

Categorisation of disease severity states in fibromyalgia: a first step to support decision-making in health care policy

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Abstract

Objective

To establish the cut-off points for disease severity states of two self-administered questionnaires (the revised version of the Fibromyalgia-Impact Questionnaire [FIQR] and the Fibromyalgia Assessment Status [FAS]) designed for the evaluation of multidimensional aspects of fibromyalgia (FM).

Methods

In this cross-sectional study, consecutive FM patients completed both FIQR and FAS. The external criterion for grading disease severity was the item one of the Short Form-36 Health Survey (SF-36). The reconciliation approach of the 75th-25th percentiles of adjacent ranks was applied to establish cut-off points distinguishing between disease activity states.

Results

521 FM patients (80.0% women, mean age 49 years) completed the assessment. The overall mean (standard deviation [SD]) FIQR and FAS were 47.87 (SD 20.69) and 5.57 (SD 2.09), respectively. The highest FIQR scored items were those related to sleep quality, fatigue/energy, pain, stiffness, tenderness, and environmental sensitivity. With the reconciliation of 75th-25th percentiles of adjacent ranks, the FIQR cut-off points obtained were: remission ≤ 30 , mild severity > 30 and ≤ 45 , moderate severity > 46 and ≤ 65 , high severity > 65 . The same approach for FAS led to: remission ≤ 4 , mild severity > 4 and ≤ 5.5 , moderate severity > 5.6 and ≤ 7.0 , high severity > 7.0 . The majority of the subjects was classified as suffering from a moderate (FIQR 28.4%; FAS 23.2%) or severe (FIQR 24.4%; FAS 30.7%) FM.

Conclusion

The FIQR and FAS cut-off points for remission, mild, moderate and high disease severity are valid measures which can be easily applied in daily clinical practice.

Key words

fibromyalgia, severity, cut-off points, revised Fibromyalgia Impact Questionnaire, fibromyalgia assessment status

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Introduction

Fibromyalgia (FM) is a chronic, multi-symptoms disease affecting the 2–3% of the general population, and more than 90% of the sufferers are female (1–5).

Pain is generally the most important symptom (6, 7).

FM imposes a heavy burden on patients: the disease requires high rates of use of healthcare resources (8, 9), and can lead to significant interference with work, determining a consequent loss of productivity (5, 10–12).

Severity and combinations of symptoms vary from patient to patient, and symptoms widely fluctuate (13, 14). These intrinsic features interfere with the application of the appropriate treatment strategies (15, 16). Moreover, the lack of unique outcome measures hinders the evaluation of the effectiveness of treatments.

In addition, a comprehensive assessment of FM is usually difficult to perform within the time available in daily clinical practice.

The assessment of FM, distinguishing between “severity states” (similar to the “disease activity states” of inflammatory rheumatic diseases), can provide several benefits, including a more precise identification of responders and prioritisation in clinical trials and daily practice. The characterisation of severity levels may also represent an important issue in the field of economic costs of resource utilisation (5, 11, 12).

In order to improve FM management, the recent guidelines recommend to take measured and individualised plans. The treatment has to be tailored to the single subject according to pain intensity, function, and according to associated features such as depression, fatigue and sleep disturbance. By analogy with inflammatory rheumatic diseases, the therapy has to be specifically targeted to patients at different levels of severity. The majority of the core domains considered by Outcome Measures in Rheumatology Clinical Trials (OMERACT) essential for evaluation, are patient-centric for FM (2–4).

Patient-centric measures and patient-reported outcomes (PROs) are increasingly accepted to evaluate disease ac-

tivity states, especially for chronic pain conditions (8, 17).

Among the PROs available for the FM assessment, the revised version of the Fibromyalgia Impact Questionnaire (FIQR), and the Fibromyalgia Assessment Status (FAS) are two of the most employed tools for evaluating disease severity on its prevalent clinical manifestations (18, 19).

However, the meaning of these instruments is hampered by the inability to fully interpret the results into a coherent framework: the major gap is the absence of cut-off points to distinguish between disease severity states.

Using this consideration as a starting point, the present study has been designed to establish the cut-off points for the FIQR and FAS to differentiate FM disease severity states.

Materials and methods

Study population

From January 2013 to December 2017, consecutive adult FM patients of the Clinica Reumatologica of the Università Politecnica delle Marche (Jesi, Ancona, Italy), fulfilling the 2010 American College of Rheumatologists (ACR) classification criteria for FM (20), were enrolled in this study. The participants are part of an ongoing longitudinal project measuring rheumatic disease outcomes. All the subjects were assessed by a rheumatologist (FS or MDC) to confirm the FM diagnosis at study entry.

Exclusion criteria were the presence of: (a) coexisting inflammatory rheumatic diseases or connective tissue disorders (*i.e.* rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, or other connective tissue diseases); (b) orthopaedic or musculoskeletal conditions prohibiting moderate-intensity exercise (*i.e.* severe knee or hip osteoarthritis); (c) known cardiovascular diseases or uncontrolled hypertension; (d) moderate-severe chronic lung diseases; (e) uncontrolled endocrine disturbances; (f) history of major depression disorder, schizophrenia or other psychosis. All patients provided informed consent and all the procedures in this work were in accordance with the ethical standards of the institutional research

Competing interests: none declared.

committee and with the 1975/83 Helsinki declaration and its later amendments or comparable ethical standards.

Measurements

A comprehensive package of questionnaires including demographic data, disease duration, disease-related variables, and quality of life items was administered to the patients.

The demographic variables were: age, sex, marital status (single, married and divorced/separated), and level of education (primary; secondary; high school/university).

FM severity was assessed through the two Italian validated versions of the FIQR and the FAS (21, 22).

The FIQR is the updated version of the Fibromyalgia Impact Questionnaire (FIQ). Developed to overcome the limitations of the original FIQ (23, 24), FIQR is made of 21 numerical rating scales (NRS) (range 0–10, with 10 being the “worst”), and explores three main domains: function, overall impact, and symptoms. FIQR tries to improve the original scale adding new questions related to memory, tenderness, balance, and environmental sensitivity. The questions are contextualised in the previous seven days. The final score (range 0–100, with greater values indicating a worse severity) is the sum of the ratings of the three domains: the algebraic sum of the 9-items function domain (range 0–90) is divided by three, the algebraic sum of the 2-items overall impact domain (range 0–20) remains as it is, and the algebraic sum of the 10-items symptom domain (range 0–100) is divided by two.

The FAS includes questions addressing fatigue (NRS 0–10), quality of sleep (NRS 0–10), and non-articular pain assessed by the Self-Assessment Pain Scale (SAPS) (range 0–10). SAPS explores pain in 16 sites, and for each site the level of experienced pain is: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. The final score ranges from 0 to 48, then transformed into a 0–10 scale. The FAS final score (range 0–10) is the arithmetic mean of the three sub-scores (22).

Statistical analysis

Data have been processed with the

MedCalc Statistical Software, version 18.0 (Ostend, Belgium), for Windows XP. The normal distribution was tested with the Kolmogorov-Smirnov test. Since data were generally not normally distributed (see below), non-parametric techniques have been employed, in order to provide a more conservative estimate of statistical significance.

Median and interquartile ranges, as well as means and standard deviations (SDs) were presented where appropriate.

Both for FIQR and FAS, interpretability was determined categorising FM patients in four disease severity states (remission, mild severity, moderate severity, and high severity). The external criterion applied to make this distinction was the answer given to the item one of the Short Form-36 Health Survey (SF-36): “In general, would you say your health is: 1=excellent, 2=very good, 3=good, 4=fair, 5=poor”. The categories “excellent” and “very good” have been condensed into the “remission state”.

For each disease severity state, arithmetic means with SDs, medians, and the 25th and 75th percentiles were calculated. To define the cut-off values distinguishing between disease severity states, we reconciled the 75th–25th percentiles of adjacent states.

The main steps of the approach described below are those of FIQR, however the same methodology was adopted for FAS. Briefly: the cut-off point between remission and mild severity state was obtained taking the FIQR mean value of the 75th percentile of remission, and the FIQR mean value of the 25th percentile of mild severity. Then, the arithmetic mean between these two values was calculated, and if necessary the mean was rounded off to the first unit number (to the first decimal for FAS). The resulting value is the FIQR cut-off point in the transition from remission to mild severity state. The same method, namely the arithmetic mean rounded off to the first decimal number between the mean values of the 75th–25th percentiles of adjacent ranks was used to define the cut-off point in the transition from mild severity to moderate severity, and from moderate severity to high severity.

This kind of approach (reconciliation of the mean value at the 75th percentile of the lower category with the mean value at the 25th percentile of the higher category) is considered a valid approach for the cut-off points determination, and has already been used in the rheumatologic setting (25, 26).

Results

Demographic characteristics and descriptive statistics

Of the 556 FM consecutive patients included, in 521 (80.0% women) data were completely available. Participants showed a mean age of 49 years, with a mean disease duration of 5.5 years. The majority of the subjects were married, and generally well educated. Patients were moderately overweight, with a mean body mass index (BMI) of 26.2 (a BMI >25 or >30 were found in 38% and in 7.3% of cases, respectively). The overall mean (SD) for FIQR was 47.87 (SD 20.69), and for FAS was 5.57 (SD 2.09) (Table I).

Central tendency and distribution of FIQR and FAS

Figure 1 shows the central tendency and the distribution of the FIQR (Fig. 1a) and of the FAS (Fig. 1b). The FIQR was not normally distributed (Kolmogorov-Smirnov test). Similarly, FAS showed a non-normal distribution. The coefficients of Skewness (degree of symmetry) were -0.005872 ($p=0.9559$) and -0.2877 ($p=0.0078$) whereas coefficient of Kurtosis (degree of peakedness/flatness) were -0.9474 ($p=0.0011$) and -0.7052 ($p=0.0083$) for the FIQR and for the FAS, respectively (Table II).

The spidergram in Figure 2 depicts the distribution of the FIQR domains. The highest scored items (greatest impact) were those related to the following categories: sleep quality (FIQR15), fatigue/energy (FIQR13), pain (FIQR12), stiffness (FIQR14), tenderness (FIQR19), and environmental sensitivity (FIQR21). The lowest scored items included functional activities such as brushing/combining hair (FIQR1), preparing a home-made meal (FIQR3), walking continuously for 20 minutes (FIQR2), and shopping for groceries (FIQR9).

Table I. Participants demographic details and baseline scores for FIQR and FAS.

	Mean	SD	Median	25 th – 75 th Percentiles
Clinical and demographics:				
Age (years)	48.9	11.4	48	42.0 – 58.0
Disease duration (years)	5.5	7.0	3.0	1.0 – 6.0
BMI	26.2	11.4	25.5	23.6 – 27.6
Marital status, no. (%)				
Single			102 (19.6)	
Married			353 (67.8%)	
Divorced/separated			66 (12.6%)	
Educational level, no. (%)				
Primary school			122 (23.4)	
Secondary school			340 (65.3%)	
High school/university			59 (11.3%)	
FIQR questionnaire:				
FIQR total score	47.8	20.6	47.5	31.7 – 64.7
FIQR physical function	12.8	6.8	12.7	7.0 – 18.0
FIQR overall impact	8.7	5.7	8.0	4.0 – 14.0
FIQR symptoms	26.4	9.7	27.0	19.0 – 34.0
FAS questionnaire:				
FAS total score	5.5	2.0	5.7	4.1 – 7.2
FAS fatigue	6.5	2.6	7.0	5.0 – 9.0
FAS sleep	6.4	2.7	7.0	5.0 – 9.0
FAS SAPS	3.7	2.0	3.8	2.3 – 5.0

BMI: body mass index; FIQR: revised fibromyalgia impact questionnaire; FAS: fibromyalgia activity score; SAPS: self-assessment pain scale.

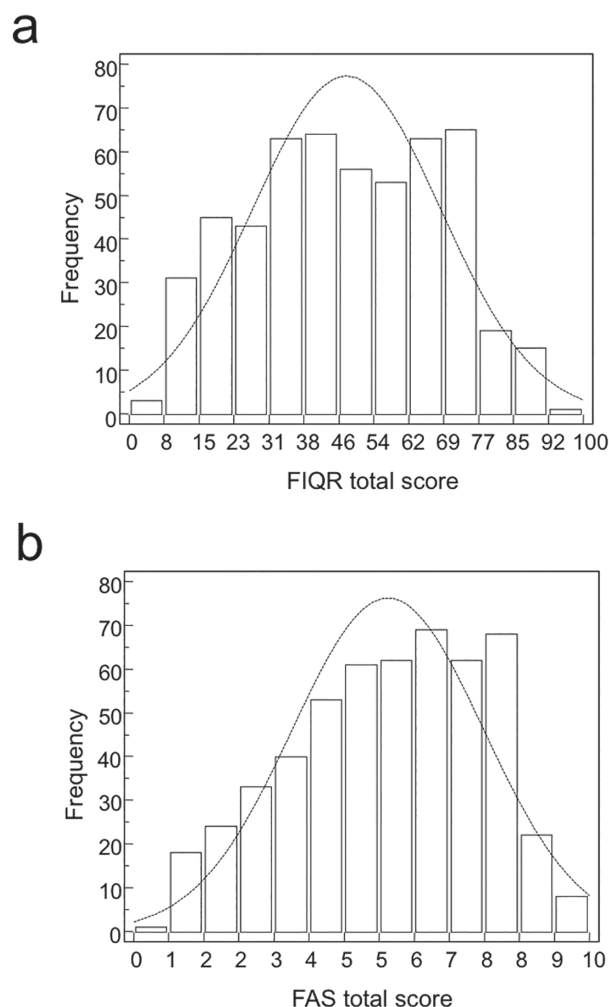


Fig. 1. Distribution of FIQR (a) and FAS (b), with higher scores indicating a worse health status (range 0-100 for FIQR, 0-10 for FAS).

Interpretability

With the reconciliation of the 75th and 25th percentile mean values of adjacent categories to define FIQR cut-off points, the numbers considered in the transition from remission to mild severity were 27 (mean value of the FIQR at the 75th percentile of remission) and 33 (mean value of the FIQR at the 25th percentile of mild severity). The arithmetic mean between these two values was 30 (not necessary to round off in this case), the FIQR cut-off point for remission. Applying the same approach, the FIQR cut-off point resulted 45 between mild severity and moderate severity (44.9 the arithmetic mean of the mean values of the FIQR at the 75th percentile of mild severity and at the 25th percentile of moderate severity, rounded off to 45), and of 65 between moderate severity and high severity (65.2 the arithmetic mean of the mean values of the FIQR at the 75th percentile of moderate disease and at the 25th percentile of high severity, rounded off to 65).

The application of these calculated cut-off points for FAS questionnaire resulted in the following values: 4 for remission, 5.5 for mild disease, 7 for moderate disease, and 7 for severe disease. Taking into account these cut-off points, in the FIQR and FAS total score, the severity of patients with FM may be divided into four disease activity states (Table III).

The application of the calculated cut-off points for FIQR and FAS showed the following distribution: remission in 22.1% and 22.9% of the patients, mild severity in 25.1% and 23.2%, moderate severity in 28.3% and 23.2%, and high severity in 24.5% and 30.7% of the patients, respectively.

According to the FIQR cut-off points, 52.8% of the patients resulted in moderate or high disease severity, while according to the FAS cut-off points this percentage is 53.5%.

The overall mean (SD) total FIQR and FAS values for each disease activity status were: 21.3 (SD 8.7) and 3.2 (SD 1.5) for remission, 37.4 (SD 7.1) and 4.9 (SD 1.3) for mild severity, 54.6 (SD 8.1) and 6.2 (SD 1.4) for moderate severity, 73.1 (SD 7.8) and 7.7 (SD 1.1) for high disease (Table IV).

Table II. Descriptive statistics of total score of the FIQR and FAS.

	FIQR total score	FAS total score
Lowest value	4.70	0.70
Highest value	94.20	9.90
Arithmetic mean	47.87	5.57
95% CI for the mean	46.09 to 49.65	5.39 to 5.75
Median	47.50	5.70
95% CI for the median	44.20 to 50.67	5.40 to 6.00
Variance	428.22	4.40
Standard deviation	20.69	2.09
Relative standard deviation	0.43 (43.23%)	0.37 (37.62%)
Standard error of the mean	0.90	0.091
Coefficient of Skewness	-0.0052 ($p=0.951$)	-0.2871 ($p=0.007$)
Coefficient of Kurtosis	-0.947 ($p=0.0011$)	-0.705 ($p=0.0083$)
Kolmogorov-Smirnov test for Normal distribution	reject Normality ($p=0.037$)	reject Normality ($p=0.029$)

FIQR: revised Revised Fibromyalgia Impact Questionnaire; FAS: Fibromyalgia Activity Score

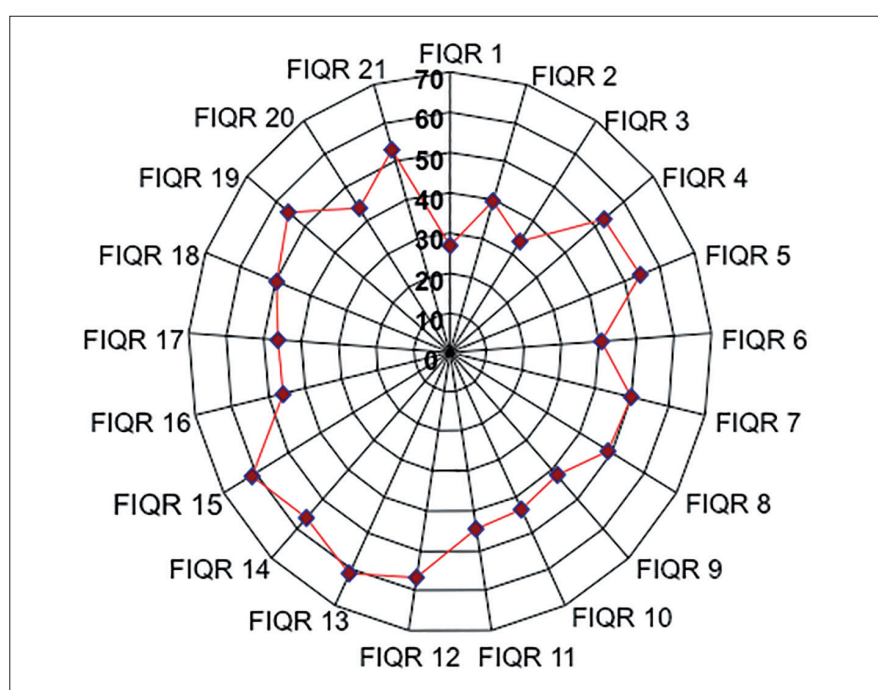


Fig. 2. Spidergram of the FIQR domains. The domains scores are plotted from 0 (best, centre) to 10 (worst, outside).

FIQR1: brush or comb hair; FIQR2: walk continuously for 20 minutes; FIQR3: prepare a homemade meal; FIQR4: vacuum, scrub or sweep floors; FIQR5: lift and carry a bag full of groceries; FIQR6: climb one flight of stairs; FIQR7: change bed sheets; FIQR8: sit in a chair for 45 minutes; FIQR9: go shopping for groceries; FIQR10: cannot achieve goals; FIQR11: feel overwhelmed; FIQR12: pain rating; FIQR13: fatigue rating; FIQR14: stiffness rating; FIQR15: sleep quality; FIQR16: depression level; FIQR17: memory problems; FIQR18: anxiety level; FIQR19: tenderness level; FIQR20: balance problems; FIQR21: environmental sensitivity. FIQR function (items 1-9); FIQR overall impact (items 10, 11); FIQR symptoms (items 12-21).

Table III. FIQR and FAS cut-off points for fibromyalgia the severity states.

FIQR cut-off points	FAS cut-off points for FM severity
Remission: ≤ 30	Remission: ≤ 4
Mild severity: >30 and ≤ 45	Mild severity: >4 and ≤ 5.5
Moderate severity: >46 and ≤ 65	Moderate severity: >5.6 and ≤ 7.0
High severity: >65	High severity: >7.0

FIQR: revised Revised Fibromyalgia Impact Questionnaire; FAS: Fibromyalgia Activity Score

Figure 3 sums up the cut-off points obtained in our analysis. The differences obtained among the 4 levels resulted in significance (Kruskal-Wallis test, $p<0.0001$).

Discussion

In this study we clearly defined the cut-off points to distinguish between severity states for FM, both for FIQR and for FAS. To the best of our knowledge, this is the first attempt to realise such kind of categorisation for the two indexes. The recent guidelines for functional somatic syndromes (including FM) suggested a treatment strategy according to severity of disease (27-29). However, up to now, the lack of international accepted instruments to categorise severity of FM represented a major gap. The severity of disease reflects major implications in the field of therapeutic prioritisation and economic costs of resource utilisation (9). Logically speaking, it seems appropriate to intensify treatment in those subjects in a high disease severity, including a multimodal (*i.e.* physical exercise programs, psychological modalities) approach (30-32).

Higher FM severity translates into an elevated use of medications, an increased frequency of co-morbidities, and a greater impact on work disability (33, 34).

The standard assessment for FM disease severity is made difficult by the presence of multifaceted symptoms.

In literature are described attempts to categorise patients into more homogeneous subgroups by cluster analysis (35-39). Recently, on the basis of patient-relevant clinical features, we identified three FM clusters from patients deriving from a large cohort using an Internet survey. Subjects in cluster 1 showed the lowest mean FIQR score, with a mild symptoms severity. Cluster 3 was characterised by severe symptoms, while cluster 2 enclosed those patients with moderate symptoms and mild levels of cognitive and psychological disturbances (40). However, this cluster distinction did not allow a measure of disease severity.

In different OMERACT meetings it has been stated that the FM domains essen-

Table IV. Total and dimensional FIQR and FAS values for each FM severity state.

	Severity states															
	Remission				Mild severity				Moderate severity				High severity			
	Mean	SD	Median	25-75 p	Mean	SD	Median	25-75 p	Mean	SD	Median	25-75 p	Mean	SD	Median	25-75 p
FIQR physical function	5.2	2.9	5.0	3.1-7.0	9.1	3.8	8.7	6.3-11.7	14.6	3.9	15.0	11.7-17.3	21.3	3.5	21.7	19.0-23.7
FIQR overall impact	2.2	2.4	2.0	0.0-3.7	6.0	2.9	6.0	4.0-8.0	10.4	3.8	10.0	8.0-13.0	15.4	3.3	16.0	14.0-18.0
FIQR symptoms	14.6	6.2	15.0	10.0-17.5	22.3	5.1	22.0	19.0-25.6	29.7	5.2	30.0	26.0-33.5	37.3	4.2	36.5	34.5-40.0
FIQR total	21.3	8.7	21.2	13.8-26.0	37.4	7.1	36.8	33.1-41.5	54.6	8.1	54.3	48.3-61.9	73.1	7.8	73.3	69.7-77.8
FAS fatigue	3.3	2.0	3.0	2.0-5.0	5.8	1.9	6.0	5.0-7.0	7.5	1.9	8.0	6.0-9.0	8.9	1.0	9.0	8.0-10.0
FAS sleep	4.1	2.6	3.0	2.0-6.0	5.7	2.3	6.0	4.0-7.2	7.1	2.3	7.0	5.0-9.0	8.6	1.5	9.0	8.0-10.0
FAS SAPS	2.1	1.3	1.9	1.2-2.9	3.2	1.6	2.9	2.0-4.4	3.9	1.6	4.2	2.9-5.0	5.6	2.1	5.6	4.4-6.9
FAS total	3.2	1.5	3.0	2.0-4.3	4.9	1.3	4.8	3.8-5.8	6.2	1.4	6.3	5.3-6.9	7.7	1.1	7.8	7.2-8.2

P: percentile; FIQR: revised Revised Fibromyalgia Impact Questionnaire; FAS: Fibromyalgia Activity Score; SAPS: Self-Assessment Pain Scale.

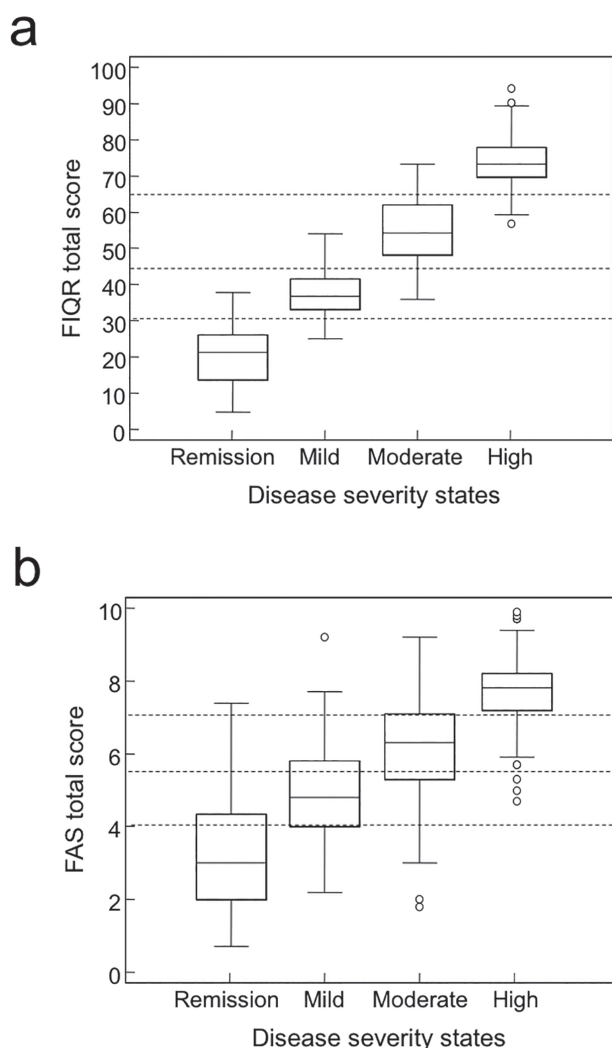


Fig. 3. Box-and-Whisker plots of the FIQR (a) and FAS (b) (y-axis) for each severity states. The boxes represent the values from the 25th to the 75th percentiles of FIQR and FAS for each severity states, respectively remission, mild severity, moderate severity, and high severity. The middle lines inside boxes represent the medians. The dotted lines are the cut-off values.

tom Severity (SS) (somatic symptoms, fatigue, unrefreshing sleep, and cognitive complaints) (42).

Serra *et al.* developed the Fibromyalgia Burden Assessment (FMBA), a FM-specific tool (43). The FMBA includes dimensions of pain, impact of disease on physical and daily activities, social and family lives, psychological aspects, work and finances.

Alternatively, two Spanish groups proposed the Combined Index of Fibromyalgia Severity (ICAF, acronym for Índice Combinado de Afectación en Fibromialgia) (44), and new combined index of symptom severity (the Core-FM symptoms and Distress - CODI) (45).

The present research was focused on FIQR and FAS. Actually, the FIQR is the most commonly used instrument to assess health status in FM patients by capturing disease related symptoms and physical functioning impact. Both tools allow a complete assessment of FM patients. Overall, the two instruments demonstrated a comparable ability to categorise the disease severity (mild/high severity in the 52.8% of the patients according to FIQR, in the 53.5% according to the FAS).

The logical consequence of the FM severity measurement is the identification of treatment responders (46).

During the last years, especially in the field of inflammatory arthritis, the categories of “remission”, “low disease activity”, “patient acceptable symptom state”, became the core business for the rheumatological clinical practice (47, 48). Such principles are the cornerstone of the treat-to-target (T2T) strategy:

tial for evaluation are patient-centric. The top five of these domains include pain, fatigue, patient global, sleep, and multidimensional function (32, 41). The literature lists different proposals to assess FM severity. For example, Wolfe *et al.* developed and validated

the Fibromyalgia Survey Diagnostic Criteria and Severity Scale (FSDC), a patient-administered questionnaire assessing diagnosis and symptoms severity. The FSDC encompasses the body pain, assessed by the Widespread Pain Index (WPI), and the associated Symp-

an intense management of a condition with frequent monitoring while escalating the treatment in order to achieve a pre-defined therapeutic target.

Of course, the comparison between FM and inflammatory arthritis is rather daring. However, the dialogue about FM and T2T strategy has been started, even though numerous uncertainties exist (49).

Characterisation of FM severity levels could also be used as a marker of disease progression. Few published studies on severity or progression of FM revealed that the natural history of FM is poorly known (50). Recently, Hoskin *et al.* suggested that FM symptoms severity and symptoms patterns do not change significantly over two years, especially in those patients with low and high symptoms intensity, but are less stable in patients with moderate symptoms intensity (51).

When interpreting the results of this study, we have to acknowledge its limitations.

Firstly, we used an anchor-based methodology. The subjectivity related to a single item answer can be wide. Future research should include external criteria offering an increased sensitivity to patient-rated improvement, such as the Patient Acceptable Symptom State (PASS) (52). Our anchor-based approach is one of the available methods for estimating cut-off points, and cut-off points obtained from different methods may be variable.

Secondly, we have not established the role of other patient features, such as age, sex, education and co-morbidity (in particular the psychiatric co-morbidities, even if a diagnosis of major depression represented an exclusion criteria). In future research evaluating the clinical importance of these factors must be carefully considered. Thirdly, an important limitation is the single centre recruitment, while a major strength of this work is the inclusion of a large patient population sample.

In conclusion this study represents a first attempt to characterise FM patients by severity in a very practical way. Our cut-off points can give to clinicians the opportunity for an efficient assessment of disease impact on patients' lives and

support future studies of categorisation of patients' symptom severity. The interpretation of disease severity could also be of great value in supporting decision-making in healthcare policy.

The utility and the validity of the FIQR and FAS cut-off points, as a measures of severity in FM, need to be tested in future studies including patients of different settings and countries.

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