A novel approach to the clinical assessment of juvenile fibromyalgia syndrome: the Juvenile Fibromyalgia Multidimensional Assessment Report

E. Drago[1,2], C. Lavarello[1], A. Alongi[3], A. Ronchetti[4], E. Pescio[5,6], M. Mazzoni[5], L. Chiarella[1,7], L. Nobili[1,7], S. Kotzeva[8], B. Gily[9], M. Gattorno[5], A. Ravelli[1,10], C. Malattia[1,5]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genova, Italy; [2]Gene Therapy Program, Dana Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA; [3]School of Medicine and Surgery, Milano-Bicocca University, Monza, Italy; [4]UOC Medicina Fisica e Riabilitazione, IRCCS Istituto G. Gaslini, Genova, Italy; [5]UOC Reumatologia e Malattie Autoinfiammatorie, IRCCS Istituto G. Gaslini, Genova, Italy; [6]UOSD Centro di Psicologia, IRCCS Istituto G. Gaslini, Genova, Italy; [7]UOC Neuropsichiatria infantile, IRCCS Istituto G. Gaslini, Genova, Italy; [8]UOC Anestesiologia e Terapia del Dolore Acuto Procedurale, IRCCS Istituto G. Gaslini, Genova, Italy; [9]UOSD Anestesia ed Analgesia Ostetrico Ginecologica, IRCCS Istituto G. Gaslini, Genova, Italy; [10]Direzione Scientifica, IRCCS Istituto G. Gaslini, Genova, Italy.

Abstract

Objectives

Development and psychometric evaluation of a disease-specific, paediatric-targeted multidimensional questionnaire for the assessment of juvenile fibromyalgia syndrome (JFS) in routine clinical practice.

Methods

The Juvenile Fibromyalgia Multidimensional Assessment Report (J-FiMAR) includes three domains: numerical rating scales to measure the severity of JFS- related symptoms (widespread pain, fatigue, sleep quality, depression, anxiety, cognitive impairment, headache and abdominal pain); a self-report questionnaire to assess physical functioning (PF) and health-related quality of life (HRQoL); and patient rating of disease severity and course. Validation analyses included assessment of construct validity, discriminant validity and responsiveness to change.

Results

The J-FiMAR was administer to 51 JFS patients (F 43, median age 16 years). Each patient completed the J-FiMAR at study entry and at each follow-up visit for a total of 194 visits. All patients found the questionnaire clear, easy to complete and quick. Correlations between J-FiMAR components and physician global assessment of patient's health status, and validated instruments for mood and sleep disorders were at least moderate. J-FiMAR discriminated well between patients who exhibited improvement and those who did not improve at follow up visits. JFS patients reported worse pain, fatigue, mood disorders, PF and HRQoL than patients with juvenile idiopathic arthritis ($p<0.05$). The majority of the items included in the J-FiMAR exhibited satisfactory responsiveness to change, with standardised response mean values exceeding 0.6.

Conclusion

The J-FiMAR is an accurate clinical tool for routine monitoring of disease course and has the potential to be successfully integrated into both outpatient clinics and research settings.

Key words

juvenile fibromyalgia, patient reported outcomes, outcome measures, health-related questionnaires

Enrico Drago, MD
Claudio Lavarello, MD, PhD
Alessandra Alongi, MD
Anna Ronchetti, MD
Elena Pescio, MD
Marta Mazzoni, MD, PhD
Lorenzo Chiarella, MD
Lino Nobili, Prof
Svetlana Kotzeva, MD
Brunella Gily, MD
Marco Gattorno, MD
Angelo Ravelli, Prof
Clara Malattia, Prof, MD, PhD

Please address correspondence to:
Prof. Clara Malattia,
UOC Reumatologia e Malattie Autoinfiammatorie,
IRCCS Istituto Giannina Gaslini,
Via G. Gaslini 5,
16147 Genova, Italy.
E-mail: claramalattia@gaslini.org

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Introduction

Juvenile fibromyalgia syndrome (JFS) is a chronic pain disorder characterised by widespread musculoskeletal pain, fatigue, non-refreshed sleep and mood disturbances that cause functional impairment and have a marked impact on the patient's quality of life (1-2). The estimated prevalence of JFS ranges from 1.2 to 6.2% in children of school age, with a mean age at symptom onset of 11.4-13.7 years (3-6). Females are predominantly affected. Despite the high prevalence and impact of JFS, the evidence base for its treatment remains limited. Valid and reliable patient-reported outcome measures (PROMs) for the assessment of pain and related experience are critical for advancing knowledge of clinical interventions for JFS.

In recent years, significant progress has been made in this field (7-10). Building on the work of the Peadiatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Ped-IMMPACT) group (11), Palermo *et al*. have updated a core outcome set for paediatric chronic pain clinical trials (12) and have recommended a set of PROMs for each of the following outcome domain: pain severity, pain-related interference with daily living, overall well-being, emotional functioning, physical functioning, and sleep (13). Despite their strong psychometric properties, these PROMs are rarely used to assess JFS patients in everyday clinical practice due to the burden they impose on both patients and clinicians, who must respectively complete and interpret multiple lengthy questionnaires. To evaluate JFS patients in busy clinical settings, it would be ideal to have one single disease-specific instrument that is able to measure the multifaceted nature of this condition in a straightforward, speedy and comprehensive manner. As stated by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Fibromyalgia Syndrome Workgroup, a multidimensional assessment of fibromyalgia is required to fully understand its broad range of symptoms and its impact on overall functioning (14). As is known, the majority of the multidimensional measures used in adults with fibromyalgia syndrome (7) are not suitable for the evaluation of paediatric patients given that they include items pertaining to adults, such as activities of shopping, laundry, and driving, and not to children. To our knowledge, only one measurement has been adapted for use in JFS, namely the Modified Fibromyalgia Impact Questionnaire (MFIQ)-Child version, having re-worded the item referring to "work" with "school" (8). However, at this time, there is limited information about its the clinical utility, as it has been used in a very small number of paediatric studies (8, 15).

Based on these considerations, we have developed a paediatric-targeted, disease-specific, multidimensional questionnaire, the Juvenile Fibromyalgia Multidimensional Assessment Report (J-J-FiMAR), specifically designed for the assessment of JFS patients in standard clinical care. This tool aims to provide the physician with a comprehensive overview of the patient's status, which enables prioritising matters that require attention and facilitate more effective clinical care.

The objective of the present study is to describe the J-FiMAR and to provide preliminary evidence of its validity in a cohort of patients with JFS.

Materials and methods

Development of the J-FiMAR

The J-FiMAR was developed by a multidisciplinary panel of experts comprising 4 paediatric rheumatologists, 2 neuropsychiatrists, 1 psychologist, 1 specialist in physical medicine and rehabilitation, and 2 pain specialists, with 2 to >20 years of clinical experience in the field of paediatric chronic pain. In the initial stage of the study, investigators were asked to identify the most pertinent items for the assessment of JFS based on both clinical experience and a systematic review of the existing literature (7-14, 16-20). To ensure the feasibility of J-FiMAR, it was decided that all measures included in the questionnaire should be concise and easy to complete. In the second phase, the experts were engaged in a discussion on the relative importance and suitability

of each selected item. Inclusion of each individual item into the J-FiMAR, required the agreement of at least 8 out of 10 members of the panel. Thus, the content validity of the measure was ensured by the members of the panel.

The resulted version of the J-FiMAR is composed of three domains. The first is to evaluate the severity of JFS symptoms. It is made up of 0 to10 numerical rating scales (NRS) (20), which quantify the intensity of musculoskeletal pain, fatigue, sleep quality, headache, anxiety and depression, attention and memory deficit and abdominal pain over the previous two weeks (0=no symptoms, 10 = maximum severity of symptoms).

The second domain comprises the assessment of physical function (PF) and health-related quality of life (HRQoL). The evaluation of PF is based on a six-item measure of impairment in daily functioning. Responses are rated on a three-point scale (0= without difficulty, 3= unable to do).

The HRQoL is evaluated through a 7-item measure of difficulties in activities such as self-care, peer relationships, among others. This questionnaire has been developed based on a comprehensive review of existing, more generic HRQoL scales (20-23). A question concerning difficulties in sexual activities has been included, given that this is a common concern among adolescents with JFS. Responses are rated on a three-point scale (0= without difficulty, 3= unable to do). The total PF and HRQoL scores are calculated by summing the scores for each task and then dividing the sum by the number of questions answered to account for missing data. Total PF and HRQoL scores range from 0 to 3, with higher scores indicating higher degrees of functional impairment and a worse HRQoL, respectively.

The last domain, entitled "overall impact" includes: 1) the number of days in the previous three months during which the patient was unable to attend school due to JFS symptoms; 2) the patient's global assessment (PGA) of well-being on a 21-numbered circle VAS; 3) rating of the disease course from the previous visit as much improved, slightly improved, stable, slightly worsened or much worsened; 4) a binary question regarding satisfaction with the outcome of the illness (yes/no).

In order to test face validity, the initial draft of the J-FiMAR was shown to a panel of health professionals, including 3 paediatric rheumatologists, 2 neuropsychiatrists, 2 paediatric residents, 2 physiotherapists, 2 specialist nurses, and 1 clinical psychologist, who were asked their opinion on its suitability. Further testing was conducted through the administration of the J-FiMAR to a convenience sample of 15 patients with JFS and their parents. Participants were invited to provide their feedback on the content, structure, and response scales of the J-FiMAR. Some issues were raised regarding the definition of the items pertaining to fatigue, emotional functioning, and overall impact. Following a discussion with the panel of experts, these items were re-worded. The English translation of the J-FiMAR is provided in the Supplementary material.

Patient clinical assessment

All patients with JFS by the 2010 American College of Rheumatology (ACR) criteria (24, 25), who were seen at the study unit between December 2020 and December 2022, were invited to complete the J-FiMAR at each 6-month follow-up visit. In addition, the J-FiMAR was administered to 50 patients with juvenile idiopathic arthritis (JIA) and active disease who were seen at the study site during the same period. At study entry, all JFS patients were administered the Children's Depression Inventory- 2nd Edition (CDI-2) (26) and the Multidimensional Anxiety Scale for Children-2nd Edition (MASC-2) (27). The sleep quality was evaluated using the Sleep Condition Indicator (SCI) (28) and the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) (29). The Physical Activity Index (PAI) questionnaire was used to evaluate physical activity; it comprises items addressing the frequency, intensity and duration of leisure-time physical activity, as well as participation in organised physical activities, including sports club training and competitive sports (30). JFS patients were classified according to the PAI as follows: 81-100 very active lifestyle; 60-80 active and healthy lifestyle; 40-59 acceptable lifestyle, but with room for improvement; 20-39 lifestyle that is not good enough; below 20 sedentary lifestyles (31, 32). At each visit, the attending physician provided a global assessment of patient's health status (PhGA) on a 0-10 NRS (0= very well; 10 = very poorly).

This study was approved by the regional review board for human subjects' research (CER Liguria: 333/2022-DB id 12460). All participants and legal guardians provided written informed consent/assent to participate in the study.

Statistics

Descriptive statistics were reported as medians and interquartile ranges for continuous variables and as absolute frequencies and percentages for categorical variables.

Validation of J-FiMAR included assessment of construct validity and responsiveness to change. The convergent validity examines the correlation of the J-FiMAR items/domains with other measures that assess a similar construct. Given that the J-FiMAR is intended to measure the full spectrum of the disease and its impact on patients' emotional and physical functioning, it was predicted that the correlations between the J-FiMAR items/domains and the PhGA would be at least moderate. It was also predicted that the correlation between the J-FiMAR subscales addressing mood, sleep disorders and PF and the scores of CDI, MASC, SCI, ESS-CHAD and PAI would be at least moderate, as they measure closely related constructs. All correlations were calculated as Spearman's correlation coefficients. Convergent validity was deemed to be met for a Spearman's correlation coefficient ≥ 0.4 (33). Discriminative validity refers to the ability of an instrument to differentiate between distinct health states or diagnostic groups. At each follow-up visit, patients were categorised as either 'improved' or 'not improved' based on the subjective evaluation of

the attending physician. The Mann-Whitney U test was used to compare the J-FiMAR scores between the improved and non-improved groups, as well as between the JFS and JIA groups. The responsiveness to change was assessed by computing the standardised response mean (SRM), calculated as the absolute mean change in score divided by the standard deviation of individual change in score (34). The threshold levels for the SRM were defined as follows: ≥0.20 small, ≥0.50 moderate, and ≥0.80 good (35). Floor and ceiling effects (frequency of items at lower and higher extremes of the scales, respectively) were also evaluated, as these factors may influence the capacity of an instrument to detect a change. Results were considered acceptable if below the recommended cut-off point of 15% (36). All the analyses were performed using R Software, version 4.1.3, R Foundation for Statistical Computing (Vienna, Austria).

Results

A total of 51 patients with JFS (F=43), whose demographic and clinical features are presented in Table I, were included in the study. The most severe symptoms at study entry were musculoskeletal pain, fatigue, and non-restorative sleep. The median scores ± DS for HRQoL and PF were 1.31±0.59 and 0.83±0.52, respectively. Irregular school attendance was reported in 45% of patients. Each patient completed the J-FiMAR in a total of 194 visits. All patients reported that the J-FiMAR was straightforward and readily understandable, with only a few patients requiring clarification and a negligible proportion of missing data. The mean time to complete the J-FiMAR was approximately 5 minutes, while the time taken to score its various components by a health professional was less than 3 minutes.

Convergent validity. The Spearman's correlation coefficient of the measures included in the J-FiMAR is shown in Figure 1. As predicted, the correlations between the J-FiMAR items and the PhGA were in the moderate range. The PhGA exhibited the strongest correlation with the PGA (r_s=0.58), musculoskeletal pain (r_s=0.53), and fatigue (r_s=0.53).

A total of 45% (23/51) of patients exhibited clinical anxiety (MASC-2 ≥ 60), while 23.5% (12/51) demonstrated clinical depression (CDI-2 ≥ 19). Furthermore, 72.5% (37/51) of patients experienced sleep disturbances. As reported in Table II, the J-FiMAR items measuring the severity of anxiety and depressive symptoms and sleep quality demonstrated moderate correlations with MASC-2 (r_s=0.61), CDI-2 (r_s=0.52) and ESS-CHD (r_s=0.4) scores, indicating satisfactory convergent validity. The PAI index revealed that 60.8% of patients had a sedentary lifestyle, 33.4% a suboptimal lifestyle, and only 5.8% an acceptable lifestyle. The correlation between the PAI and the PF scale was below the validity threshold (Table II).

Discriminant validity. At the study entry, 17 patients (33.3%) were not receiving any treatment, 17 patients (33.3%) were given pharmacotherapy, and 17 patients (33.3%) were on non-pharmacological treatment. Therapeutic interventions are outlined in Table I. According to the attending physician, improvement in patient condition was observed in 40 out of 143 follow-up visits (28.7%). The measures included in the J-FiMAR were found to be effective in discriminating between patients who exhibited improvement and those who did not. As shown in Figure 2, median NRS value of JFS symptom

Table I. Demographic and clinical features of the 51 JFS patients at study entry.

Characteristics	n (% or range)
JFS patients	51
Gender, female	43 (84.3)
Median age, years (range	16.0 (11.5-20.1)
Median symptom duration prior to diagnosis, years (range)	1.8 (0.2-9.6)
Family history of FM	13 (25.4)
Secondary JFS	5 (9.80)
Body mass index (Mean ± SD)	22.7 ± 5.7
JFS-related symptoms NRS	**Median VAS ± SD**
Widespread musculoskeletal pain	7.8 ± 2.2
Fatigue	8.0 ± 2.6
Non-restorative sleep	8.0 ± 2.7
Anxiety	6.5 ± 3.1
Depressive symptoms	6.0 ± 3.3
Headache	7.0 ± 3.1
Concentration or memory problems	6.0 ± 3.1
Abdominal pain	3.0 ± 2.9
Median HRQoL total score	1.3 ± 0.6
Median physical function total score	0.8 ± 0.5
Patient's Global Assessment	6.3 ± 2.5
Irregular school attendance	23 (45.1%)
Physical therapy	3 (5.9)
Family history of FM	11 (21.6)
Secondary JFS	5 (9.80)
Body Mass Index (Mean ± SD)	22.7 ± 5.7
Treatment	
FKT	6 (11.8)
Aerobic and strengthening exercise	12 (23.5)
Cognitive behavioural therapies	3 (5.9)
NSAIDs	11 (21.6)
Melatonin	12 (23.5)
Pregabalin/Gabapentin	5 (9.8)
SNRIs/SSRIs	5 (9.8)
Amitriptyline	3 (5.9)
Opioids	1 (2)
Cyclobenzaprine	3 (5.9)
Benzodiazepines	3 (5.9)

FM: fibromyalgia; HRQoL: health-related quality of; JFS: juvenile fibromyalgia syndrome; NRS: numbered rating scales; NSAIDs: non-steroidal anti-inflammatory drugs; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors.

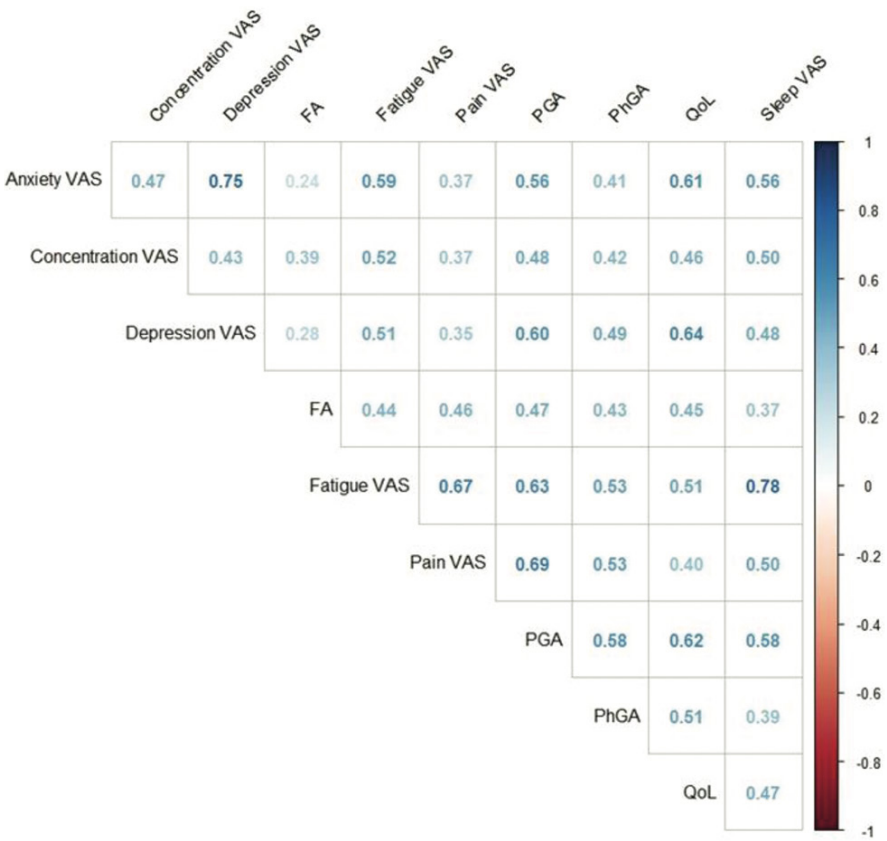

Fig. 1. Pairwise Spearman's correlation between the variables included in the J-FiMAR.
PGA: patient's global assessment of overall wellbeing; PhGA: physician's global assessment of disease; QoL: quality of life scale; FA: functional ability scale.

Table II. Spearman's coefficients with 95% confidence intervals for correlations between J-FiMAR and validated measures for specific domains.

Variables	R	CI	*p*-value
Anxiety VAS - MASC	0.61	0.50-0.70	0.001
Depression VAS - CDI	0.52	0.39-0.63	0.001
Sleep VAS - ESS-C	0. 40	0.24-0.51	0.001
FA - PAI	0.01	-0.15, 0.17	0.88

MASC: Multidimensional Anxiety Scale for Children; CDI: Children's Depression Inventory; ESS-CHAD: Epworth Sleepiness Scale-Children and Adolescents; FA: functional ability scale; PAI: Physical activity index.

severity, PGA and PhGA were lower in patients who improved compared with those who did not. Furthermore, JFS patients reported higher levels of pain, fatigue and psychological distress than patients with JIA. JFS patients also had worse PF and HRQoL (Fig. 3). These results indicate that the J-FiMAR can differentiate well patients with JFS from those with other connective tissue disorders.

Responsiveness. As shown in Table III, the majority of the items included in the J-FiMAR demonstrated satisfactory responsiveness to change, with SRM values consistently above 0.6, except for attention/memory (SRM=0.0). A floor effect above the target threshold (15%) was observed exclusively for the concentration/memory difficulties (Supplementary Table S1).

Discussion

In JFS, studies have typically employed generic paediatric instruments applicable across various pain conditions. This study introduces an advancement in the field of JFS clinical assessment as it provides clinicians with a novel, disease-specific, multidimensional questionnaire that enables a fully comprehensive assessment of the severity of JFS-specific symptoms, along with their impact on overall functioning.

From a conceptual point of view, while the J-FiMAR shares similar objectives and a comparable structure to MFIQ-C, an adult multidimensional measure that was modified for use in JFS, it differs considerably in several key aspects. Regarding the development method, the items for the MFIQ-C were initially adapted from the adult version of the FIQ by replacing references to 'work' with 'school.' However, children and adolescents were not involved in this adaptation process. Finally, the MFIQ-C was not sufficiently validated in the child and adolescent population, significantly limiting its clinical usefulness (8, 15). On the other hand, the J-FiMAR has been designed specifically for JFS patients. Its items have been selected by a panel of experts in the management of this condition. The suitability of the J-FiMAR domain framework has also been validated through a rigorous and iterative qualitative methodology that has gained the input of various stakeholders. The inclusion of medical experts, patients, and their families as part of the development of the J-FIMAR, along with field testing of the measurements, guarantees solid evidence for content. Furthermore, unlike the MFIQ-C, the J FIMAR expands the range of symptoms to include cognitive difficulties, headaches and abdominal pain. These are the cardinal symptoms included in the Pain and Symptom Assessment Tool (PSAT), which was developed to enable consistent classification of adolescents with JFS based on the 2010 American College of Rheumatology (ACR) criteria for fibromyalgia. Finally, the preliminary validation of the J-FiMAR was conducted by testing its psychometric properties on a cohort of patients with JFS.

The J-FiMAR has been designed for regular administration in daily clinical practice, with the objective of recording all data in a single instrument

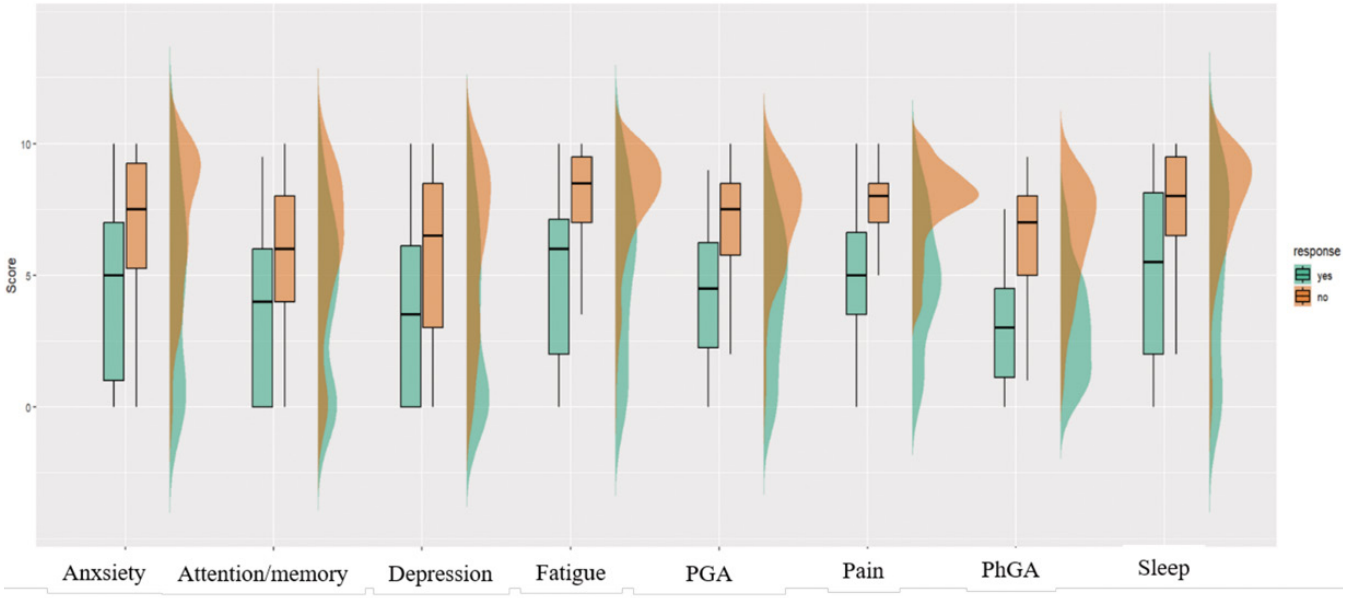

Fig. 2. Median value of the symptoms 'severity numerical rating scales in patients who exhibited improvement at the follow-up visits (green column) compared to those who did not (orange column). $p<0.001$ for all the comparisons.
PGA: patient's global assessment of overall wellbeing; PhGA: physician's global assessment of disease.

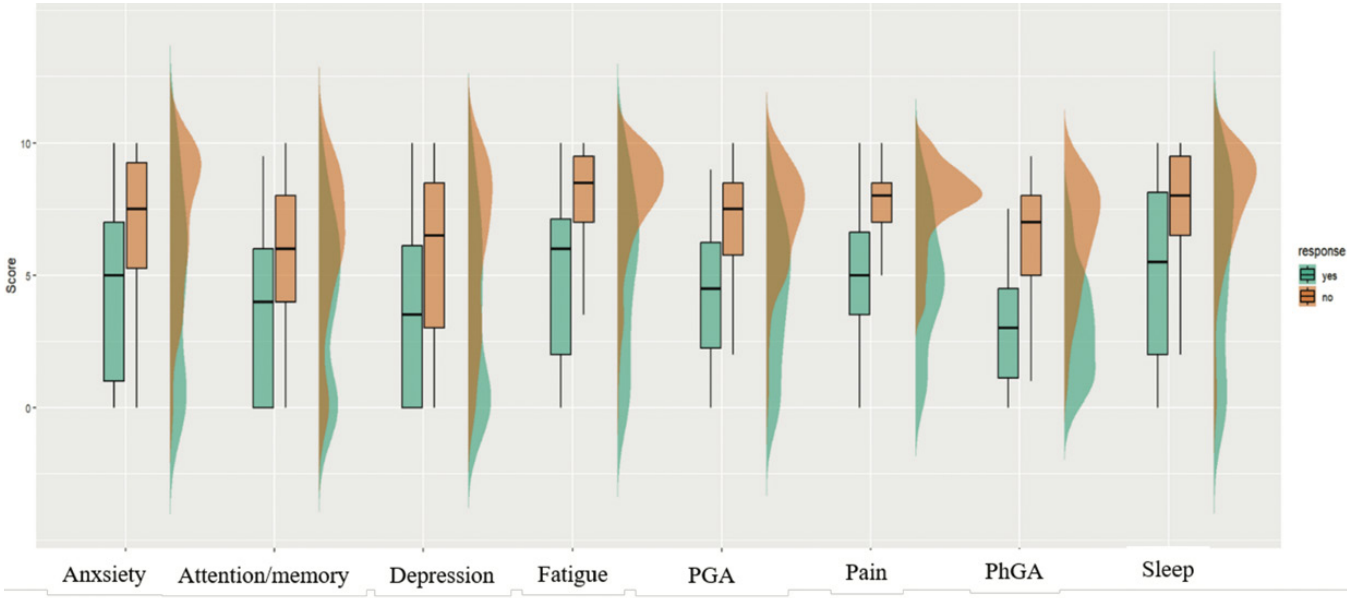

Fig. 3. Violin plots comparing each patient-reported outcomes between patients with juvenile fibromyalgia and Juvenile idiopathic arthritis; p values are indicated for each comparison (Mann-Whitney test).
JIA: juvenile idiopathic arthritis.

in a standardised manner. To this end, particular attention was paid to ensuring feasibility and acceptability in busy out-patient clinical settings. The questionnaire format has been demonstrated to be highly user-friendly, easily understood and readily answered by patients.

The psychometric properties of the J-FiMAR were found to be satisfactory across all domains, apart from a few exceptions. Indeed, the J-FiMAR demonstrated a significant correlation with PhGA, particularly in relation to musculoskeletal pain and fatigue, which are cardinal symptoms of JFS. Moreover, correlations of NRS reflecting mood and sleep disorders and the other measures of the same construct (CDI, MASC and SCI) were in accordance with a priori predictions, thereby providing evidence of convergent validity. Consistent with previous studies (3, 37-39), a substantial percentage of our patients had psychiatric comorbidity. Notably, in a cross-sectional study involving 31 patients with JFS depression and anxiety have been associated with a high risk of suicidal ideation (40). Thus, a multidisciplinary approach aimed at facilitating an early diagnosis of psychiatric comorbidities in JFS is a priority. In this context, the J-FiMAR has the potential to expeditiously identify patients who require an in-depth psychiatric assessment.

Table III. Responsiveness of each variable from baseline (T0) to 6 months (T1) in responders, assessed using Standardized Response Means (SRMs) with 95% Confidence Intervals and *p*-values.

Variable	SRM (95% CI)	P value
Widespread musculoskeletal Pain	1.132 (0.408-1.857)	0.002
Fatigue	1.025 (0.326-1.724)	0.004
Sleep	0.813 (0.160-1.466)	0.015
Depression	0.875 (0.210-1.541)	0.010
Concentration/memory	0.000 (-0.566-0.566)	1.000
Anxiety	0.571 (-0.039 -1.181)	0.067
PGA	0.949 (0.237-1.660)	0.009
PhGA	1.953 (0.988-2.917)	0.000
QO	0.646 (-0.116-1.408)	0.096
FA	0.618 (-0.138-1.374)	0.109

PGA: patient's global assessment of overall wellbeing; PhGA: physician's global assessment of disease; QoL: quality of life scale; FA: functional ability scale.

The J-FiMAR also enables the assessment of sleep quality, which is of paramount importance for the physical and mental wellbeing of adolescents with JFS. A bidirectional link between sleep disorders, depression and anxiety has been recently demonstrated in JFS patients who underwent overnight polysomnography (41). Moreover, sleep complaints and depressive symptoms are known to have a marked effect on relevant clinical domains of the disease, such as physical daily functioning and pain thresholds (42, 43).

The primary goal in the treatment of JFS is to enhance quality of life through pain relief and improved function (44). PF is therefore an essential component of any outcome measure for JFS (9, 11-13). Unexpectedly, convergent validity was not entirely satisfactory for the assessment of this domain. This result is likely influenced by the selection of the PAI as comparator for assessing functioning. The PAI, in fact, comprises items addressing the leisure-time physical activity and the participation in organised physical activities, including sports club training and competitive sports (30-32). The weak correlation between the PAI and physical function may be attributable to the sedentary lifestyle of the majority of patients and their lack of participation in sporting activities. It is acknowledged that the Functional Disability Inventory (FDI) would have constituted the optimal measure for testing convergent validity in this module (8, 9, 11, 13). However, the inclusion of the FDI in our study was not feasible because the adapted Italian version of the FDI is currently unavailable.

The J-FiMAR components demonstrated a notable ability to distinguish between different severity levels of the disease, as well as between JFS and JIA. This finding thus supports the discriminant validity of the tool. Despite the non-interventional nature of the study, the J-FiMAR proved to be a sensitive indicator of improvement, as demonstrated by the strong responsiveness to change observed for most of its components, further supported by the availability of responsiveness data from 194 follow-up visits. It is noteworthy that there was no substantial change in the cognitive functioning scale throughout the course of the disease. The poor responsiveness to change in this subscale is most likely attributable to the fact that our patients were not receiving treatments specifically targeted at this issue. It is also possible that the results were influenced by a floor effect. In line with literature data (45), approximately 80% of our patients reported experiencing subjective cognitive impairment, also referred to as "brain fog". This term pertains to a range of symptoms including loss of mental clarity and difficulties with attention and memory. These findings are of particular concern because cognitive impairments might contribute to school absenteeism and social withdrawal, which in turn, may lead to socioeconomic and psychosocial consequences in adulthood (46).

Our results should be interpreted in light of some potential caveats. The study population consisted of patients with JFS recruited from a paediatric rheumatology clinic and therefore, the findings may not be representative of individuals with JFS from community-based studies. Furthermore, the sample was predominantly composed of white female individuals, thus limiting the generalisability of the results to other groups of JFS patients. Another limitation of the study is the relatively small sample size and the fact that the validation analysis was conducted at a single centre. Although the Institute G. Gaslini is a large tertiary-care paediatric rheumatology centre, larger multicentre cohorts will be required to externally validate our findings and to further support the longitudinal validity of the tool. In addition, future cross-cultural adaptation studies will be important to broaden the applicability of the J-FiMAR in international contexts. Finally, the authors acknowledge that a composite J-FiMAR total score is not currently available. The transition to a digital version of the J-FiMAR, which includes the implementation of an integrated software system for a real-time automated calculation of a weighted composite score, is still in progress.

In conclusion, we have developed a novel disease-specific, multidimensional clinical instrument that enables the comprehensive evaluation of JFS symptoms and of their impact on overall functioning, which may contribute to the decision-making process and facilitate the success of patient care.

The completion of the J-FiMAR also enables patients to focus on the information required for their care and increases the capacity to express their concerns within the limited time available during a clinical visit. The J-FiMAR was found to be feasible and to possess both face and content validity. Additionally, it exhibited good convergent validity, discriminant validity, and responsiveness to clinically important change. The documentation of the satisfactory psychometric properties of the J-FiMAR provides support to its use for assessing the multidimensional impact of JFS in standard clinical care.

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