Prospective Register of Systematic Reviews (PROSPERO, Register ID=CRD42020173568). This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.(16)

We used two stage approach. In the first stage, we meta-reviewed fatigue as a primary outcome in inflammatory and autoimmune diseases. The PubMed/MEDLINE and SCOPUS databases were searched from inception through March 10th, 2020. Search string available in supplementary material (Appendix 1). The reference lists of the shortlisted studies were then screened.

In the second stage, we extracted the fatigue tools adopted in the selected studies and performed a review of the psychometric properties of each tool. The search strategy of this secondary review was to hand-search the manuscripts that assessed psychometric properties of each scale in the PubMed/MEDLINE.

Outcomes

The primary outcome was to identify fatigue instruments used in inflammatory and autoimmune diseases. The secondary outcome was the measurement properties (i.e., reliability, validity, burden to the patient) collected in the second stage part of the fatigue instruments obtained from each study. The measurement properties assessed of the available fatigue tools may not be directly adopted across various medical conditions as previous validation is required, however, it may

assist future studies to select a proper tool to be validated in a specific medical condition. The selected instruments were classified as unidimensional and multidimensional. The unidimensional scales focused on one dimension, most typically severity. Multidimensional scales assessed information on more than one dimension of fatigue, for instance, severity and nature of fatigue, allowing for the calculation of segregated scores and a global score.

Eligibility criteria

Included studies met the following eligibility criteria: (1) systematic reviews or meta-analyses which assessed fatigue as main outcome or as part of study in the following inflammatory disorders: HS, Crohn's Disease (CD), Ulcerative Colitis (UC), Psoriasis, Psoriatic Arthritis (PsA), SLE, Lupus, Systemic Sclerosis (SS), Atopic Dermatitis (AD), Rheumatoid Arthritis (RA), Sjögren's Syndrome (SS); (2) they provided tools to measure specifically fatigue; (3) only adult participants were included; (4) they were published in English.

Studies were excluded if: (1) fatigue was not assessed; (2) tools adopted to measure fatigue were not provided; (3) paediatric samples were included; (4) studies published in languages other than English; and (5) abstracts and/or poster presentations were also excluded.

Study selection

Following the database search, studies were compiled into a single list with all duplicates removed. Titles and abstracts were then independently screened for possible eligibility by three reviewers (FT, NK, and RS) and conflicts were resolved by discussion with a fourth investigator (MM). Full-text publications were retrieved and assessed eligibility. Figure 1 depicts the study selection process.

Data collection, synthesis, and management

Data were independently extracted by two authors onto a Microsoft Excel spreadsheet. The data from the primary outcomes were extracted in accordance to the following information: general identification (first author's name, year of publication); study design; medical condition; and tools adopted to measures fatigue. Any differences were discussed and resolved. The data from the secondary outcomes were the selected tools for fatigue, and their main measurement/psychometric properties were synthesised.

Validity and Reliability Assessment

The tools were assessed according to their content, criterion, and construct validity as well their reliability (i.e. test-retest reliability, internal consistency and inter-rater reliability). Definition and categorization of each measurement property available in supplementary material (Appendix S2).

Methodologic Quality Appraisal

Quality appraisal of eligible systematic reviews and meta-analyses was assessed according to the Quality Assessment Tools developed by the National Institute of Health and the National Institute of Mental Health (NIH/NIMH).(17)

RESULTS

Study identification

<Fig 1>

The literature search identified 403 references (Fig 1). After removal of 16 duplicates, 387 records underwent title/abstract screening, and 22 studies were selected for full-text review. Thereafter, fourteen studies were excluded with reasons. Qualitative methodological appraisal of eligible studies is present in table 1. The overall methodological quality of included references was fair [Median = 4 Interquartile Range = 2.5 (7 – 9)].

Description of studies

Eight studies were included in the final review: two were meta-analyses and systematic reviews, and six were systematic reviews (Table 1). Eleven fatigue scales were identified: five unidimensional [the FACIT-F Scale, Visual Analog Scale – Fatigue (VAS-F), Numerical Rating Scale – Fatigue (NRS-F), Fatigue Severity Scale (FSS), Brief Fatigue Inventory (BFI)] and five multidimensional [Checklist Individual Strength (CIS), Chalder Fatigue Scale (CFS), Multidimensional Assessment of Fatigue (MAF), MFI, Piper Fatigue Scale (PFS), and Fatigue Impact Scale (FIS)] (Table 2).

Outcomes

Functional Assessment of Chronic Illness Therapy – Fatigue Scale

The FACIT-F was originally developed as an addition to the Functional Assessment of Cancer Therapy (FACT) instrument, but it has been validated and found to be a reliable stand-alone tool.(18, 19) The content validity was assessed by Cella *et al*., in a group of patients with PsA. After performing cognitive interview in 12 adults patients with PsA, they found out that the FACIT presents good content validity.(20) In a study by Butt *et al*. (2013), the construct validity of FACIT-F was assessed in patients with cancer, stroke, and HIV; results were comparable to the FACT-general which measures quality of life. The Pearson's correlation coefficients was strong in all three samples – cancer ($r = 0.78$, $p<0.001$), stroke ($r = 0.66$, $p<0.001$), and HIV ($r = 0.80$, $p<0.001$).(21) In a study by Chandran *et al.* (2007), in patients with PsA, the criterion validity was assessed through Pearson's correlation between modified FSS (mFSS) and FACIT-F ($r = -0.79$, 95% CI -0.85 to -0.72).(22) In

addition, FACIT-F has demonstrated good internal consistency (Cronbach's alpha > 0.90) and strong test-retest reliability.(18, 21, 23-25) The scale has clear instructions and detailed scoring guidelines at www.facit.org.

Visual Analog Scale

The VAS has the advantage of extreme simplicity and a low patient burden.(26) It is typically a line of fixed length with words that anchor the scale at the extreme ends and no words describing intermediate positions. Patients are instructed to indicate the place on the line corresponding to their self-perceived state. There are multiple validated tools, in addition, researchers often create individual items for individual studies; hence, the introductory question, time recall period, and verbal descriptors may vary.(27-30) There is a VAS scale, Bristol Rheumatoid Arthritis Fatigue Visual Analog Scale (BRAF VAS), developed by Nicklin et al. (2010) that was validated in patients with RA which includes standardized wording for VAS to measure fatigue severity, effect, and coping. It demonstrated strong criterion validity, and weak to moderate construct validity.(31)

Numerical Rating Scale – Fatigue

NRS-F is a Likert type version of the VAS, in which the most frequently used version is the 11-point (0-10) NRS.(32) NRS is easier and quicker to score compared to the VAS. Lack of standardization limits the interpretation of data and researchers often generate items for individual studies. The introductory question, time recall period, and verbal descriptors may vary.

Fatigue Severity Scale

The FSS is a questionnaire developed by Krupp *et al.* (1989).(33) It has been previously validated in healthy adults and in patients with multiple medical conditions [e.g. SLE, multiple sclerosis (MS), and Inflammatory Bowel Disease] but not in dermatological conditions.(33-36) The FSS has demonstrated strong content, construct, and criterion validity across several medical conditions. In a study by Learmonth *et al*. (2013), the authors assessed 86 patients with MS with the FSS and the mFIS, and Spearman correlation coefficients were strong and significant ($r = 0.75$, $p<0.001$), thereby indicating strong criterion validity. They also demonstrated that the FSS has an ICC of 0.751 for the test–retest reliability after a six-month follow-up.(37) The construct validity was previously assessed in patients with SLE (N=32) through its correlation with SF-36 questionnaire which correlated significantly with the subscale Vitality of SF-36 (r=0.63).(38) The Cronbach's alpha was tested by Krupp *et al.* in a group of 25 patients with MS, 29 patients with SLE, and 20 healthy controls, and the resulted ranged from 0.81 to 0.89.(33)

Brief Fatigue Inventory

The BFI is a nine-item questionnaire (39, 40) assessed by Nunes *et al.* (2019) in 100 outpatients with cancer. The criterion validity was strong, measured through its correlation with the PFS (PFS; r = 0.84, p<0.05). The BFI showed a strong internal consistency (Cronbach's alpha = 0.94), and substantial test-retest [ICC (95% CI) = 0.87 (0.81 to 0.91)].(41) To assess its construct validity, Mendonza *et al.* performed a study with 305 patients with cancer and found out that the Pearson's correlations between BFI and disease-related anemia presented statistically significant association (r = -0.36, p<0.001). A Strong ICC of 0.96 of the BFI was also evidenced. (39)

Checklist Individual Strength

The CIS is a 20-item questionnaire developed to assess four dimensions of fatigue (fatigue severity, concentration, reduced motivation and reduced activity levels), that was first tested in a large sample of patients with Chronic Fatigue Syndrome. (42) The CIS showed strong internal consistency (Cronbach's alpha > 0.89) in general population, multiple sclerosis, rheumatoid arthritis, fibromyalgia syndrome, as well as high test-retest reliability (r =0.74–0.86). The criterion validity was moderate to strong, when compared to other fatigue scales, as the correlation with Chalder Fatigue Scale was 0.439, and the correlation with SF-36 vitality was −0.606 in a general population sample.(43)

Multidimensional Assessment of Fatigue

The MAF is tool developed as a revision of the PFS to measure multiple dimensions of fatigue. The construct validity was assessed in a population with RA (N = 51) through the correlation with the Profile of Mood States fatigue and vigor subscales with results of 0.84 and -0.62, respectively.(44) Furthermore, criterion validity was evaluated through Pearson's correlation with VAS-F (N = 7760) and presented strong correlation (r = 0.80, p<0.05).(45) The Cronbach's alpha for internal consistency was 0.92 for the final NRS version performed in a study including 122 patients with RA.(46)

Multidimensional Fatigue Inventory Scale

The MFI-20 is a questionnaire developed by Smets *et al.* (1995) with five dimensions [i.e. General Fatigue (GF), Physical Fatigue (PF), General Activity (GA), Reduced Motivation (RM), and Mental Fatigue (MF)]. Validity has been evaluated in different populations, including cancer patients, army recruits, and medical students. Smets *et al.* demonstrated that all correlations obtained in the group of patients with cancer between VAS-F scores and MFI ranged from 0.23 for MF to 0.77 for GF (p<0.01). Internal consistency is adequate for the GF, PF, and MF dimensions (Cronbach's alpha >0.84) and unsatisfactory for the RA and RM (Cronbach's alpha >0.65). In this study, there were a few unexpected findings as patients with cancer and students did not differ on GF, and scores of patients presented better outcome on MF.(47) In another study by Wintermann *et al.* (2018), the MFI-20 could not be ascertained as a reliable and valid tool in a population of 195 chronically critically ill patients following intensive care. (48) The MFI was also assessed by Hinz *et al.* (2020), where the factorial validity was insufficient.(49)

Fatigue Impact Scale

The FIS was validated by Fisk *et al.* (1994) in a group of 105 patients with MS, and 34 patients with mild hypertension, in which they obtained Cronbach's alpha values for all FIS items of 0.98. The construct validity was tested through the correlation with the sickness impact profile [i.e. MS ($r = 0.53$, $p<0.001$)], and HT [$r = 0.55$, $p<0.005$)].(50) The criterion validity was not assessed in the original study. The modified FIS (MFIS) is a shorter version of FIS with 21 items, which was previously used to assess a group of 82 patients with MS where it demonstrated strong criterion and construct validities. In this study, construct validity was assessed through its correlation with Hospital Anxiety and Depression Scale (HADS) - Depression ($r = 0.51$, $p<0.01$), and HADS-Anxiety ($r = 0.41$, $p<0.01$).(37) The criterion validity was tested through its correlation with FSS ($r = 0.75$, $p<0.001$), and reliability was adequate over six months [ICC (95%CI) = 0.86 (0.79 to 0.91)].

Chalder Fatigue Scale

The CFS is a questionnaire which assesses two dimensions of fatigue (i.e. physical and mental fatigue). To assess criterion validity, Chalder *et al.* (1993) applied the CFS and the fatigue item of the revised Clinical Interview Schedule (CIS-R) in 100 consecutive general practice patients. After Relative Operating Characteristic (ROC) analysis comparison using a cut off score of 0.75, they demonstrated a sensitivity of 75.5% and specificity of 74.5%. In addition, they found a Cronbach's alpha of 0.89.(51) Picariello *et al.* (2016) studied 174 haemodialysis patients, and found out that the CFS had strong correlation with the HADS ($r = 0.64$, $p<0.01$) and a weak association with comorbidity (Charlson Comorbidity Index; $r= 0.27$, $p<0.01$).(52)

Piper Fatigue Scale

The original version of Piper Fatigue Scale was developed to assess fatigue in patients with cancer.(53, 54) This first version contains 40 items and was initially evaluated in a population of 42 patients, and resulted in an adequate Cronbach's alpha of 0.85. The criterion validity and the construct validity were evaluated through the comparison of the PFS with the "Fatigue Symptom Checklist: Subscales & Intensities" and "Profile of Mood States: Subscales", respectively. Criterion validity ($r = - 0.47$, $p<0.01$) demonstrated moderate correlation, whilst construct validity ($r = - 0.50$, $p<0.01$) demonstrated strong correlation.(55) The original version of PFS has been criticized for its length and lack of clarity(56) and newer versions were subsequently developed. The revised PFS (PFS-R) includes 22 items, and in 2012, a further reduction in length was performed by Reeve *et al.* (57, 58) Further details in table 2.

DISCUSSION

To the best of our knowledge, there are no validated questionnaires to measure fatigue in patients with inflammatory skin disorders, and often studies adopt tools developed for other medical

conditions. The absence of validated tools to assess fatigue in patients with inflammatory skin disorder is clearly an unmet need in the field and applying a non validated tool may compromise the quality of the data. The main purpose of assessing content validity and quantitative measurements is to assess if the tool fits for the purpose of fatigue measurement in a group of patients. In addition, a consensus to stablish a proper tool may be needed, as the lack of standardized tools may challenge the comparison of outcomes from different tools in future studies.

Notwithstanding the ubiquitous nature of fatigue in medical practice, the choice of an instrument to assess fatigue may be challenging for both clinicians and researchers, and psychometric/measurement properties should guide this selection. In addition, it is important to have an open dialogue with patients to prevent extra burden in clinical and research settings. Through the meetings promoted by the International Dermatology Outcome Measures (IDEOM) group , patients from its committee requested a short tool to assess symptoms.(59)

From this review, the FACIT was the only tool in which the content validity was assessed for patients with a skin-related disorder, as it was validated for patients with PsA.(20) It is worth highlighting that the content validity is the most important measurement property of a patient-reported outcome measure according to the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN).(14) The FACIT-F is a widely adopted questionnaire tested in multiple chronic illnesses and is the most adopted fatigue instrument in psoriatic disease. The FACIT-F has been used in different settings (i.e. community and in/outpatient clinics).(18, 21, 23-25) If the main objective is to screening patients with fatigue, it must be able to differentiate cases from non-cases. the FACIT-F and FSS were the only two tools which presented a cutoff point to differentiate fatigued versus non-fatigued patients.

From the multidimensional scales assessed in this meta-review, the MAF demonstrated consistently robust psychometric properties with the advantage of having a short length compared to the other multidimensional scales.(36, 60, 61) The other assessed scales in this study present features that should be highlighted. For instance, the FIS may present an appropriate literacy for patients with MS as the 13th item assesses fatigue through the expression “muscle weakness”, however, it may be inadequate for patients with skin, neuropsychiatric and medical conditions. It is important to hightlight that none of the multidimentional scales selected has been validated for patients with inflammatory skin disorder up to this point.

If a scale needs to be used to detect disease progression or to measure fatigue response to treatment, it must have the ability to detect change over time. From the scales assessed in this study, seven (i.e. FACIT,(62) FSS,(63) BFI,(64) CIS,(43) MAF,(63) MFI,(65) FIS/MFIS,(66) CFS(67)) have this demonstrated ability.

Before choosing a fatigue scale, it is necessary to ascertain exactly which aspects of fatigue need to be measured. If the clinician or researcher expect to assess severity or to adopt a screening tool, a unidimensional scale may be appropriate, for instance, FACIT and FSS. On the other hand, if it is necessary to evaluate a more comprehensive experience of fatigue, a measure to explore the affective, cognitive, somatic, and behavioral manifestations of fatigue should be adopted, for example, MAF. Multidimensional fatigue evaluation, which captures multiple features of fatigue and its impact on function, is more informative than a measure of severity alone; however, it is usually longer and more time consuming for patients.

Additionally, even though the fatigue symptom is unspecific, there may be differences in features of fatigue between diseases, although little is known about it. Use of generic measurement instruments may facilitate the documentation of such differences, which may be of scientific as well as clinical importance.(68) Hence, it is interesting to adopt and validate previously developed questionnaires in other medical conditions in patients with dermatologic conditions, as it may facilitate futures studies.

Some limitations of the present study must be addressed. First, the psychometric and measurement properties discussed were assessed in conditions outside of the inflammatory dermatosis, hence, adopting a questionnaire without a proper validation may be unadvisable, as these properties may various across medical conditions. Second, we only screened studies in English, thus, other tools validated in other languages were not selected. Third, due to the screening method of only selecting meta-analysis and systematic reviews, it is possible that some instruments have not been selected in our study. The main strength of our study was the comprehensive screening of tools adopted in multiple medical conditions which may provide us a broad view of fatigue tools available currently.

CONCLUSION

A vast variety of instruments has been used across inflammatory diseases, which may challenge comparison across studies. In addition, the use of instruments lacking validity data compromises interpretation of results, as their content may not be appropriate for patients with skin diseases. From the tools assessed in this meta-review, the FACIT has been validated in patients with PsA,(22) which is a population of interest in dermatology and may be a suitable instrument to be validated in other dermatological condition. From the instruments assessed in this meta-review, FACIT-F, FSS, MAF presented a broad array of studies assessing their psychometric properties in inflammatory medical conditions. Those scales have been tested frequently, and have demonstrated consistent measurement properties, hence, to develop and test a new tool for patients with inflammatory skin disorders may be not necessary. Future studies to validate fatigue instruments in patients with inflammatory skin conditions are required.

QUESTIONS (ANSWERS PROVIDED AFTER REFERENCES)

True/False

1 Fatigue has been described in patients suffering a range of inflammatory conditions, including psoriatic disease, hidradenitis suppurativa, cutaneous lupus erythematosus, amyopathic dermatomyositis, and autoimmune blistering diseases.

2 Increased levels of pro-inflammatory cytokines, e.g., interleukin-1 (IL-1), IL-6, tumor necrosis factor α and interferon α are often augmented in fatigue phenomenon and in inflammatory skin disorder.

3 There is no validated tools to measure fatigue in patients with inflammatory skin disorder.

4 If the main objective is to screening patients with fatigue, it must be able to differentiate cases from non-cases. the Multidimensional Assessment of Fatigue was the only tool which presented a cutoff point to differentiate fatigued versus non-fatigued patients.

5 The FACIT was the only tool in which the content validity was assessed for patients with a skin-related disorder, as it was validated for patients with Psoriatic Arthritis.

6 Adopting a questionnaire without a proper validation may be acceptable, as fatigue is a widely described phenomenon across medical conditions.

7 Before choosing a fatigue scale, it is necessary to ascertain exactly which aspects of fatigue need to be measured and psychometric property needed, such as the ability to detect change over time, screening properties, severity measurement.

8 A multidimensional fatigue evaluation, which captures multiple features of fatigue and its impact on function, is more informative than a measure of severity alone; and should be always preferred adopted.

9 The main purpose of assessing content validity and quantitative measurements is to assess if the tool fits for the purpose of fatigue measurement in a group of patients and applying a non validated tool may compromise the quality of the data.

10 The FACIT-F is a widely adopted questionnaire tested in multiple chronic illnesses and is the most adopted fatigue instrument in psoriatic disease.

REFERENCES

1. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Curr Opin Neurol. 1996;9(6):456-60.

2. Skoie IM, Dalen I, Ternowitz T, Jonsson G, Kvivik I, Norheim K, et al. Fatigue in psoriasis: a controlled study. Br J Dermatol. 2017;177(2):505-12.

3. Pilgaard T, Hagelund L, Stallknecht SE, Jensen HH, Esbensen BA. Severity of fatigue in people with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis - Results of a cross-sectional study. PLoS One. 2019;14(6):e0218831.

4. Reygaerts T, Mitrovic S, Fautrel B, Gossec L. Effect of biologics on fatigue in psoriatic arthritis: A systematic literature review with meta-analysis. Joint Bone Spine. 2018;85(4):405-10.

5. Matusiak L, Bieniek A, Szepietowski JC. Psychophysical aspects of hidradenitis suppurativa. Acta Derm Venereol. 2010;90(3):264-8.

6. Ring HC, Theut Riis P, Zarchi K, Miller IM, Saunte DM, Jemec GB. Prodromal symptoms in hidradenitis suppurativa. Clin Exp Dermatol. 2017;42(3):261-5.

7. Riis PT, Sigsgaard V, Boer J, Jemec GBE. A pilot study of fatigue in patients with hidradenitis suppurativa. Br J Dermatol. 2018;178(1):e42-e3.

8. Druce KL, Basu N. Predictors of fatigue in rheumatoid arthritis. Rheumatology (Oxford). 2019;58(Suppl 5):v29-v34.

9. Morris G, Berk M, Galecki P, Walder K, Maes M. The Neuro-Immune Pathophysiology of Central and Peripheral Fatigue in Systemic Immune-Inflammatory and Neuro-Immune Diseases. Mol Neurobiol. 2016;53(2):1195-219.

10. Louati K, Berenbaum F. Fatigue in chronic inflammation - a link to pain pathways. Arthritis Res Ther. 2015;17:254.

11. Vossen A, van der Zee HH, Prens EP. Hidradenitis Suppurativa: A Systematic Review Integrating Inflammatory Pathways Into a Cohesive Pathogenic Model. Front Immunol. 2018;9:2965.

12. Georgescu SR TM, Caruntu C, Sarbu MI, Mitran CI, Mitran MI, Matei C, Constantin C, Neagu M. . Advances in Understanding the Immunological Pathways in Psoriasis. Int J Mol Sci. 2019 Feb 10;;20(3):739. .

13. Tarazi M, Gaffney RG, Pearson D, Kushner CJ, Werth VP. Fatigue in systemic lupus erythematosus and other autoimmune skin diseases. Br J Dermatol. 2019;180(6):1468-72.

14. Terwee CB, Prinsen CA, Chiarotto A, Vet HCd, Bouter LM, Alonso J, et al. COSMIN methodology for assessing the content validity of PROMs

User manual version 10. 2018.

15. Ryan RE, Kaufman CA, Hill SJ. Building blocks for meta-synthesis: data integration tables for summarising, mapping, and synthesising evidence on interventions for communicating with health consumers. BMC Med Res Methodol. 2009;9:16.

16. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

17. U.S. Department of Health and Human Services NIoH, National Institute of Mental Health. . Study Quality Assessment Tools. Bethesda, MD: US Government Printing Office. 2015.

18. Montan I, Lowe B, Cella D, Mehnert A, Hinz A. General Population Norms for the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. Value Health. 2018;21(11):1313-21.

19. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13(2):63-74.

20. Cella D, Wilson H, Shalhoub H, Revicki DA, Cappelleri JC, Bushmakin AG, et al. Content validity and psychometric evaluation of Functional Assessment of Chronic Illness Therapy-Fatigue in patients with psoriatic arthritis. J Patient Rep Outcomes. 2019;3(1):30.

21. Butt Z, Lai JS, Rao D, Heinemann AW, Bill A, Cella D. Measurement of fatigue in cancer, stroke, and HIV using the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scale. J Psychosom Res. 2013;74(1):64-8.

22. Chandran V, Bhella S, Schentag C, Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. Ann Rheum Dis. 2007;66(7):936-9.

23. Junghaenel DU, Christodoulou C, Lai JS, Stone AA. Demographic correlates of fatigue in the US general population: results from the patient-reported outcomes measurement information system (PROMIS) initiative. J Psychosom Res. 2011;71(3):117-23.

24. Hagell P, Hoglund A, Reimer J, Eriksson B, Knutsson I, Widner H, et al. Measuring fatigue in Parkinson's disease: a psychometric study of two brief generic fatigue questionnaires. J Pain Symptom Manage. 2006;32(5):420-32.

25. Lai JS, Beaumont JL, Ogale S, Brunetta P, Cella D. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. J Rheumatol. 2011;38(4):672-9.

26. Freyd M. The Graphic Rating Scale. Journal of Educational Psychology. 1923;14(2):83-102.

27. Fahndrich E, Linden M. [Reliability and validity of the Visual Analogue Scale (VAS) (author's transl)]. Pharmacopsychiatria. 1982;15(3):90-4.

28. Luria RE. The validity and reliability of the visual analogue mood scale. J Psychiatr Res. 1975;12(1):51-7.

29. Remington M, Tyrer PJ, Newson-Smith J, Cicchetti DV. Comparative reliability of categorical and analogue rating scales in the assessment of psychiatric symptomatology. Psychol Med. 1979;9(4):765-70.

30. Klimek L, Bergmann KC, Biedermann T, Bousquet J, Hellings P, Jung K, et al. Visual analogue scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). Allergo J Int. 2017;26(1):16-24.

31. Nicklin J, Cramp F, Kirwan J, Greenwood R, Urban M, Hewlett S. Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. Arthritis Care Res (Hoboken). 2010;62(11):1559-68.

32. Center USDoHaHSFaDACfDEaRCCfBEaRC. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009.

33. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121-3.

34. Impellizzeri FM, Agosti F, De Col A, Sartorio A. Psychometric properties of the Fatigue Severity Scale in obese patients. Health Qual Life Outcomes. 2013;11:32.

35. Ozyemisci-Taskiran O, Batur EB, Yuksel S, Cengiz M, Karatas GK. Validity and reliability of fatigue severity scale in stroke. Top Stroke Rehabil. 2019;26(2):122-7.

36. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manage. 2009;37(1):107-28.

37. Learmonth YC, Dlugonski D, Pilutti LA, Sandroff BM, Klaren R, Motl RW. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. J Neurol Sci. 2013;331(1-2):102-7.

38. Mattsson M, Moller B, Lundberg I, Gard G, Bostrom C. Reliability and validity of the Fatigue Severity Scale in Swedish for patients with systemic lupus erythematosus. Scand J Rheumatol. 2008;37(4):269-77.

39. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999;85(5):1186-96.

40. Toh C, Li M, Finlay V, Jackson T, Burrows S, Wood FM, et al. The Brief Fatigue Inventory is reliable and valid for the burn patient cohort. Burns. 2015;41(5):990-7.
41. Nunes AF, Bezerra CO, Custodio JDS, Friedrich CF, Oliveira IS, Lunardi AC. Clinimetric Properties of the Brief Fatigue Inventory Applied to Oncological Patients Hospitalized for Chemotherapy. J Pain Symptom Manage. 2019;57(2):297-303.
42. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. J Psychosom Res. 1994;38(5):383-92.
43. Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HWM, van Engelen BGM, van Riel P, et al. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. J Psychosom Res. 2017;98:40-6.
44. Belza BL. Comparison of self-reported fatigue in rheumatoid arthritis and controls. J Rheumatol. 1995;22(4):639-43.
45. Wolfe F. Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. J Rheumatol. 2004;31(10):1896-902.
46. Jump RL, Fifield J, Tennen H, Reisine S, Giuliano AJ. History of affective disorder and the experience of fatigue in rheumatoid arthritis. Arthritis Rheum. 2004;51(2):239-45.
47. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39(3):315-25.
48. Wintermann GB, Rosendahl J, Weidner K, Strauss B, Hinz A, Petrowski K. Fatigue in chronically critically ill patients following intensive care - reliability and validity of the multidimensional fatigue inventory (MFI-20). Health Qual Life Outcomes. 2018;16(1):37.
49. Hinz A, Benzing C, Brahler E, Zenger M, Herzberg PY, Finck C, et al. Psychometric Properties of the Multidimensional Fatigue Inventory (MFI-20), Derived From Seven Samples. J Pain Symptom Manage. 2020;59(3):717-23.
50. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994;18 Suppl 1:S79-83.
51. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res. 1993;37(2):147-53.
52. Picariello F, Moss-Morris R, Macdougall IC, Chilcot J. Measuring fatigue in haemodialysis patients: The factor structure of the Chalder Fatigue Questionnaire (CFQ). J Psychosom Res. 2016;84:81-3.

53. Romkens TE, van Vugt-van Pinxteren MW, Nagengast FM, van Oijen MG, de Jong DJ. High prevalence of fatigue in inflammatory bowel disease: A case control study. J Crohns Colitis. 2011;5(4):332-7.

54. Miles LF, Litton E, Imberger G, Story D. Intravenous iron therapy for non-anaemic, iron-deficient adults. Cochrane Database Syst Rev. 2019;12:Cd013084.

55. Piper BF, Lindsey AM, Dodd M, Ferketich SL, Paul SM, Weller S. The Development of an Instrument to Measure the Subjective Dimension of Fatigue. Conference Proceedings. 1989.

56. Wu HS, McSweeney M. Measurement of fatigue in people with cancer. Oncology Nursing Forum. 2001; 28 (9), 1371–1384.

57. Al Maqbali M, Hughes C, Gracey J, Rankin J, Dunwoody L, Hacker E. Quality assessment criteria: psychometric properties of measurement tools for cancer related fatigue. Acta Oncol. 2019;58(9):1286-97.

58. Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM. The revised Piper Fatigue Scale: psychometric evaluation in women with breast cancer. Oncol Nurs Forum. 1998;25(4):677-84.

59. Elman SA, Merola JF, Armstrong AW, Duffin KC, Latella J, Garg A, et al. The International Dermatology Outcome Measures (IDEOM) Initiative: A Review and Update. J Drugs Dermatol. 2017;16(2):119-24.

60. Santos EJF DC, da Silva JAP, Ferreira RJO. . The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. . Rheumatology (Oxford). 2019;;58(Suppl 5):v3–v9. doi:10.1093/rheumatology/kez351.

61. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S263-86.

62. Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, J. M. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. . Ann Rheum Dis 2007:66(2):163–8. .

63. Pouchot J, Kherani RB, Brant R, Lacaille D, Lehman AJ, Ensworth S, et al. Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis. J Clin Epidemiol. 2008;61(7):705-13.

64. Pyszora A, Budzynski J, Wojcik A, Prokop A, Krajnik M. Physiotherapy programme reduces fatigue in patients with advanced cancer receiving palliative care: randomized controlled trial. Support Care Cancer. 2017;25(9):2899-908.

65. Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clin Ther. 2008;30(11):1988-2004.

66. Moller F, Poettgen J, Broemel F, Neuhaus A, Daumer M, Heesen C. HAGIL (Hamburg Vigil Study): a randomized placebo-controlled double-blind study with modafinil for treatment of fatigue in patients with multiple sclerosis. Mult Scler. 2011;17(8):1002-9.

67. Tench CM, McCarthy J, McCurdie I, White PD, D'Cruz DP. Fatigue in systemic lupus erythematosus: a randomized controlled trial of exercise. Rheumatology (Oxford). 2003;42(9):1050-4.

68. Hjollund NH, Andersen JH, Bech P. Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. Health Qual Life Outcomes. 2007;5:12.

ANSWERS TO QUESTIONS

1. True
2. True
3. True
4. False
5. True
6. False
7. True
8. False
9. True
10. True

Table 1.

Author, Year	Study Design	Primary Medical Condition	Fatigue Assessment Tool	Quality Appraisal[&]
Skoie et al., 2019(1)	Systematic Review and Meta-analysis	Psoriasis	Functional Assessment of Chronic Illness Therapy Fatigue Scale	6
Reygaerts et al., 2018(2)	Systematic Review and Meta-analysis	Psoriatic Arthritis	Functional Assessment of Chronic Illness Therapy Fatigue Scale Visual Analogue Scale – Fatigue	4
Hojgaard et al., 2018(3)	Systematic Review	Psoriatic Arthritis	Functional Assessment of Chronic Illness Therapy Fatigue Scale Numerical Rating Scale – Fatigue Visual Analogue Scale – Fatigue	6
Orbai et al., 2016(4)	Systematic Review	Psoriatic Arthritis	Functional Assessment of Chronic Illness Therapy Fatigue Scale Visual Analogue Scale – Fatigue	2
van Langenberg et al., 2010(5)	Systematic Review	Inflammatory Bowel Disease	Functional Assessment of Chronic Illness Therapy Fatigue Scale Visual Analogue Scale – Fatigue Fatigue Severity Scale Fatigue Impact Scale Chalder Fatigue Scale Brief Fatigue Inventory	3
Hindryckx P(6)	Systematic Review	Inflammatory Bowel Disease	Multidimensional Assessment of Fatigue Multidimensional Fatigue Inventory Scale Functional Assessment of Chronic Illness Therapy Fatigue Scale	3
Czuber-Dochan(7)	Systematic Review	Inflammatory Bowel Disease	Multidimensional Fatigue Inventory Scale	4

			Functional Assessment of Chronic Illness Therapy Fatigue Scale Chalder Fatigue Scale Piper Fatigue Scale Checklist Individual Scale	
Hermans(8)	Systematic Review	Sjögren's Syndrome	Visual Analogue Scale – Fatigue Multidimensional Fatigue Inventory Scale	4

[&]Quality assessment developed by the National Insitute of Health. (9)

Table 2.

Scale	Purpose/Content	Method of Administration	Respondent Burden	Scale Type	Score Interpretation	Reliability Evidence	Validity Evidence	Strengths	Limitations
Unidimensional Scales									
FACIT-F(10-15)	Measures fatigue in patients with chronic illness (e.g. cancer, HIV, stroke, Parkinson's Disease, SLE)	Self-administration	3-4 minutes	13 items with a 5-point Likert scale Scores range from 0-52 Recall period: one week	Higher = better	Cronbach alpha >0.90 in the US general population, and in several medical conditions Test-retest: strong	Content validity: strong Construct validity: strong Criterion validity: strong Cutoff : ≤30[&]	Widely used and evaluated in several medical conditions Can be used in a variety of clinical settings (community health, inpatient, and outpatient)	The FACIT-F Scale is a unidimensional scale with long content compared to other unimesional scales such as BFI and FSS
VAS-F(16)	Psychometric response scale which measures subjective symptoms and has been used in the past for several medical disorders	Self-administration	1 minute	100 mm length line with words that anchor the scale at the extreme ends Recall period: variable	Higher = worse	Reliability not assessed due its lack of standardized format	Validity not assessed due its lack of standardized format	Widely used, quick screening of patient-reported outcome	Lack of standardization limits the interpretation of data and researchers often create individual items for individual studies Introductory question, time recall period, and verbal descriptors can vary

NRS-F (17-19)	Measures fatigue with NRS in which the patient can select one number that best describes the pain	Self-administration	1 minute	A numbered version of VAS The most frequently used : the 11-point (0-10) NRS Recall period: variable	Higher = worse	Reliability not assessed due its lack of standardized format	Validity not assessed due its lack of standardized formats	Widely used, quick screening of patient-reported outcome	Lack of standardization limits the interpretation of data and researchers often create individual items for individual studies Introductory question, time recall period, and verbal descriptors can vary
FSS(20-25)	Measures fatigue in multiple medical conditions (e.g. SLE, MS, IBD, stroke, obesity)	Self-administration	2-3 minutes	Nine items with a 7-point Likert scale Recall period: one week	Higher = worse	Cronbach alpha > 0.80 in healthy adults, SLE, MS, stroke, and obesity Test-retest: strong	Content validity: strong Construct validity: strong Criterion validity: strong Cutoff: ≥4[&]	Evaluated in several medical conditions Widely used, quick screening of patient-reported outcome	Original construct validity was tested with small number of subjects
BFI(26-28)	Assess fatigue in multiple medical conditions (e.g. cancer, stroke, RA, and IBD)	Self-administration	2-3 minutes	Nine questions scored on a 0-10 point numeric scale Recall period: 24 hours	Higher = worse	Cronbach's alpha >0.94	Content validity: strong Criterion validity: strong Construct validity: moderate	Widely used; it is shorter and easier to understand than other fatigue assessment tools available	Assesses fatigue on a short period (past 24 hours) and it is possible that responses may be confounded by factors related to daily fluctuations in fatigue levels

							Cutoff: ≥ 7*		
Multidimensional Scales									
CIS(29, 30)	Initially developed to assess fatigue in Chronic Fatigue Syndrome, it is used in othre conditions such as cancer, multiple sclerosis, fibromyalgia, Rheumatoid Arthritis	Self-administration	4-5 minutes	20 questions scored on a 1-7 point numeric scale. Recall period: 2 weeks	Higher = worse	Cronbach's alpha >0.89 in healthy adults, rheumatoid arthritis, fibromyalgia syndrome.	Content validity: strong Criterion validity: moderate to strong Construct validity: strong Cutoff: >35&	Widely used; Evaluated in several medical conditions.	Lengthy questionnaire may increase respondent burden
MAF(22, 23, 31)	Initially developed to assess fatigue in RA; it is used in multiple medical conditions (e.g. cancer, stroke, lupus, and IBD)	Self-administration	>5 minutes	15 questions scored on a 0-10 point numeric scale Recall period: one week	Higher = worse	Cronbach's alpha >0.92 for patients with RA Test–retest: strong	Content validity: strong Construct validity: strong Criterion validity: strong	Widely used Evaluated in several medical conditions (e.g. SLE, ankylosing spondylitis, and cancer)	Lengthy questionnaire may increase respondent burden
MFI(23, 32, 33)	Measures fatigue in patient with cancer, sarcoidosis, transplant, chronically ill, Sjögren's Syndrome, IBD, and general population	Self-administration	4-5 minutes	20 items, with a 5-point Likert scale with five dimensions [General Fatigue (GF), Physical Fatigue (PF), General Activity	Higher = worse	Cronbach's alpha >0.84 for GF, PF, and MF; Cronbach's alpha >0.65@ for RA and RM	Content validity: variable Construct validity: variable Criterion validity: variable	Evaluated in long-term conditions	Subscale Reduced Motivation showed insufficient reliability in chronically critically ill patients following intensive care

				(GA), Reduced Motivation (RM), Mental Fatigue (MF)]. Recall period: lately					Lengthy questionnaire may may increase respondent burden
FIS (22, 34, 35)	Assess functional limitation attributed to fatigue in three domains: physical functioning, cognitive functioning, and psychosocial functioning Previously applied in patients with MS and IBD	Self-administration	>5 minutes	**FIS:** 40 items with a 5-point Likert scale **MFIS**: 21 items with a 5-point Likert scale Recall period: one month	Higher = worse	**FIS:** Cronbach's alpha = 0.98 in patients with MS and mild Hypertension. Test-retest: strong **MFIS:** ICC: 0.86 (0.79–0.91) Test-retest: strong	**FIS:** Content validity: strong Construct validity: strong Criterion validty: not assessed **MFIS:** Content validity: strong Construct validity: modarete Criterion validity: strong	Comprehensive questionnaire with good property measurements Previously used several medical conditions (e.g. MS, IBD, and Parkinson's Disease)	The FIS is a longer fatigue tool compared to other available fatigue tools It was developed for patients with MS, and some contents such as "muscle weakness" that may be not appropriate for patients with dermatology disorders

CFS(36-38)	Measures fatigue in various conditions including cancer, postpolio syndrome, MS, PsA, and IBD	Self-administration	2-3 minutes	11-item questionnaire with a 4-point Likert scale; assesses two dimensions of fatigue (physical and mental) Recall period: one month	Higher = worse	Cronbach's alpha >0.89	Content validity: strong Construct validity: variable Criterion validity: variable Cutoff: ≥4	It has been used in a variety of settings including randomized controlled trials, general population, and primary and secondary care	The response options comprise one positive, one neutral, and two negative responses, which might bias the final response
PFS(28, 39, 40)	Measures fatigue in patietns with cancer and IBD	Self-administration	**PFS:** the original version may take longer than 5 minutes **PFS-R:** may take longer than 5 minutes **PFS-12:** may take 3-4 minutes	**PFS:** the original version consisted of 40 items **PFS-R:** PFS-R includes 22 items Recall period: one week **PFS-12:** PFS-12 consisted of 12 items Recall period: one month	Higher = worse	**PFS:** Cronbach's alpha 0.85 **PFS-R:** Cronbach's alpha > 0.96 Test-retest: strong **PFS-12:** Cronbach's alpha > 0.92	**PFS:** Content valididity: strong Construct validity: strong Criterion validity: moderate **PFS-R:** Content validity: strong Construct validity: strong	**PFS-R:** presents strong reliability and validity; scale previously validated in IBD and cancer	**PFS:** the length of PFS original version may be a burden to patients **PFS-R:** shorter, but remains long **PFS-12:** needs to have further assessment in construct and criterion validation

	All scales are scored on a 0–10 point numeric scale	Criterion validity: strong **PFS-12:** Content validity: strong Construct validity: not assessed Criterion validity: not assessed

Abbreviations: BFI, Brief Fatigue Inventory; BRAF, Bristol Rheumatoid Arthritis Fatigue; CIS, Checklist Individual Scale; CFS, Chalder Fatigue Scale; FACIT-F, Functional Assessment of Chronic Illness Therapy Fatigue Scale; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; IBD, Inflammatory Bowel Disease; MAF, Multidimensional Assessment of Fatigue; MFI, Multidimensional Fatigue Inventory Scale; MFIS, Modified Fatigue Impact Scale; MS, Multiple Sclerosis; NRS, Numerical Rating Scale; PFS, Piper Fatigue Scale; PFS-R, revised PFS; PsA, psoriatic arthritis; SLE, Systemic Lupus Erythematosus; VAS-F, The Visual Analog Fatigue Scale.

* Cut off to discriminate severe and non-severe fatigue.

& Cut off to discriminate fatigued and non fatigued patients.

@ Cronbach's alpha coefficient < 0.7 considered unsatisfactory

1. Skoie IM, Dalen I, Omdal R. Effect of Biological Treatment on Fatigue in Psoriasis: A Systematic Review and Meta-Analysis. Am J Clin Dermatol. 2019.
2. Reygaerts T, Mitrovic S, Fautrel B, Gossec L. Effect of biologics on fatigue in psoriatic arthritis: A systematic literature review with meta-analysis. Joint Bone Spine. 2018;85(4):405-10.
3. Hojgaard P, Klokker L, Orbai AM, Holmsted K, Bartels EM, Leung YY, et al. A systematic review of measurement properties of patient reported outcome measures in psoriatic arthritis: A GRAPPA-OMERACT initiative. Semin Arthritis Rheum. 2018;47(5):654-65.
4. Orbai AM, Ogdie A. Patient-Reported Outcomes in Psoriatic Arthritis. Rheum Dis Clin North Am. 2016;42(2):265-83.

5. van Langenberg DR, Gibson PR. Systematic review: fatigue in inflammatory bowel disease. Aliment Pharmacol Ther. 2010;32(2):131-43.

6. Hindryckx P, Laukens D, D'Amico F, Danese S. Unmet Needs in IBD: the Case of Fatigue. Clin Rev Allergy Immunol. 2018;55(3):368-78.

7. Czuber-Dochan W, Ream E, Norton C. Review article: Description and management of fatigue in inflammatory bowel disease. Aliment Pharmacol Ther. 2013;37(5):505-16.

8. Hermans A-M, Vulsteke J-B, Lenaerts J, De Langhe E. Can We Expect Any Effect of Rituximab on Fatigue in Primary Sjögren Syndrome?: A Systematic Review and Critical Appraisal. JCR: Journal of Clinical Rheumatology. 2019:1.

9. U.S. Department of Health and Human Services NIoH, National Institute of Mental Health. . Study Quality Assessment Tools. Bethesda, MD: US Government Printing Office. 2015.

10. Montan I, Lowe B, Cella D, Mehnert A, Hinz A. General Population Norms for the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. Value Health. 2018;21(11):1313-21.

11. Junghaenel DU, Christodoulou C, Lai JS, Stone AA. Demographic correlates of fatigue in the US general population: results from the patient-reported outcomes measurement information system (PROMIS) initiative. J Psychosom Res. 2011;71(3):117-23.

12. Butt Z, Lai JS, Rao D, Heinemann AW, Bill A, Cella D. Measurement of fatigue in cancer, stroke, and HIV using the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scale. J Psychosom Res. 2013;74(1):64-8.

13. Hagell P, Hoglund A, Reimer J, Eriksson B, Knutsson I, Widner H, et al. Measuring fatigue in Parkinson's disease: a psychometric study of two brief generic fatigue questionnaires. J Pain Symptom Manage. 2006;32(5):420-32.

14. Lai JS, Beaumont JL, Ogale S, Brunetta P, Cella D. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. J Rheumatol. 2011;38(4):672-9.

15. Leung YW, Brown C, Cosio AP, Dobriyal A, Malik N, Pat V, et al. Feasibility and diagnostic accuracy of the Patient-Reported Outcomes Measurement Information System (PROMIS) item banks for routine surveillance of sleep and fatigue problems in ambulatory cancer care. Cancer. 2016;122(18):2906-17.

16. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res. 1991;36(3):291-8.

17. Center USDoHaHSFaDACfDEaRCCfBEaRC. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009.

18. Nicklin J, Cramp F, Kirwan J, Greenwood R, Urban M, Hewlett S. Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. Arthritis Care Res (Hoboken). 2010;62(11):1559-68.

19. Minnock P, Kirwan J, Bresnihan B. Fatigue is a reliable, sensitive and unique outcome measure in rheumatoid arthritis. Rheumatology (Oxford). 2009;48(12):1533-6.

20. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121-3.

21. Impellizzeri FM, Agosti F, De Col A, Sartorio A. Psychometric properties of the Fatigue Severity Scale in obese patients. Health Qual Life Outcomes. 2013;11:32.

22. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manage. 2009;37(1):107-28.

23. Hewlett S, Dures E, Almeida C. Measures of fatigue: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ), Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scales (BRAF NRS) for severity, effect, and coping, Chalder Fatigue Questionnaire (CFQ), Checklist Individual Strength (CIS20R and CIS8R), Fatigue Severity Scale (FSS), Functional Assessment Chronic Illness Therapy (Fatigue) (FACIT-F), Multi-Dimensional Assessment of Fatigue (MAF), Multi-Dimensional Fatigue Inventory (MFI), Pediatric Quality Of Life (PedsQL) Multi-Dimensional Fatigue Scale, Profile of Fatigue (ProF), Short Form 36 Vitality Subscale (SF-36 VT), and Visual Analog Scales (VAS). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S263-86.

24. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. Sleep. 2008;31(11):1601-7.

25. Kaynak H, Altintas A, Kaynak D, Uyanik O, Saip S, Agaoglu J, et al. Fatigue and sleep disturbance in multiple sclerosis. Eur J Neurol. 2006;13(12):1333-9.

26. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999;85(5):1186-96.

27. Toh C, Li M, Finlay V, Jackson T, Burrows S, Wood FM, et al. The Brief Fatigue Inventory is reliable and valid for the burn patient cohort. Burns. 2015;41(5):990-7.

28. Nunes AF, Bezerra CO, Custodio JDS, Friedrich CF, Oliveira IS, Lunardi AC. Clinimetric Properties of the Brief Fatigue Inventory Applied to Oncological Patients Hospitalized for Chemotherapy. J Pain Symptom Manage. 2019;57(2):297-303.

29. Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HWM, van Engelen BGM, van Riel P, et al. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. J Psychosom Res. 2017;98:40-6.

30. Panitz S, Kornhuber M, Hanisch F. The checklist individual strength (CIS20-R) in patients with amyotrophic lateral sclerosis - a longitudinal study. Acta Neurol Scand. 2015;131(6):372-80.

31. Santos EJF DC, da Silva JAP, Ferreira RJO. . The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. . Rheumatology (Oxford). 2019;;58(Suppl 5):v3–v9. doi:10.1093/rheumatology/kez351.

32. Hinz A, Benzing C, Brahler E, Zenger M, Herzberg PY, Finck C, et al. Psychometric Properties of the Multidimensional Fatigue Inventory (MFI-20), Derived From Seven Samples. J Pain Symptom Manage. 2020;59(3):717-23.

33. Wintermann GB, Rosendahl J, Weidner K, Strauss B, Hinz A, Petrowski K. Fatigue in chronically critically ill patients following intensive care - reliability and validity of the multidimensional fatigue inventory (MFI-20). Health Qual Life Outcomes. 2018;16(1):37.

34. Lundgren-Nilsson A, Tennant A, Jakobsson S, Simren M, Taft C, Dencker A. Validation of Fatigue Impact Scale with various item sets - a Rasch analysis. Disabil Rehabil. 2019;41(7):840-6.

35. Learmonth YC, Dlugonski D, Pilutti LA, Sandroff BM, Klaren R, Motl RW. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. J Neurol Sci. 2013;331(1-2):102-7.

36. Picariello F, Moss-Morris R, Macdougall IC, Chilcot J. Measuring fatigue in haemodialysis patients: The factor structure of the Chalder Fatigue Questionnaire (CFQ). J Psychosom Res. 2016;84:81-3.

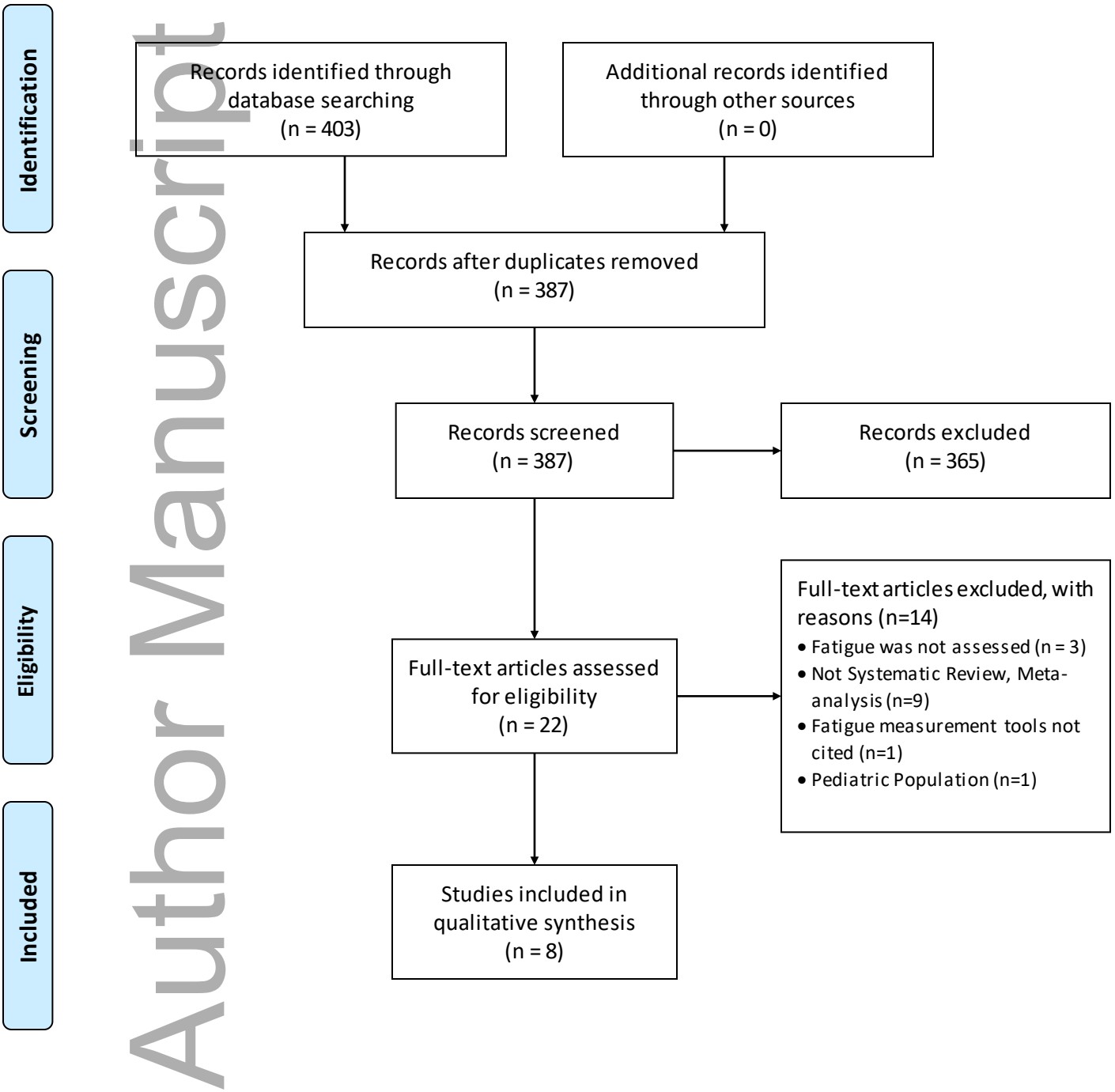
37. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res. 1993;37(2):147-53.

38. Cella M, Chalder T. Measuring fatigue in clinical and community settings. J Psychosom Res. 2010;69(1):17-22.

39. Reeve BB, Stover AM, Alfano CM, Smith AW, Ballard-Barbash R, Bernstein L, et al. The Piper Fatigue Scale-12 (PFS-12): psychometric findings and item reduction in a cohort of breast cancer survivors. Breast Cancer Res Treat. 2012;136(1):9-20.

40. Al Maqbali M, Hughes C, Gracey J, Rankin J, Dunwoody L, Hacker E. Quality assessment criteria: psychometric properties of measurement tools for cancer related fatigue. Acta Oncol. 2019;58(9):1286-97.

PRISMA 2009 Flow Diagram



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