ORIGINAL RESEARCH

Identifying the symptom and functional domains in patients with fibromyalgia: results of a cross-sectional Internet-based survey in Italy

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Objective: The aims of this cross-sectional study were to investigate the usefulness of using an Internet survey of patients with fibromyalgia in order to obtain information concerning symptoms and functionality and identify clusters of clinical features that can distinguish patient subsets.
Methods: An Internet website has been used to collect data. Fibromyalgia Impact Questionnaire Revised version, self-administered Fibromyalgia Activity Score, and Self-Administered Pain Scale were used as questionnaires. Hierarchical agglomerative clustering was applied to the data obtained in order to identify symptoms and functional-based subgroups.
Results: Three hundred and fifty-three patients completed the study (85.3% women). The highest scored items were those related to sleep quality, fatigue/energy, pain, stiffness, degree of tenderness, balance problems, and environmental sensitivity. A high proportion of patients reported pain in the neck (81.4%), upper back (70.1%), and lower back (83.2%). A three-cluster solution best fitted the data. The variables were significantly different ($P<0.0001$) among the three clusters: cluster 1 (117 patients) reflected the lowest average scores across all symptoms, cluster 3 (116 patients) the highest scores, and cluster 2 (120 patients) captured moderate symptom levels, with low depression and anxiety.
Conclusion: Three subgroups of fibromyalgia samples in a large cohort of patients have been identified by using an Internet survey. This approach could provide rationale to support the study of individualized clinical evaluation and may be used to identify optimal treatment strategies.
Keywords: fibromyalgia, Internet, FIQR, FAS, cluster analysis, SAPS, pain

Introduction

Fibromyalgia (FM) is a chronic heterogeneous syndrome that affects ~2%–3% of the general population.[1–3] Its primary symptom is chronic, widespread pain associated with generalized tenderness on light palpation. Many patients report a multitude of additional complaints and symptoms,[4] including fatigue, exhaustibility and stiffness, and impaired concentration and memory (a complaint that is increasingly recognized as an independent symptom, namely, "fibrofog" or "dyscognition", according to medical literature).[5] The combinations and severity of symptoms may vary from patient to patient, and this makes it difficult to understand the disease and the development of appropriate treatment strategies.[6] However, stratifying patients by cluster analysis into more homogeneous subgroups on the basis of their patient-relevant clinical features may help to overcome these limitations.[7–14] Cluster analysis allows to identify clinical features and quantifies the importance of each cluster.[15,16]

A comprehensive assessment of main symptoms and the evaluation of the impact on the multidimensional aspects of function should be a routine part of patient care

in FM. Patient-reported outcomes (PROs) are playing an increasingly significant role in the evaluation of symptoms, health-related quality of life, and medical compliance.[17] The Fibromyalgia Impact Questionnaire Revised version (FIQR) is currently the recommended tool for assessing function and health-related quality of life in patients with FM. FIQR assesses six domains (pain, tenderness, fatigue, stiffness, multidimensional function, and sleep) identified as core dimensions by Outcome Measures in Rheumatology Clinical Trials.[18] Psychometric properties of FIQR (ie, rating scale functioning, internal construct validity, reliability indices, and dimensionality) have been validated.[19,20] Routine PROs collection can be facilitated by using more advanced interactive computer technologies such as Internet-based home telemonitoring and can support a transition from institution to patient-centered applications.[21–26]

The aims of this cross-sectional study were to investigate the usefulness of an Internet-based national survey of patients with FM in order to obtain information concerning symptoms and functionality and to identify clusters of symptoms that helps to distinguish patient subsets.

Methods

Study population

The participants were selected from a large database of patients with FM referring to the Rheumatology Department of the Polytechnic University of Marche in Jesi (Ancona, Italy), the Internal Medicine and Rheumatology Unit of Parma Hospital, and the Rheumatology Unit of "L. Sacco" University Hospital in Milan (Italy). The following subjects have been excluded from the study: those affected by cardiovascular disease, moderate-to-severe chronic lung disease, uncontrolled hypertension, uncontrolled thyroid disturbances, inflammatory rheumatic conditions (ie, rheumatoid arthritis, systemic lupus erythematosus, and other connective tissue diseases), and/or psychoses or active suicidal ideation. A total of 496 patients have been screened, of which 143 refused to participate. The remaining 353 patients satisfied the American College of Rheumatology classification criteria for FM.[27] All patients have provided written informed consent, and the study was approved by the hospital Ethics Committee (Comitato Unico Regionale - ASUR Marche).

Internet-based PROs

The patients logged into the website (http://www.fibromialgiaitalia.it) developed for the present study. During the first login to the website, each patient was asked to provide

consent and to complete the questionnaires. The questions were displayed using radio buttons. Each question had to be completed before the software continued to the following page. During the first visit, each patient has received a secure username/password combination in order to have access to the website and a brief training on the use of FIQR[19] and the self-administered Fibromyalgia Activity Score (FAS)[28] questionnaires. The FIQR was developed by Burckhardt et al[29] in an attempt to address the limitations of the original FIQ.[29] The Italian version of FIQ[20] is composed of 21 items that are rated using an 11-point numerical scale (0–10, with 10 being the worst) and cover three domains: physical function, overall impact, and symptoms over the previous 7 days. The total score for the 9-item "function domain" (range: 0–90) is divided by three, the total score for the 2-item "overall impact domain" (range: 0–20) is divided by one, and the total score for the 10-item "symptom domain" (range: 0–100) is divided by two. The global score is given by the sum of the scores of the three domains (range: 0–100). FM is classified as mild (from 0 to 38), moderate (from 39 to 58), or severe (from 59 to 100).[30] The FAS is a valid, reliable, and responsive disease-specific composite measure for patients with FM.[30] The FAS index combines scores related to fatigue (range: 0–10) and the quality of sleep (range: 0–10) and scores obtained by the Self-Administered Pain Scale (SAPS) in order to provide a single measure of disease activity (range: 0–10). The SAPS asks patients to classify pain in 16 non-articular sites (0 =none, 1 =mild, 2 =moderate, 3 =severe), and the final total score of 0–48 is transformed into a scale of 0–10. At the end of the study, the electronically collected raw data were extracted as anonymous. The database was completed by the demographic characteristics of the patients.

Statistical analysis

The descriptive statistics of the continuous variables are given as mean values $\pm$ standard deviation and median values with their 25th to 75th percentiles, and those of the categorical variables as absolute numbers and percentages. The number of clusters was chosen by examining the dendrogram and considering clinical interpretability and usefulness. The variables of interest in the clusters were subsequently compared using analysis of variance followed by between-cluster pairwise comparisons with Bonferroni adjustment to a significance level of 0.05. Analysis of variance was also used to compare the behavior of the measured clinical subscales of the FIQR in the defined FM subgroups. The level of significance for all of the tests was 5%. The data were analyzed using the

Table 1 Participant demographics (n=353)

Characteristics	Mean (SD) or n (%)
Sex	
Female, n (%)	301 (85.3)
Male, n (%)	52 (14.7)
Age, years (SD)	50.9 (11.3)
Disease duration, years, mean (SD)	4.7 (3.8)
Education	
Primary school, n (%)	38 (10.7)
Secondary school, n (%)	230 (65.2)
High school/university, n (%)	85 (24.1)
Employment status	
Employed, n (%)	182 (51.5)
Work disabled, n (%)	31 (8.8)
Other (student, full-time homemaker, other), n (%)	79 (22.4)
Unemployed, n (%)	61 (17.3)
Marital status	
Married, n (%)	215 (60.8)
Divorced/separated, n (%)	49 (13.8)
Single, n (%)	64 (18.3)
Widowed, n (%)	25 (7.1)
BMI, kg/m^2, mean (SD)	28.5 (5.2)

Abbreviations: BMI, body mass index; SD, standard deviation.

Statistical Package for Social Sciences, Windows release 11.0 (SPSS Inc., Chicago, IL, USA), and MedCalc, version 12.7.0 (Mariakerke, Belgium).

Results

Demographic characteristics

Table 1 shows the demographic characteristics of the 353 responders (85.3% women). Mean age of responders was 50.9 years, 60.8% were married and only 24.1% had a high school/university education. The mean duration of pain was 4.7 years (range: 1–18 years). Patients were moderately overweight as their mean body mass index was 28.5 (body mass index of >25 and >30 were found in 40% and 7% of cases, respectively). No significant differences of demographic characteristics were observed between patients who agreed to participate in the study and those who did not.

Descriptive statistics

Table 2 shows FIQR item, subscale, and total scores. The highest scoring items (those with the greatest disease impact) were the following symptoms related: sleep quality (FIQR15),

Table 2 Scores obtained on the FIQR (mean and median values, SDs and 95% confidence intervals for each item, subdimensions and total score of the FIQR, and for total score of the FAS) by the study patients (n=353)

Item number	Item description	Mean	SD	Median	25–75th Percentiles
1	Brush or comb hair	3.82	2.34	4.00	2.00–5.00
2	Walk continuously for 20 minutes	3.78	2.84	3.00	2.00–6.00
3	Prepare a homemade meal	3.46	2.39	3.00	2.00–5.00
4	Vacuum, scrub, or sweep floors	4.87	2.85	5.00	3.00–7.00
5	Lift and carry a bag full of groceries	5.18	2.97	5.00	3.00–8.00
6	Climb one flight of stairs	4.72	2.32	5.00	3.00–7.00
7	Change bed sheets	4.72	2.64	5.00	3.00–7.00
8	Sit in a chair for 45 minutes	4.82	2.79	5.00	3.00–7.00
9	Go shopping for groceries	4.23	2.77	4.00	2.00–7.00
FIQR function subtotal		12.36	6.81	11.70	6.30–17.70
10	Cannot achieve goals	4.49	2.69	5.00	2.00–7.00
11	Feel overwhelmed	4.67	2.73	5.00	2.00–7.00
FIQR overall impact subtotal		9.16	5.64	8.00	4.00–13.00
12	Pain rating	5.69	2.32	6.00	4.00–8.00
13	Fatigue rating	6.04	2.54	6.00	4.00–8.00
14	Stiffness rating	5.64	2.45	6.00	4.00–8.00
15	Sleep quality	6.18	2.57	6.00	4.00–8.00
16	Depression level	4.94	2.49	5.00	3.00–7.00
17	Memory problems	4.90	2.33	5.00	3.00–7.00
18	Anxiety level	4.99	2.46	4.00	3.00–7.00
19	Tenderness level	5.42	2.42	6.00	4.00–7.00
20	Balance problems	5.33	2.01	5.50	4.00–7.00
21	Environmental sensitivity	5.32	2.48	6.00	3.00–7.00
FIQR symptoms subtotal		26.76	8.78	27.50	20.50–33.50
FIQR total score		48.28	19.20	47.65	32.30–63.50

Abbreviations: FAS, Fibromyalgia Activity Score; FIQR, Fibromyalgia Impact Questionnaire Revised version; SD, standard deviation.

fatigue/energy (FIQR13), pain (FIQR12), stiffness (FIQR14), tenderness (FIQR19), balance problems (FIQR20), and environmental sensitivity (FIQR21). The lowest scored items included functional activities such as brushing/combing hair (FIQR1), preparing a home-made meal (FIQR3), walking continuously for 20 minutes (FIQR2), shopping for groceries (FIQR9), and changing bed sheets (FIQR7).

Figure 1 shows the distribution of the FIQR scores. The impact of the disease on functional domains such as personal care (FIQR1) and activities of daily living (FIQR3, FIQR4, FIQR5, FIQR7, and FIQR9) was greater among women, but the differences were not significant. Similarly, pain (FIQR12), fatigue (FIQR13), rigidity (FIQR14), and sleep quality (FIQR15) were not significantly associated with sex.

SAPS was used to assess the presence of pain in 16 body sites. A high proportion of patients reported pain in the neck (81.4%), upper back (70.1%), and lower back (83.2%) (Figure 2). There was no difference between sexes in relation to any of the sites.

Cluster analysis

It was used hierarchical agglomerative clustering of the 21 subscales of the FIQR, respectively, accounting for 33.1%, 34%, and 32.9% of the sample. The three-cluster solution distinguished three broad levels of severity. Clusters 1 and 3

correspond to the lowest and highest average scores, respectively, and cluster 2 to lower levels of depression, anxiety, and less severe memory problems compared to the other scales of the FIQR (Table 3 and Figure 3). The pairwise comparisons showed significant differences between each cluster for all but a few symptoms. Clusters 2 and 3 were not significantly different in terms of walking continuously for 20 minutes (P=0.11) or lifting and carrying a bag full of groceries (P=0.21) (Figure 3).

Discussion

Over the last few years, the ongoing evolution of computer software and technology has greatly improved the ability to collect PROs data. One major advantage of computerized questionnaires is to collect good-quality data without any missing or problematic responses commonly found by using paper questionnaires.[21–25,31] Online surveys enable respondents to answer questionnaires according to their preferences (eg, ways and connection times) while connected to the Internet browser.[22–24]

Our questionnaire was completed by 353 patients with FM, and demographic features of respondents were similar to previous epidemiologic studies and surveys.[17,28,32–34] Respondents have reported several symptoms mainly including poor quality sleeping, fatigue/lack of energy, pain, stiffness, tender-
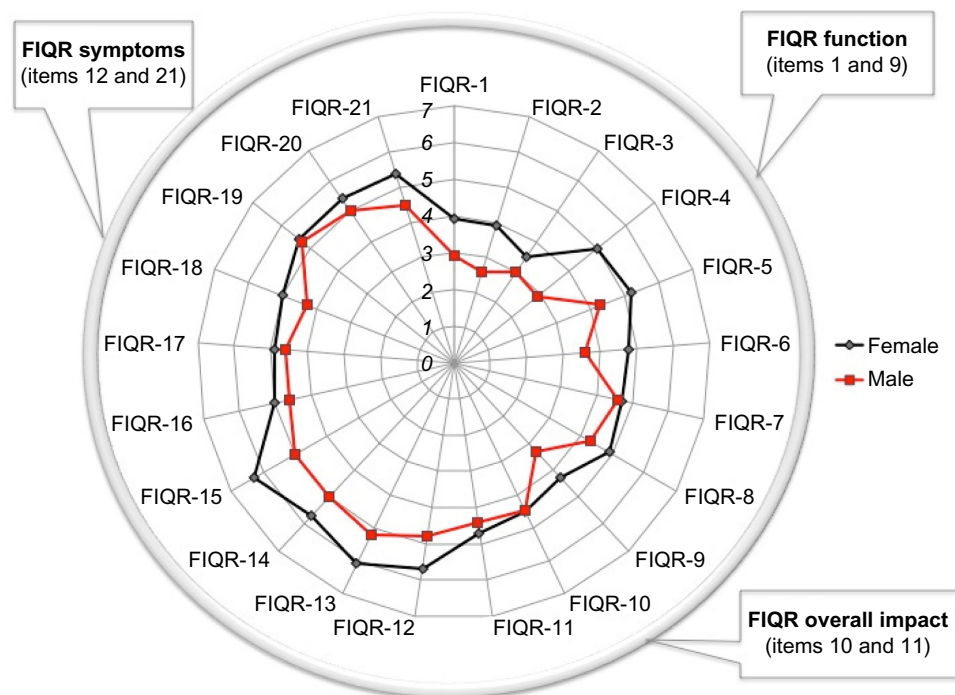

Figure 1 Spydergrams of the FIQR domains.
Notes: The domain scores are plotted from 0 (best, at the center) to 10 (worst, at the outside).
Abbreviation: FIQR, Fibromyalgia Impact Questionnaire Revised version.
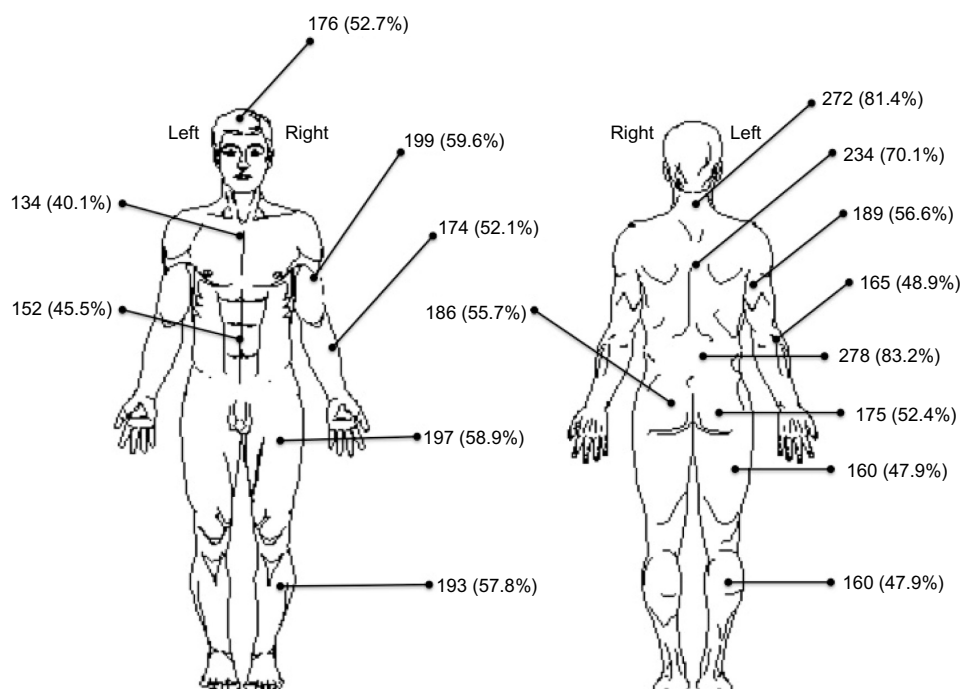
Figure 2 Pain by location expressed in terms of percentage (%) as revealed by the Self-Administered Pain Scale.
Note: Data are presented as n (%).

Table 3 Subgrouping of fibromyalgia samples based on scores obtained on the FIQR (mean and standard deviations) for each item, subdimensions and total score

Item no	Item description	Cluster 1 (n=117)		Cluster 2 (n=120)		Cluster 3 (n=116)		F-ratio
		Mean	SD	Mean	SD	Mean	SD	
1	Brush or comb hair	1.64	1.05	4.14	1.95	5.70	1.81	178.90
2	Walk continuously for 20 minutes	1.75	1.54	4.22	3.02	5.38	2.44	67.51
3	Prepare a homemade meal	1.44	1.09	3.30	1.85	5.69	1.90	192.73
4	Vacuum, scrub, or sweep floors	2.74	1.40	4.97	3.03	6.94	2.11	98.36
5	Lift and carry a bag full of groceries	3.16	2.32	5.45	2.95	6.95	2.26	65.83
6	Climb one flight of stairs	2.39	1.46	5.28	1.62	6.51	1.59	213.56
7	Change bed sheets	2.73	2.17	4.53	1.99	6.94	1.86	126.76
8	Sit in a chair for 45 minutes	2.85	2.18	4.80	2.60	6.85	1.99	88.64
9	Go shopping for groceries	1.61	1.37	4.39	1.98	6.74	2.05	227.56
FIQR physical function		6.50	3.64	13.62	6.06	17.02	5.65	123.37
10	Cannot achieve goals	2.04	1.78	4.54	1.93	6.94	1.67	216.11
11	Feel overwhelmed	1.87	1.56	5.13	1.86	7.05	1.71	271.60
FIQR overall impact		4.00	3.93	10.13	4.96	11.35	4.97	84.44
12	Pain rating	3.13	1.43	6.35	1.47	7.62	1.18	343.82
13	Fatigue rating	3.60	1.83	6.09	1.56	8.49	1.34	287.57
14	Stiffness rating	3.16	1.50	6.01	1.67	7.79	1.46	276.56
15	Sleep quality	3.59	1.86	6.55	1.51	8.44	1.52	270.29
16	Depression level	2.55	1.39	4.46	0.95	7.87	1.21	589.57
17	Memory problems	2.66	1.35	4.55	1.07	7.54	1.18	487.14
18	Anxiety level	3.01	1.48	4.16	0.93	7.86	1.58	401.85
19	Tenderness level	3.30	2.08	5.85	1.85	7.13	1.50	137.22
20	Balance problems	3.34	1.42	5.72	1.22	6.96	1.37	219.63
21	Environmental sensitivity	2.66	1.64	6.00	1.39	7.31	1.59	281.67
FIQR symptoms		18.06	5.94	28.12	6.10	34.19	5.21	233.51
FIQR total		28.57	10.31	51.88	14.77	62.57	13.44	210.32

Notes: Cluster 1 reflecting the lowest average levels across all symptoms, cluster 3 reflecting the highest average levels across all symptoms, and cluster 2 capturing moderate symptom levels with lower levels of depression, anxiety, and memory problems.
Abbreviations: FIQR, Fibromyalgia Impact Questionnaire Revised version; SD, standard deviation; no, number.
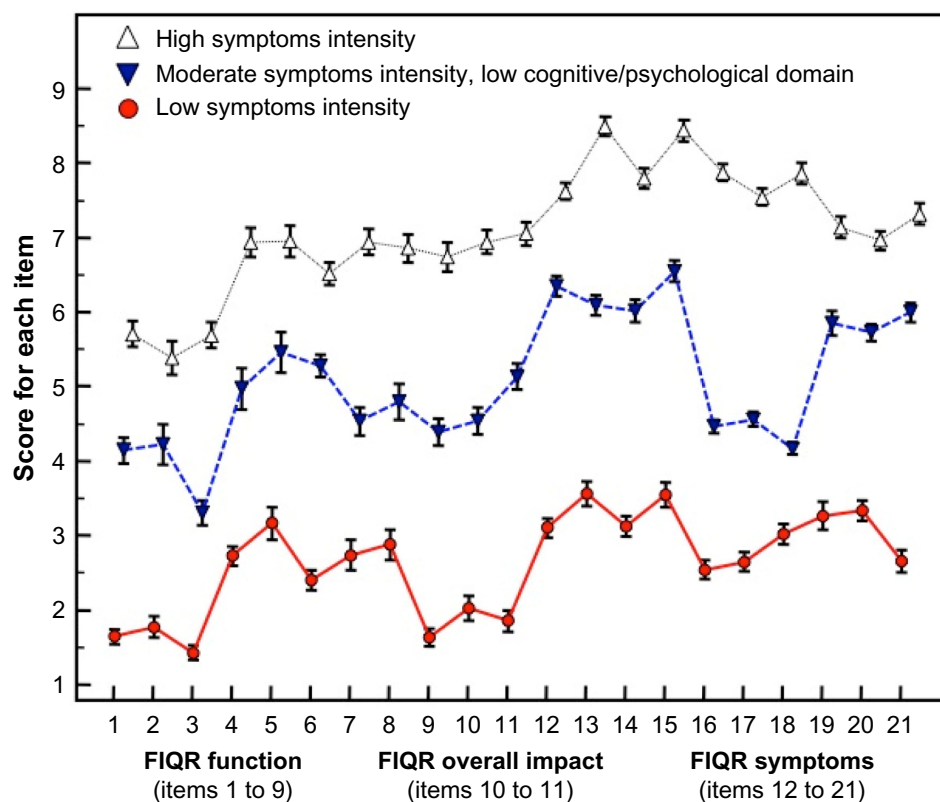
Figure 3 Cluster profiles.
Notes: Cluster 1 (n=117, red line) showed generally low symptom intensity; cluster 2 (n=120, blue line) was characterized by moderate symptoms and low cognitive/psychological domain scores; cluster 3 (n=116, gray line) showed the least control over pain, considerable tenderness, high symptom levels, and considerable cognitive/psychological problems.
Abbreviation: FIQR, Fibromyalgia Impact Questionnaire Revised version.

ness, and increasing environmental sensitivity. There were no significant differences between sexes in these domains. The tendency for women to have higher scores in some domains (eg, brushing/combing hair, preparing home-made meals, vacuum cleaning, scrubbing/sweeping floors, or shopping) seems related to the fact that those daily activities are peculiar to female sex.

Cluster analysis has revealed three distinctive subgroups of symptoms: cluster 1 lowest mean total FIQR and FIQR scores (ranging from 0 to ≤39);[35] cluster 2 moderate symptoms and mild levels of cognitive/psychological impairment (scores ranging from 39 to ≤59); and cluster 3 severe symptoms (scores ranging from 59 to 100). Our findings have some similarities with results from previous cluster analyses in patients with FM. Vincent et al[15] found that a four-cluster solution best fit their results: clusters 1 and 4 correspond to the lowest and highest scores among all symptoms and clusters 2 and 3 intermediate levels of anxiety and depression, with cluster 2 having lower levels of depression and anxiety than cluster 3, despite higher levels of pain. Similarly, the cluster analysis of Wilson et al[36] identified four clusters: cluster 1 had high scores

in all three domains, cluster 2 had moderate scores in the two physical symptoms domains and high cognitive/psychological symptom scores, cluster 3 had moderate scores in the two physical symptoms domains and low cognitive/psychological symptoms scores, and cluster 4 had low scores in all symptoms domains. Clusters 2 and 3 were therefore distinguished by differences in the severity of depression and anxiety, which is also consistent with the findings of Giesecke et al.[8] In this study, the authors have identified three patient-subsets mainly on the basis of differences in pain and psychopathology as follows: first one characterized by moderate levels of mood, catastrophizing and perceived pain control, and low levels of tenderness; second one characterized by high degree of mental impairment, highest catastrophizing subscales and severe pain; third one characterized by normal mood ratings, very low levels of catastrophizing and the highest level of perceived pain control even though they showed extreme tenderness when evoked pain was tested. However, our findings are not directly comparable with those of these studies[8,15,36] because they used measurements of experimental pain and some variables were not included in our study.

De Souza et al[13] also highlighted anxiety and depression as differentiating factors in their two-cluster model based on the FIQ: both FM subgroups showed hyperalgesic responses to experimental pain, but type I was characterized by the lowest levels of anxiety, depression, and morning tiredness and type II by high levels of pain, fatigue, morning tiredness, stiffness, anxiety, and depression. Similarly, Docampo et al[37] have identified three subgroups in a series of 1,446 Spanish patients. One with low symptom scores and few comorbidities; second one with high symptom scores and multiple comorbidities; and third one with high symptom scores but few comorbidities. Psychological and cognitive impairments (such as memory deficits) are associated with a wide variety of pain conditions.[38–40] The fact that these clinical features seem to be more severe in patients with FM suggested that a group of alterations in a disorder may enhance the magnitude of specific symptoms such as pain. Williams et al[41] found that the domains of mood and fatigue were closely associated with perceived dyscognitions in FM, whereas pain was uniquely associated with perceived language deficits and, unexpectedly, was not related to attention or concentration. In line with this, our findings indicate that memory problems and psychological symptoms (anxiety and depression) were not associated with pain intensity in cluster 2.

Our study has some methodological limitations. First of all, the use of the Internet browser was associated with various socioeconomic and demographic factors, including age, sex, location, and education, and users could not to be representative of target population. However, Internet-based assessments have been accepted by a sizeable percentage (71.2%) of the eligible patients. Second, we did not select patients on the basis of their ongoing pharmacological therapy, although this is an important factor that may mediate dyscognition in FM. It is extremely rare to find a diagnosed subject who is not taking continuous doses of antidepressants (eg, amitriptyline, duloxetine), antiepileptic drugs (gabapentin, pregabalin), or strong analgesics (tramadol, opioids),[42,43] and it is entirely reasonable to expect that medications may reduce cognitive test performances,[44] thus making difficult to distinguish which deficits may be attributable to FM and which to drugs. A final limitation is that the analysis was based on a population of adults from a relatively limited geographical area in central and northern Italy.

Conclusion

We have identified three subgroups of FM samples in a large cohort of FM using an Internet survey. Cluster 1 had the lowest mean total FIQR score, which also fell within the mild symptom severity range of the FIQR, whereas cluster 3 was characterized by severe symptoms, cluster 2

captured moderate symptoms with mild levels of cognitive/psychological symptoms. Web surveys allow rapid updating of questionnaire content and question ordering according to user responses and could provide rationale to support the study of individualized clinical evaluation and may be used to identify optimal treatment strategies.

Acknowledgments

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. FS was the principal investigator, was responsible for the everyday coordination and management of the study, created and managed the data collection web platform, analyzed the data, and contributed to writing the manuscript. FM and PSP participated in conceiving the study, provided clinical support, and were involved in the study design. AD, MDC, AC, and FA provided clinical support and contributed to writing the manuscript. AD, AC, and RC participated in data acquisition of data and were involved in revising the intellectual content of the paper. All of the authors have read and approved the final paper.

Disclosure

The authors report no conflicts of interest in this work.

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