Chapter 5

Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis

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Abstract

Objective
The usefulness of any questionnaire in clinical management and research trials depends on its ability to indicate a likelihood of treatment success during follow-up. The Minimal Clinically Important Difference (MCID) reflects a clinically relevant change score. The aim of this study was to estimate the MCID for the Fatigue Assessment Scale (FAS) in patients with sarcoidosis.

Methods
Outpatients (n = 321) of the ild care team of the Department of Respiratory Medicine of the Maastricht University Medical Centre, the Netherlands, participated in this prospective follow-up study. Anchor-based and distribution-based methods were used to estimate the MCID. Based on the anchor physical quality of life, a Receiver Operating Characteristic (ROC) was obtained. The distribution-based methods consisted of the Effect Size and Standard Error Measurement (SEM).

Results
The anchor-based MCID found with ROC was 3.5. The distribution-based methods showed that the corresponding change scores in the FAS for a small effect was 4.2. The SEM criterion was 3.6 points change in the FAS.

Conclusions
Based on the anchor-based and distribution-based methods, the MCID is a 4-point difference on the FAS. This MCID can be used in the follow-up of fatigue (FAS) in clinical trials and in the management of individual sarcoidosis cases.

Introduction

Fatigue is the most common symptom in sarcoidosis that often leads to a decreased quality of life (QOL)[1-3]. Furthermore, fatigue is associated with symptoms of depression[4], cognitive impairment[5], exercise intolerance[6], and stress[7]. Because of this substantial influence on the patient's life, it is important to appropriately assess fatigue with a valid and reliable measure in clinical practice as well as in clinical trials.

Combined with clinical outcomes assessment, measurement of fatigue provides greater insight into suitable clinical interventions and patients' response to treatment. In the absence of an objective measure for fatigue, it is usually measured by means of self-reported questionnaires. The Fatigue Assessment Scale (FAS) is a short self-report questionnaire for measuring fatigue. This instrument has shown to be a valid and reliable fatigue measure among sarcoidosis patients[8,9]. Several studies found significant differences in the score of the FAS between subgroups of sarcoidosis patients[2,5,7,10-12]. Although these differences were statistically significant, they may be irrelevant from the patients' point of view.

A limitation of questionnaires in general is that their statistical scores do not provide directly a clinical interpretation. The minimal clinically important difference (MCID) has been developed as a measure for the smallest change score of interest which patients perceive as relevant[13]. Treatment effects that exceed the MCID denote clinical significance and support implementation into clinical practice. Thus, the MCID indicates that the minimal change in fatigue scores across time of individual patients represents a clinically relevant difference, thereby helping clinicians to interpret the clinical meaning of changes on fatigue scores of individual patients. In addition, the MCID is relevant in both the planning of clinical trials and interpretation of the results when evaluating outcomes of intervention studies using the FAS. Till now, no MCID has been established for this fatigue questionnaire in sarcoidosis. Moreover, the MCID criteria that are already established for fatigue questionnaires in other populations[14-17] cannot be applied to a sarcoidosis population, because the MCID criteria vary by population[18].

Therefore, the aim of this study was to estimate the MCID for the FAS in patients with sarcoidosis in order to evaluate clinical outcome of interventions.

As recommended by Revicki et al.[19] we have employed both anchor-based and distribution-based methods to establish the MCID of the FAS. Distribution-based and anchor-based methods have been used to determine a MCID in fatigue[14-17]. The anchor-based method compares measures of fatigue to other measures or phenomena that have clinical relevance. The distribution-based method is based on the characteristics of the particular patient population, such as sample variability and precision of the questionnaire[20]. An anchor-based approach was chosen for this study in order to link the change in fatigue with a meaningful external anchor. In addition, two distribution-based methods were used to evaluate the responsiveness of the MCID found with the anchor-based approach.

Methods

Patients

All sarcoidosis outpatients (n = 588) of the ild care team of the Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC+) a tertiary referral center in the Netherlands, were asked to participate. The flowchart of the patient participation is shown in Figure 5.1. Patients were diagnosed with sarcoidosis based on consistent clinical features and bronchoalveolar lavage (BAL) fluid analysis results according to the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines[21]. The exclusion criteria were poor expression in the Dutch language (n = 3), relevant co-morbidity, such as malignancy (n = 7), dementia (n = 1), and a history of psychiatric illness (n = 2).

Procedure

The patients received information about the study by mail and were asked to return an informed consent form when they were willing to participate in the study. Patients who agreed to participate received the first set of questionnaires in May 2007 and were asked to return the completed set to the hospital in an enclosed envelope. In May 2008 the same patients received a second set of questionnaires with an envelope. The most common reason for not completing the second set of questionnaires was 'insufficient time'. The data were collected by the ild care team. The Medical Ethical Committee of the MUMC+ approved the study protocol and written informed consent was obtained from all patients.

Measures

The patients were sent questionnaires at baseline and after 12 months. The patients completed the Fatigue Assessment Scale (FAS)[8] to assess the change in fatigue during the one-year follow-up. For the anchor-based method, the change in physical quality of life (Physical QOL) across time was assessed with the World Health Organization Quality of Life BREF (WHOQOL-BREF)[22]. This anchor was chosen because previous research found strong associations between the FAS and this instrument in sarcoidosis[3].

The FAS is a 10-item self-report fatigue questionnaire. The reliability and validity of the FAS are good, also in sarcoidosis patients[8,9]. The response scale is a 5-point Likert scale (1 *never* to 5 *always*). Total scores on the FAS can range from 10 to 50, with high scores indicating more fatigue. Consequently, possible changes in FAS scores of patients could range from -40 to 40 between baseline and follow-up.

The domain 'Physical Health' of the WHOQOL-BREF was used for the anchor Physical QOL. This anchor was based on the change score in the domain Physical Health during the one-year follow-up period. The WHOQOL-BREF is a 26-item instrument to assess quality of life from the patients' perspective[22]. The content validity, construct validity, and the reliability of the WHOQOL-BREF are good[23,24].

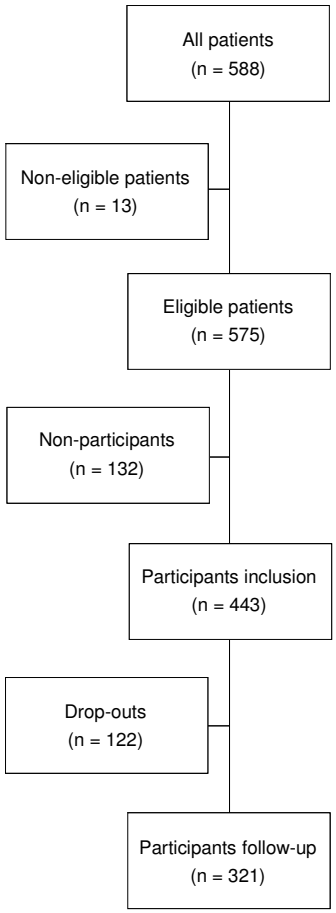

Figure 5.1 Flowchart of patient selection

The domain Physical Health consists of the following questions: 'To what extent do you feel that physical pain prevents you from doing what you need to do?', 'How much do you need any medical treatment to function in your daily life?', 'Do you have enough energy for everyday life?', 'How well are you able to get around?', 'How satisfied are you with your sleep?', 'How satisfied are you with your ability to perform your daily living activities?', and 'How satisfied are you with your capacity for work?'. The response scale of the domain Physical Health is a 5-point Likert scale (1 to 5) and scores can range from 4 to 20, with high scores indicating a better Physical QOL[22]. Consequently, change scores on the anchor Physical QOL between baseline and follow-up could range from -16 to 16.

Statistical Procedures

Patients who dropped-out after the baseline measurement and patients who remained in the study were compared on demographical (sex, age, ethnicity), clinical (lung function tests, radiographic staging, (extra) pulmonary involvement, time since diagnosis), and psychological variables (FAS total score, WHOQOL-BREF domain scores) by means of t-tests and chi-square tests.

Change scores for the FAS and the anchor were calculated by subtracting the baseline score from the 12-month score. A positive change on the anchor describes an improvement whereas a positive change on the FAS indicates an increase in fatigue. Because the different meaning of a positive change may complicate the interpretation of the results, the sign of the FAS change score was reversed, so that a positive change score represents an improvement (decline in fatigue).

As recommended by Revicki et al.[19] both distribution-based and anchor-based methods were used to estimate the minimal clinically important difference.

Distribution-based method

Two distribution-based methods were used to estimate the MCID for the FAS. According to Norman et al.[25], an effect size (*ES*) of 0.5 approximates the threshold of discrimination for changes in health-related quality of life for chronic diseases. Therefore, the expected change scores in the FAS were calculated for an effect size of 0.5 to estimate the minimal change[26]. The corresponding change scores on the FAS (*Δx12*) were the product of these indices and the standard deviation (*SD*) at baseline, i.e., $\Delta x12 = ES \cdot SDx1$.

In addition, the Standard Error Measurement (SEM)[27,28] was used to identify the minimal clinically important change in the FAS. The SEM was calculated to identify the minimal clinical important change using the revised Jacobson formula[29,30]. An observed change that exceeded the standard measurement error was considered to reflect a change. Patients with a score that did not exceed the measurement error were considered to be stable. In addition, patients were considered to have a minimally improved or minimally worsened fatigue, if their score increased or decreased one-SEM, respectively.

Anchor- based method

Concerning the anchor-based method, Pearson's correlations were calculated to measure whether the change score of the anchor Physical QOL was associated with the change score of the FAS. Revicki et al.[19] recommended a correlation threshold of 0.30 between an anchor and patient-reported outcome measure such as QOL, to establish a MCID.

Subsequently, patients were divided into one of three groups: improved, stable, or worsened Physical QOL. Patients were considered to be either improved or worsened in Physical QOL if the change score (between baseline and follow-up) exceeded the measurement error of the WHOQOL-BREF domain Physical Health[27-30]. In addition, patients with a score that did not exceed the measurement error were considered to

be stable in Physical QOL. Frequencies and means were calculated for each group of the anchor Physical QOL.

The receiver operating characteristic (ROC)[31] method is another anchor-based method that was used to estimate the MCID[32]. For this method, the FAS was considered as the diagnostic test and the anchor Physical QOL functioned as the golden standard. The anchor Physical QOL distinguished persons who improved or worsened from persons who remained stable on Physical QOL. Additional ROC curves were obtained for the anchor change score with a $CI_{95\%}$. This change score is the smallest change that can be considered above the measurement error with a 95% level of confidence[33]. These change scores were calculated by multiplying the change scores of the anchor by 1.96. The ROC was obtained by plotting the sensitivity against 1-specificity for each possible FAS change score. The area under the ROC curve represents the probability that FAS scores will correctly discriminate between patients who improved and worsened on Physical QOL. Probabilities range from 0.5 to 1, with 0.5 representing the ability to discriminate on chance and 1 representing the ability to correctly discriminate all the patients. An area under the curve of 0.7 to 0.8 is considered acceptable and an area of 0.8 to 0.9 is considered excellent[34]. The ROC cut-off point is the value for which the sum of percentages of true positive and true negative classifications is largest (sensitivity + specificity). Because we are interested in the minimal change, the smallest value was chosen as the cut-off point when several options were found for the largest sum (rounded to two decimals). This optimal cut-off point is the estimation of the anchor-based MCID for the FAS.

Results

Demographical, clinical, and psychological characteristics at baseline are presented in Table 5.1. No differences were found in these variables between the patients who dropped-out of the study and the patients remaining in the study.

Anchor-based method

The anchor Physical QOL was found to be eligible for estimating a MCID for the FAS, because the correlation between the change scores of the FAS and the anchor ($r = 0.47$ ($p < 0.001$, $CI_{95\%}$ 0.38 - 0.55)) exceeded the threshold of $r = 0.30$[19,24]. The measurement error of Physical Health was $|1.63|$. Based on this value, the three groups of the anchor Physical QOL (worsened, stable, and improved) were distinguished: a change score of -1.63 or lower for patients who had worsened ($n = 62$), a change score between -1.63 and 1.63 for patients who remained stable ($n = 186$), and a change score of 1.63 or higher for patients who had improved ($n = 67$). The corresponding mean change scores on the FAS were -3.8, 0.3, and 3.0 for each anchor group, respectively.

The ROC was obtained to estimate the anchor-based MCID for the FAS for both improved patients and worsened patients. The area under the ROC curve for the

improved patients was 0.6, this means that the ability of the FAS to discriminate patients who improved in Physical QOL was just above chance level. Thus, the cut-off value for a MCID in the FAS was 3.5 points, which corresponded to an optimal balance between a sensitivity of 45% and a specificity of 81%, e.g., 45% of the patients were correctly identified as improved and 81% of the patients were correctly identified as *not* improved.

Table 5.1 Descriptive statistics of the participants and dropouts[a]

	Participants n = 321	Dropouts n = 122	Statistics[b]
Demographics			
Male%	55.8	48.4	$\chi^2(1, n = 443)= 1.7$
Caucasian/African/Asian/other%	95.6/3.1/0.3/0.9	93.4/3.3/0.8/2.5	χ^2 (4, n = 442)= 2.1
Age (range in years)	48.5 ± 10.8 (28-79)	46.8 ± 12.1 (19-80)	*t* (441)= -1.2
Medical variables			
Time since diagnosis (years)	7.8 ± 7.7 (0-65)	7.2 ± 7.9 (0-42)	*t* (439)= -0.8
Multisystemic involvement%	48.0	48.3	χ^2 (1, n = 439)= 0
Radiographic stage: 0/I/II/III/IV%	42.6/8.2/23.5/ 11.6/14.1	34.4/9.8/27.0/ 14.8/13.9	χ^2 (4, n = 441)= 2.9
FVC	99.4 ± 19.4	96.8 ± 20.6	*t* (429)= -1.2
FEV_1	90.2 ± 22.4	87.1 ± 21.9	*t* (431)= -1.2
DLCO	82.2 ± 17.8	79.6 ± 16.7	*t* (431)= -1.4
Psychological variables			
Fatigue Assessment Scale score	29.5 ± 8.4	28.8 ± 8.4	*t* (433)= -0.8
Quality of life:			
Overall Facet	5.9 ± 1.6	6.2 ± 1.6	*t* (443)= 1.6
Physical Health	12.5 ± 3.1	12.8 ± 3.1	*t* (430)= 1.0
Psychological Health	13.8 ± 2.5	13.8 ± 2.6	*t* (431)= 0.1
Social Relationships	15.4 ± 2.9	14.5 ± 3.0	*t* (430)= -0.1
Environment	15.4 ± 2.5	15.2 ± 2.6	*t* (432)= -0.7

[a]Data are expressed in mean ± standard deviation or in percentages. [b] All statistical values are not significant. DLCO = Diffuse capacity of the lung for carbon monoxide; FEV_1 = Forced Expiratory Volume in 1 s; FVC = Forced Vital Capacity.

When the analysis was repeated with patients who were worsened versus patients who remained stable in Physical QOL, the area under the curve was 0.7. This means that the FAS fairly discriminated patients who worsened in Physical QOL. The cut-off value of the FAS is -3.5, which corresponded to a sensitivity of 82% and a specificity of 51%.

When selecting the patients with an anchor change score in Physical QOL with a 95% interval, the same cut-off of 3.5 points change on the FAS was found for both the improved and the worsened patients. The area under the curve was 0.8 for the improved patients, and 0.9 for the worsened patients. This means that the ability of the FAS to discriminate patients who changed in Physical QOL was good. In addition,

the sensitivity and specificity increased to 79% and 84% for the worsened patients and 71% and 78% for the improved patients, respectively.

Distribution-based methods

The corresponding minimal change on the FAS for an effect size of 0.5 was 4.2. The reliability coefficient Cronbach's alpha of the FAS was 0.9, resulting in a one-SEM of 3.6. This reflects the cut-off point of a statistical minimal change in the FAS.

Minimal clinically important change

In sum, for the anchor-based method, mean scores of -3.8 for the worsened patients and 3.0 for the improved patients were found, and the ROC cut-off was |3.5|. For the distribution-based method, the ES was |4.2| and the SEM was |3.6|. These estimates for the minimal clinically important changes found with both methods are rounded to 4 points change on the FAS, because the FAS is measured in whole points. This cut-off of the minimal clinically important change is represented in Figure 5.2 with two dashed lines. Patients who scored above or below these lines were considered to be either minimally improved or minimally worsened in fatigue, respectively.

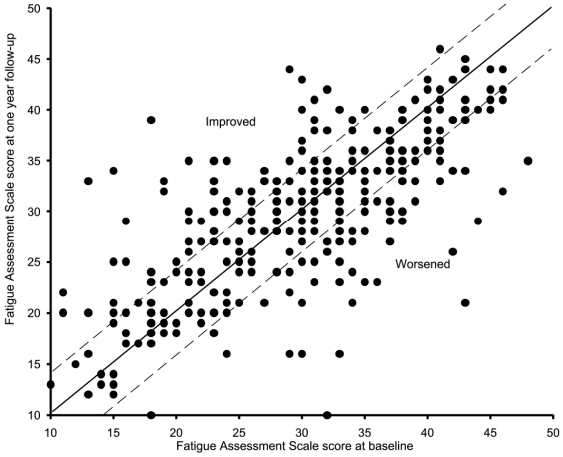

Figure 5.2 Minimal Clinically Important difference of the Fatigue Assessment Scale.

Discussion

The FAS is a validated fatigue questionnaire used in the management and follow-up of sarcoidosis patients as well as an outcome measure in clinical trials. However, until now a minimal clinically important difference (MCID) was lacking. Therefore, the aim of this study was to determine the MCID of the FAS in sarcoidosis patients. To estimate the MCID both anchor-based and distribution-based methods were used in this study because they are complementary, i.e., each has different advantages[20]. Both methods revealed similar results. The MCID was estimated on a change of 4 points indicating that when the FAS scores of a patient changes between two time points with at least 4 points, this change in fatigue is clinically meaningful.

Anchor-based method

The anchor Physical QOL takes into account Physical health from the patients' perspective. Based on the anchor Physical QOL, the minimal change was estimated at 3.5 points change on the FAS by means of a ROC curve. The same threshold for a minimal clinically important change in fatigue was found for patients with a large and a small change in Physical QOL, which strengthens the criterion for change. The high percentages provided by the ROC curve for the anchor with a 95% confidence interval indicate that the chance to incorrectly define a patient as changed or unchanged is low when using a threshold of 4 points on the FAS (rounded). This may be important when the negative effects of group assignment are large, e.g., when treatment has side-effects or is expensive.

Other studies applied anchor-based methods, based on non-clinical anchors to determine a MCID for fatigue instruments[13,14]. Pouchot et al.[15] matched the scores of the fatigue measures with the self-reported ratings of fatigue on a global scale. A limitation of this method is that the differences between patients may be incomparable to longitudinal changes within patients. Moreover, a global rating is frequently used in anchor-based methods, but coincides with several difficulties: patients have to rate the change in fatigue in an extended period of time in the past, these retrospective ratings are susceptible for recall bias and current mood states. In addition, little information is available about the validity and reliability of these global ratings. Furthermore, depending on the magnitude of the correlation with fatigue, the global ratings do not explain the total variance in fatigue[20]. Purcell et al.[14] determined in a follow-up study MCID scores for the Multidimensional Fatigue Inventory using the anchors Health-related quality of life, performance status, and productive hours. No associations between performance status or productive hours and fatigue have been reported in sarcoidosis. Therefore, in the current study, we chose to select an anchor from the WHOQOL-BREF, which is a validated and reliable instrument[23,24] and associated with fatigue in sarcoidosis[2]. Clinical anchors were not selected, because previous studies showed no significant relationships between the FAS and widely used medical data in sarcoidosis[2]. In addition, in this study longitudinal changes within patients were examined to evaluate the development of fatigue.

Distribution-based methods

An advantage of the distribution-based methods is that they provide a MCID which exceeds random variation[20]. Wyrwich et al.[27,28] and Rejas et al.[35] showed that the SEM criterion is a promising measure to estimate the MCID, because the SEM relies on the precision of the instrument, is independent of sample size, and takes spurious change due to measurement error into account. Moreover, the SEM criterion is a frequently used measure in studies which determined a minimal change in diseases similar to sarcoidosis[36-40]. In addition, the effect size represents the individual change, also is independent of sample size[20], and also is commonly used to determine a change[41,42]. In this study, it appeared that the MCID based on the anchor approximated the MCID found with the distribution-based methods. The similar result from both the anchor-based and distribution-based method might suggest that the estimation for the MCID is robust.

Systemic manifestations are considered important in sarcoidosis. The extent of physiological impairment or organ system loss of function is still applied to classify the severity of sarcoidosis: most often still based on stratification of respiratory functional impairment[21,43]. It has been widely accepted now that an integral assessment frame work of health status, incorporating physiological functioning, complaints like fatigue, exercise impairment and quality of life, improves conceptual insight in the impact of sarcoidosis on patients' lives and offers the clinician directions in individual management[6].

The results of this study are relevant for researchers and clinicians who want to assess clinically important changes in fatigue in sarcoidosis patients. Researchers should consider clinical significance from the patients' perspective, as well as statistical significant results. The MCID also improves conceptual insight in the impact of sarcoidosis on patients' lives. Moreover, the MCID is a clinically important concept, as it may assist clinicians with the interpretation of observed changes in the FAS and may influence the perceived success of an intervention. In addition, the MCID could have implications for the design of clinical trials in terms of the selection of a useful clinical outcome measure. Therefore, in the management of sarcoidosis it is recommended to have insight in the MCID of the validated fatigue questionnaire in sarcoidosis, i.e., the FAS. The MCID identified in this study is aimed to improve the clinical interpretation of changes in sarcoidosis-associated fatigue as measured by the FAS.

One limitation of this study may be that the patients were recruited in a tertiary referral centre, which may have caused selection bias and, therefore, the results may be not representative for every sarcoidosis patient. Consequently, we recommend using the MCID found in this study as a guideline. A limitation of the Standard Error Measurement is that this approach relies on the assumption that measurement error is constant across the range of possible scores[20]. For future studies it is important to take into account that a change of one point may be different for a patient who shows an impaired energy level at baseline in contrast to a patient who shows little or no impairment.

In conclusion, using various methods the present study showed that a change in a patient's FAS score across time of at least 4 represents a clinically important difference, i.e., the fatigue of the patient has increased or decreased.

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