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Published in:
Pain Medicine

DOI (link to publication from Publisher):
10.1093/pm/pnac206

Publication date:
2023

Document Version
Accepted author manuscript, peer reviewed version

Title Page

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Conflict of interest: No Conflict of Interest has been declared by the author(s).

Funding: This research received no external funding

Running Head: Clusters in Fibromyalgia Syndrome

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Abstract

Objective: Since identification of groups of patients can help to better understand risk factors related to each group and to improve personalized therapeutic strategies, this study aimed to identify subgroups (clusters) of women with fibromyalgia syndrome (FMS) according to pain-related, related-disability, neuro-physiological, cognitive, health-related, psychological or physical features. **Methods**: Demographic, pain-related, sensory-related, related-disability, psychological, health-related, cognitive, and physical variables were collected in 113 women with FMS. Widespread pressure pain thresholds (PPTs) were also assessed. K-means clustering was used to identify groups of women without any previous assumption. **Results**: Two clusters exhibiting similar widespread sensitivity to pressure pain (PPTs) but differing in the remaining variables were identified. Overall, women in one cluster exhibited higher pain intensity and related-disability, more sensitization-associated and neuropathic pain symptoms, higher kinesiophobia, hypervigilance and catastrophism levels, worse sleep quality, higher anxiety/depressive levels, lower health-related function, and worse physical function than women in the other cluster. **Conclusions**: Cluster analysis identified one group of women with FMS exhibiting worse sensory, psychological, cognitive and health-related features. Widespread sensitivity to pressure pain seems to be a common feature of FMS. Current results suggest that this group of women with FMS may need to be treated differently.

Keywords: Fibromyalgia; Clustering; Pain; Groups; Sensitization.

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Introduction

Fibromyalgia syndrome (FMS) is a chronic pain condition affecting up to the 6.6% of the worldwide population [1]. Its symptomatology is heterogeneous and includes widespread pain, fatigue, stiffness, exacerbated pain responses, sleep disorders, mood disturbances, and cognitive dysfunctions [2]. Similarly, FMS patients also exhibit generalized muscle weakness, decreased physical capacity, and reduced health-related quality of life [3]. The presence of a plethora of sign and symptoms suggest complex mechanisms explaining the heterogeneity in the clinical presentation observed in people with FMS and suggests the presence of different subgroups.

Identification of subgroups of patients can help to better understand modifiable risk factors related to each group and to improve personalized therapeutic strategies [4]. Although no consensus exists concerning the most suitable method or data set optimally to be used for subgrouping, different studies have attempted to identity subgroups of women with FMS by using cluster analysis, an unsupervised learning methodology whose pursuit is to find typical profiles within a dataset without the need of *a priori* hypotheses provided by the clinician. Additionally, from a clinical viewpoint, it appears important that subgrouping is built on the most useful and representative data of a particular condition.

Previous studies have identified subgroups of women with FMS according to different features. Pain-related, related-disability, cognitive, or psychological aspects (i.e., anxiety and depressive levels) have been previously used in several studies trying to

identify subgroups of patients with FMS [5-10]. All these studies identified subgroups of patients combining higher/lower sensitivity with/without psychological stress [5-10]. Similarly, Giesecke et al. [11] and Luciano et al. [12], by using the tender point construct, described different groups of FMS patients, one exhibiting high tenderness but not psychological/cognitive factors and other with high psychological/cognitive factors but conditioning the severity of tenderness [11,12].

Petzke et al. found that tender point construct is influenced by personal distress whereas random assessment of pressure pain sensitivity is not [13]. Considering that one of the most common features of FMS is pressure pain hyperalgesia (expressed as decreased pressure pain thresholds), it is important to determine that most of published studies did not include this neuro-physical outcome evaluating the altered nociceptive pain processing in their analyses [5-12]. Interestingly, subgrouping of patients according to their sensitization level (evaluated with quantitative sensory tests) has been found in patients with chronic musculoskeletal pain such as painful knee osteoarthritis [14] or chronic whiplash associated-disorders [15]. Two studies have used quantitative sensory tests for classifying women with FMS. Hurtig et al. [16] evaluated thermal pain thresholds for classifying sensitive vs. non-sensitive patients in a small sample (n=29). de Souza et al. [17] evaluated sensitivity to pressure pain but they used the Fibromyalgia Impact Questionnaire for the subclassification of patients. Based on this "a priori" subclassification, no differences in sensitivity to pressure pain were observed [17].

Since an ideal theoretical framework of FMS integrates reciprocal interactions between biology (clinical, sensory and physical aspects) and behaviors (psychological and cognitive aspects) [18], we expanded here previous studies by including pain-related, related-disability, sensory, neuro-physiological, cognitive, psychological health-related, and physical features in the current cluster analysis. The objective of this study was to

determine groups (clusters) of women with FMS differing in pain-related (clinical), related-disability, sensory, neuro-physiological, cognitive, health-related, psychological or physical features to further identify different profiles of patients susceptible of potentially different therapeutic interventions.

Methods

Participants

A group of 113 (mean age: 52.5±11 years) women with FMS was voluntarily recruited from a Fibromyalgia Association located in Madrid (Spain). To be eligible to participate, women should have a diagnosis of fibromyalgia syndrome by their medical doctor/rheumatologist according to the 2010 American College of Rheumatology [19]. These criteria showed sensitivity and specificity values of 88.3 and 91.8, respectively, in a Spanish population of women with FMS [19]. Exclusion criteria included no previous whiplash injury, surgeries, neuropathic pain conditions, underlying medical conditions, or current use of medication affecting muscle tone or perception (except symptomatic use of non-steroidal anti-inflammatory drugs if needed). The data collection protocol was supervised and approved by the Local Ethics Committee of Universidad Rey Juan Carlos and all participants signed the written informed consent before participating in the study. Although the findings and data analyzed in this article are completely new and not previously published elsewhere, the participants forming the sample used in this study are the same used in a previous article published by this research group [20].

Pain and Disability

For measuring the patient's pain intensity perception, the Numerical Pain Rate Scale (NPRS) was used. This tool consists of a 11-point scale where 0 means no pain and 10 means the worst pain imaginable. The mean of three measurements (mean pain

intensity at rest, worst pain intensity at rest, and their mean pain intensity experienced during daily living activities) was calculated and used for analyses [21]. In the cluster analysis, we pooled the average value between the mean pain intensity and the worst pain intensity at rest due to the presence of multicollinearity between these variables.

On the other hand, the Central Sensitization Inventory (CSI) (which is a self-reported questionnaire evaluating 25 symptoms associated to sensitization) was used for assessing sensitization-associated symptoms. Each item is scored in a 5-points Likert scale. Therefore, final scores range from 0 to 100, where greater scores indicate worse severity. According with Neblett et al. [22], a minimum score of 40 points is needed to consider an altered nociceptive pain processing.

Finally, the Fibromyalgia Impact Questionnaire (FIQ) was used for determining the impact of FMS in patients' pain-related disability. This questionnaire is made up of 10 subscales assessing the daily-tasks function, number of days feeling good during the last seven days, the interference of FMS with their work activity, intensity of pain, fatigue, night resting, stiffness, anxiety, and depression [23]. Scores range from 0 to 100 points, where greater scores involve greater related-disability and symptoms-severity [23].

Neuropathic Pain

For assessing neuropathic pain components, we used two questionnaires with acceptable sensitivity, specificity and positive predictive accuracy, internal consistency and validity [24,25]: The Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and the PainDETECT questionnaire.

The S-LANSS is a tool used to confirm whether patients experience symptoms to be considered of predominantly or non-predominantly neuropathic origin [24]. The score

ranges from 0 to 24, where those patients obtaining ≥12 points are susceptible of neuropathic pain [24].

Additionally, the PainDETECT self-reported questionnaire was used for measuring the presence of a neuropathic pain. This questionnaire consists of nine items (seven pain-symptom items, one pain-course, and one pain-irradiation) completed into different scales. The total score ranges from 0 to 38, where higher scores indicate higher levels of neuropathic pain. The PainDETECT assesses if a neuropathic pain component if unlikely (<12 points), ambiguous (12-18 points), or likely (>18 points) [25].

Psychological Health

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate the levels of anxiety (HADS-A, 7-items, 0-21 points) and depression (HADS-D, 7-items, 0-21 points). A higher score is associated with higher depressive and anxiety levels [26]. Although a cut-off score of ≥8 points on each scale has shown good sensitivity and specificity [27], we considered the cut-off scores recommended for Spanish population (HADS-A ≥12 points; HADS-D ≥10 points) suggestive of clinical anxiety and depressive symptoms, respectively [28].

In addition to anxiety and depression, the self-perceived sleep quality was also assessed using the Pittsburgh Sleep Quality Index (PSQI) [29]. With a total of 24 items, this tool evaluates the quality of sleep of the previous month by asking questions such as usual bedtime, usual wake-up time, actual number of hours slept, and number of minutes to fall asleep. Questions are answered on a Likert-type scale (0-3), creating a score ranging from 0 to 21 where a higher score indicates worse sleep quality, being a minimum of 8 points the cut-off for considering a poor sleeping quality [29].

Pressure Pain Thresholds

In order to assess widespread pain sensitivity, pressure pain thresholds (PPTs) were evaluated. The mastoid process, upper trapezius muscle, elbow, hand, posterosuperior iliac spine, greater trochanter, knee, and tibialis anterior were the locations assessed, following the procedure described by Cheatham et al. [30]. A single rater with +10 years of experience used an electronic algometer (Somedic AB©, Farsta, Sweden), increasing the applied pressure at a rate of 30 kPa/s on each point.

The mean of three trials on each point, with a resting period of 30 seconds between each (for avoiding temporal summation), was calculated and used in the cluster analysis. Since no side-to-side differences were observed at any location (independent student t-tests, $p>0.05$), the mean of both sides was used in the clustering analysis.

Cognitive Variables

The short-form 9-items Pain Vigilance and Awareness Questionnaire (PVAQ-9) was used to evaluate pain hypervigilance, e.g., ideas of observing, monitoring, and focusing on pain in patients with FMS [31]. This tool demonstrated good reliability, internal consistency, sensitivity, specificity, convergent validity and divergent validity. The optimal cutoff point for identifying female FMS patients with worse daily functioning was a score of 24.5 points [31].

Also, the 11-item short-form of the Tampa Scale for Kinesiophobia (TSK-11) was used to quantify the fear of movement perceived by the patient [32]. This self-reported questionnaire includes 11 items where the patients choose into a 4-point Likert scale how much they agree with each item (1: “complete disagreement” to 4: “complete agreement”), leading to a score ranging from 11 to 44, where higher scores indicate greater fear of pain, movement, and injury [32].

Finally, the Pain Catastrophizing Scale (PCS) was used to assess pain catastrophizing responses (e.g., rumination, magnification and despair aspects) in individuals with pain [33]. It consists of 13 items answered into a 5-point Likert scale ranging from 0 ("never") to 4 ("always"), leading to a total score ranging from 0 to 52 points, where higher scores reflect higher levels of pain catastrophizing [33].

Quality of life

The Fibromyalgia Health Assessment Questionnaire (FHAQ) is a disease-specific tool used for assessing functional ability in FMS throughout 8 items scoring from 0 to 3 points [33]. Its score is calculated as the mean of the eight items, where lower scores reflect less difficulties during their daily functional activities [34].

The paper-based five-level version of EQ-5D-5L questionnaire was used to determine health-related quality of life [35]. The EQ-5D-5L consists of five health-related dimensions evaluated from 1 (no problem) to 5 (severe problems). Responses are converted into a single index number between 0 (health state judged to be equivalent to death) and 1 (optimal health status) by applying crosswalk index values for Spain life [36].

Physical Condition

The Timed Up and Go (TUG) was used as a physical test for evaluating predictive info to identify patients with high risk of falls. Patients are placed in sitting position in an armchair and is asked to stand up without the use of the arms, to walk at a comfortable and safe speed up to a line placed at 3m from the chair, to turn back to the chair, and sit down again. The TUG has shown to be a reliable physical fitness test for assessing agility/dynamic balance in women with FMS [37].

Data Analysis

Preprocessing and Imputation

The data analysis used here was very similar to two previous studies including women with carpal tunnel syndrome [38] or tension-type headache [39]. Firstly, the features (i.e. the variables) were standardized by applying $\tilde{x} = \frac{x - \mu_x}{\sigma_x}$, where x is the original feature, σ_x represents its sample standard deviation, μ_x its sample mean, and $\tilde{x}$ is the standardized feature; this ensures that all features have zero mean and unit variance, so that the similarity between them (typically Euclidean) is not affected by the scale that they were measured in. Secondly, missing values were imputed using k-Nearest Neighbors imputation ($k = 5$), which replaces the missing value by the mean value of the k nearest points (in terms of Euclidean distance) to that feature. Imputation was only applied for the clustering phase and, after obtaining the clusters, any further statistical tests were performed on the actual data, with no imputation applied.

K-means clustering

Intuitively, clustering techniques seek to automatically detect sets of points that are similar among themselves (thus forming a cluster) but different from the rest [40]. K-means, in particular, starts by randomly positioning k centroids among all the data points (k is chosen beforehand and represents the number of clusters to find). Then, it iteratively assigns each data point (each patient) to the closest centroid (in terms of Euclidean distance) and recalculates the position of each centroid as the mean of all the points assigned to it. This process repeats until convergence.

Other clustering algorithms (gaussian mixture, hierarchical clustering, and spectral clustering) as well as different numbers of clusters k (k=1,2,3,4,5,6) were tested and compared in terms of Silhouette coefficient, Calinski-Harabasz index, and Davies-Bouldin index. K-means algorithm with k=2 clusters was found to dominate over the rest for all metrics, except for the David-Bouldin score, for which k-means with k=3 was optimal. This is shown in **Figure 1**.

Statistical Analysis of the Clusters

Once the data was separated into two clusters by means of the k-means algorithm, the mean and standard deviation of each feature was determined for each of the clusters, and the Student t-test (corrected with Holmes-Bonferroni for multiple comparisons) was employed to determine if, within a particular feature, the distributions of the two clusters were significantly different. The statistical significance was established at a 0.05 level.

Results

From 127 women with FMS screened for eligibility criteria, 14 (19%) were excluded due to previous surgery (n=8), previous whiplash (n=4), and pregnancy (n=2). A total of 113 women (mean age: 52.5±11 years) satisfied all eligibility criteria, agreed to participate, and signed the informed consent. All participants took non-steroidal anti-inflammatory drugs regularly when the pain was intense; however, they were asked for avoid taking any medication from t least 24 hours before the examination.

The cluster analysis revealed two clusters with different distributions in the variables as visualized within **Figure 2**. To analyze the differences of each cluster, means and standard deviations of each variable for each cluster were computed and compared (**Table 1**). Both clusters showed similar PPTs at all locations, except for differences in the greater trochanter where women within cluster 0 exhibited lower values than those

within cluster 1 (P=0.002). On the contrary, women in the first cluster (number 0) exhibited worse pain-related, related-disability, cognitive, health-related, psychological and physical features when compared with women in the second cluster (number 1). Overall, women of cluster 0 showed higher intensity of pain and related-disability, more sensitization associated symptoms, more neuropathic pain symptomatology, more kinesiophobia, hypervigilance and catastrophism levels, worse sleep quality, higher anxiety/depressive levels, lower health-related quality of life, and worse physical function than those women of cluster 1 (see **Table 1**).

Discussion

Although there are published results exploring the association between multiple psychological, histological, hormonal, physical, neurophysiological, clinical factors in female patients with FMS by using network analyses, Bayesian analyses and structural equation models [20,41-50], this study provides a clustering algorithm that identified two subgroups of women with FMS. In general, women with FMS showed similar widespread pressure pain sensitivity, but they were different, from a statistical viewpoint, in patient-reported outcome measures, e.g., pain, related-disability, cognitive, psychological, health -related, and physical features.

The first finding revealed by the current analysis is that the presence of widespread pressure pain sensitivity seems to be a common finding in women with FMS since both clusters had similar widespread PPTs. The fact that women with FMS exhibit excitability of the nervous system is well accepted in the literature [51]. Sensitivity to pressure pain is a clinical manifestation of altered nociceptive processing, but it should be considered that PPT is a quantitative sensory test used for evaluating the patient's response against a stimulus and it is influenced by patient's subjective perception and also expectations [52].

It should be expected that pressure pain hyperalgesia would be related to the presence of sensitization-associated symptoms, assessed by the CSI, or with pain intensity, however, these assumptions were not supported. In fact, previous studies did not find an association between PPTs and the CSI in other chronic pain conditions [53,54]. Similarly, PPTs are not linearly associated with pain or related disability [55]. These findings were also seen in our study where both clusters of women with FMS exhibited similar PPTs, but different CSI scores and pain and related-disability features. It is possible that PPTs represent the mechanism construct whereas sensory-related and related-disability represents a clinical construct of the pain spectrum.

We did not identify a "more sensitive" subgroup of women with FMS based on PPTs. In agreement with our results, de Souza et al. [17] also identified two groups of women with FMS based on the FIQ, but without differences in sensitivity to pressure pain. However, other studies identified groups of patients with FMS with more or less sensitivity and with/without psychological stress [5-12]. These studies classified patients based on the tender point count, pain intensity or related-disability, but they did not evaluate PPTs. These discrepancies could be explained by the fact that pain or tender point construct are highly influenced by personal distress whereas PPTs did not [13]. However, our analysis also identified a potential "sensitive group" (cluster 0) considering pain and related-disability outcomes. In fact, the sensitive group had higher sensitization-associated symptomatology, in agreement with a recent study showing that sensitization was associated with higher pain intensity [56]. Current results would suggest that patient-reported outcome measures (e.g., CSI or pain-related variables) could be better for classifying sensitive women with FMS instead of neurophysiological outcomes (e.g., PPTs).

Our cluster analysis revealed that the subgroup of women with FMS with higher pain sensitization and related-disability also exhibited higher anxiety/depressive levels, poor sleep quality, and more kinesiophobia, hypervigilance and catastrophism levels. The association between emotional disorders and sensitization is not new in individuals with chronic pain since mood disorders had a significant impact on pain sensitivity [57,58]. Similarly, poor sleep quality is also a risk factor for developing widespread chronic pain and fatigue [59]. In such scenario, cognitive factors e.g., kinesiophobia or catastrophism also mediate the association between pain and sensitization [60,61]. In fact, Angarita-Osorio et al. found that emotional (e.g., higher depressive symptoms) and cognitive (more pain catastrophizing level) factors are associated with higher pain and disability scores in women with FMS [62]. Our analysis also revealed that the group of women with FMS (cluster 0) with higher pain-related and related-disability also exhibited worse health-related and physical outcomes, in agreement with Angarita-Osorio et al. [62]. Based on previous and current research, it seems that there is a subgroup of women with FMS exhibiting more sensory, emotional, cognitive, and physical impairments.

Previous and current results support the hypothesis that FMS resembles a nociplastic pain condition [63]. Early identification of higher levels of sensitization could play a relevant role as a prognostic factor for treatment since sensitization of the central nervous system is associated with poorer treatment outcomes in individuals with musculoskeletal pain [64]. The hypothesis that a subgroup of FMS should be classified as a nociplastic condition supports why exercise programs, a therapeutic strategy able to reduce pain sensitivity throughout adaptations in the central nervous system [65], usually shows the highest level of evidence for the management of FMS [66]. In fact, it has been recently discussed that pain mechanisms underpinning each patient must be considered for proper prescription of exercise programs in people with nociplastic conditions such as FMS [67].

The fact that FMS can be considered as a nociplastic condition does not exclude the presence of neuropathic pain features in FMS since mixed pain phenotypes are also considered [63]. In fact, evidence supports the presence of small fiber neuropathy in FMS patients compatible with the presence of a neuropathic pain component [64-66]. Further, the use of self-reported questionnaires e.g., the S-LANSS and PainDETECT also supports that some patients with FMS exhibit neuropathic pain features [67,68]. Current analysis revealed that cluster 0, the "sensitive group", also showed higher scores in the S-LANSS and PainDETECT, suggesting a higher neuropathic component in this subgroup of FMS women. Nevertheless, the lack of identification of structural lesions in the somatosensory system in FMS does not permit to classify FMS as neuropathic pain condition [69], and probably these patients would exhibit neuropathic pain features which should be treated if identified.

These results, based on clustering algorithms, have two main implications for clinical practice. First, identification of this subgroup of women with FMS showing worse sensory, psychological, cognitive, health-related and higher sensitization symptomatology may suggest different underlying mechanisms. It is accepted that prolonged nociception from peripheral tissues is a primary triggering factor for centralized sensitization [68]. The presence of higher pain levels and sensitization-associated symptoms could lead to a long-lasting nociceptive barrage to the nervous system contributing to this process. In fact, the magnitude of the peripheral input is a relevant factor to consider in FMS [69], although the topic of peripheral/central sensitization in chronic pain is questioned and both mechanisms are connected. It is also possible that these women with FMS exhibit different brainstem processing [70], explaining the observed differences in sensitization and emotional/cognitive variables. These hypotheses should be investigated in future studies.

The second clinical application pointed out to patient-centered treatment strategies. First, the role of sensory-related intensity supports the relevance of early treatment of pain in women with FMS to decrease sensitization symptomatology and related-disability. In fact, several strategies are advocated for decreasing pain intensity in FMS. Nevertheless, it is important to consider that anxiety plays a promoting role for pain amplification. Accordingly, physical therapy should be combined with psychological interventions for managing these aspects [71], particularly in the group of FMS women with emotional disturbances (cluster 0). Therefore, clinicians should consider into which group of those identified in the current study falls each patient for better applying the most appropriate treatment approach, e.g., physical therapy, cognitive behavior, anxiety management, pain education, or exercise programs [72]. This clinical reasoning agrees with a meta-analysis supporting that treatment interventions for individuals with FMS should be individualized according to the predominant mechanism [73].

Finally, this study presents some potential limitations. First, just women with FMS were included. Current subgrouping cannot be extrapolated to FMS males. Second, we only tested widespread pressure pain sensitivity as a clinical feature of sensitization. It would be interesting to investigate other sensitization outcomes, e.g., thermal or electrical thresholds, conditioning pain modulation or nociceptive flexor reflex, to assess potential differences between the identified clusters. Third, it should be recognized that most of the variables included in the current study are subjective and can be affected by expectations and patient's perception. Finally, the last topic to consider is that cluster analyses had identified two subgroups of women with FMS where some variables can overlap. In fact, although statistically significant, some clinical variables overlap between both clusters as it can be observed within Figure 2. In fact, the graphical representation of the variables revealed that the identified clusters represent the distribution of symptom severity among

the current cohort of women with FMS. This interpretation would suggest that FMS could also represent a continuum process. In fact, the consideration of FMS as a nociplastic condition would support this clinical assumption since some patients exhibit a more physical presentation whereas others a more psychological presentation.

Conclusions

The application of a cluster analysis has identified two groups of women with FMS differing in sensory, psychological, cognitive and health-related features but not in pressure pain hyperalgesia. This analysis supports that widespread sensitivity to pressure pain seems to be a common feature of this condition, but one group (e.g., the "sensitive" or "impaired" group) exhibits worse sensory, psychological, cognitive or health-related features than the other. Current results suggest that this subgroup of women with FMS may need to be treated differently.

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Legend of Figures

Figure 1. Score comparison (left to right: Calinski-Harabasz index, Silhouette coefficient, and Davies-Bouldin index) for different number of clusters (2 to 6) and different clustering algorithms (red: K-Means; green: Spectral clustering with 10 neighbors; orange: Hierarchical clustering; blue: Gaussian Mixture).

Figure 2. Cluster analysis showing the different distributions in the variables assessed

Table 1: Demographic, pain-related, related-disability, psychological, psychophysical, health-related, and cognitive data on each identified cluster.

Variables	Cluster 0 (n=63)	Cluster 1 (n=50)	p-value
Age (years)	51 ± 10	55 ± 11	0.212
Weight (kg)	73.5 ± 17.3	71.2 ± 16.2	0.469
Height (cm)	157.1 ± 26.7	164.3 ± 45.2	0.321
Years with pain	19.2 ± 15.0	21.4 ± 15.0	0.400
Years with diagnosis	10.2 ± 8.8	10.3 ± 8.0	0.950
Pain with activity (NPRS, 0-10)*	8.8 ± 1.4	7.1 ± 2.0	<0.001
Mean-worst pain (NPRS, 0-10)*	7.27 ± 1.3	6.25 ± 1.8	0.01
Test up and go (TUG, sec.)*	14.01 ± 5.2	10.3 ± 2.95	<0.001
Related disability (FIQ, 0-100)*	69.8 ± 10.3	57.3 ± 12.4	<0.001
Function (FHAQ, 0-3)*	1.57 ± 0.4	0.85 ± 0.45	<0.001
Quality of life (EQ-5D-5L, 0-1)*	0.27 ± 0.2	0.6 ± 0.2	<0.001
S-LANSS (0-24)*	19.4 ± 4.2	15.5 ± 5.7	<0.001
Pain DETECT (0-38)*	23.06 ± 5.0	15.5 ± 6.7	<0.001
CSI (0-100)*	76.9 ± 9.3	62.0 ± 9.5	<0.001
HADS-A (0-21)*	13.2 ± 3.1	9.2 ± 3.4	<0.001
HADS-D (0-21)*	11.7 ± 3.6	7.7 ± 3.4	<0.001
Hypervigilance (PVAQ)*	29.7 ± 7.8	24.2 ± 7.5	0.004
Catastrophizing (PCS, 0-52)*	29.3 ± 10.6	14.1 ± 8.6	<0.001
Kinesiophobia (TSK-11, 11-44)*	29.4 ± 5.6	19.4 ± 5.8	<0.001
Sleep (PSQI, 0-21)	14.8 ± 3.9	12.35 ± 3.8	0.01
PPT mastoid (kPa)	146.9 ± 53.0	183.6 ± 116.75	0.198
PPT upper trapezius (kPa)	123.75 ± 54.5	148.5 ± 55.9	0.175
PPT elbow (kPa)	141.05 ± 67.5	177.1 ± 99.5	0.192
PPT second metacarpal	113.85 ± 56.0	142.85 ± 53.5	0.061
PPT PSIC (kPa)	214.7 ± 117.3	283.2 ± 134.7	0.056
PPT greater trochanter (kPa)*	233.7 ± 103.6	318.25 ± 122.1	0.002
PPT knee (kPa)	141.2 ± 107.4	178.6 ± 99.15	0.300
PPT tibialis anterior (kPa)	175.2 ± 83.9	229.9 ± 120.5	0.058
PPT tibialis anterior (kPa)	175.2 ± 83.9	229.9 ± 120.5	0.058

NPRS: Numerical Pain Rate Scale; PPT: Pressure Pain Thresholds; S-LANSS: Self-reported version of the Leeds Assessment of Neuropathic Symptoms and Signs; CSI: Central Sensitization Inventory; HADS: Hospital Anxiety and Depression Scale (A: Anxiety, D: Depression); FIQ: Fibromyalgia Impact Questionnaire; FHAQ: Fibromyalgia Health Assessment Questionnaire; PCS: Pain Catastrophizing Scale; PVAQ: Pain Vigilance and Awareness Questionnaire; PSQI: Pittsburgh Sleep Quality Index; TSK-11: 11-items Tampa Scale for Kinesiophobia. * Statistically significant differences between both clusters $p<0.05$.

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