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Title Page

TITLE

Clustering Analysis Identifies Two Subgroups of Women with Fibromyalgia with Different Psychological, Cognitive, Health-Related and Physical Features but Similar Widespread Pressure Pain Sensitivity

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Running Head: Clusters in Fibromyalgia Syndrome

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3 40 Clustering Analysis Identifies Two Subgroups of Women with
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5 41 Fibromyalgia with Different Psychological, Cognitive, Health-Related and
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7 42 Physical Features but Similar Widespread Pressure Pain Sensitivity
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11 44 **Abstract**

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14 45 **Objective:** Since identification of groups of patients can help to better understand risk
15
16 46 factors related to each group and to improve personalized therapeutic strategies, this study
17
18 47 aimed to identify subgroups (clusters) of women with fibromyalgia syndrome (FMS)
19
20 48 according to pain-related, related-disability, neuro-physiological, cognitive, health-
21
22 49 related, psychological or physical features. **Methods:** Demographic, pain-related,
23
24 50 sensory-related, related-disability, psychological, health-related, cognitive, and physical
25
26 51 variables were collected in 113 women with FMS. Widespread pressure pain thresholds
27
28 52 (PPTs) were also assessed. K-means clustering was used to identify groups of women
29
30 53 without any previous assumption. **Results:** Two clusters exhibiting similar widespread
31
32 54 sensitivity to pressure pain (PPTs) but differing in the remaining variables were
33
34 55 identified. Overall, women in one cluster exhibited higher pain intensity and related-
35
36 56 disability, more sensitization-associated and neuropathic pain symptoms, higher
37
38 57 kinesiophobia, hypervigilance and catastrophism levels, worse sleep quality, higher
39
40 58 anxiety/depressive levels, lower health-related function, and worse physical function than
41
42 59 women in the other cluster. **Conclusions:** Cluster analysis identified one group of women
43
44 60 with FMS exhibiting worse sensory, psychological, cognitive and health-related features.
45
46 61 Widespread sensitivity to pressure pain seems to be a common feature of FMS. Current
47
48 62 results suggest that this group of women with FMS may need to be treated differently.
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55 63 **Keywords:** Fibromyalgia; Clustering; Pain; Groups; Sensitization.
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3 64 Clustering Analysis Identifies Two Subgroups of Women with
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5 65 Fibromyalgia with Different Psychological, Cognitive, Health-Related and
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7 66 Physical Features but Similar Widespread Pressure Pain Sensitivity
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12 68 **Introduction**
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14 69 Fibromyalgia syndrome (FMS) is a chronic pain condition affecting up to the
15
16 70 6.6% of the worldwide population [1]. Its symptomatology is heterogeneous and includes
17
18 71 widespread pain, fatigue, stiffness, exacerbated pain responses, sleep disorders, mood
19
20 72 disturbances, and cognitive dysfunctions [2]. Similarly, FMS patients also exhibit
21
22 73 generalized muscle weakness, decreased physical capacity, and reduced health-related
23
24 74 quality of life [3]. The presence of a plethora of sign and symptoms suggest complex
25
26 75 mechanisms explaining the heterogeneity in the clinical presentation observed in people
27
28 76 with FMS and suggests the presence of different subgroups.
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31

32
33 77 Identification of subgroups of patients can help to better understand modifiable
34
35 78 risk factors related to each group and to improve personalized therapeutic strategies [4].
36
37 79 Although no consensus exists concerning the most suitable method or data set optimally
38
39 80 to be used for subgrouping, different studies have attempted to identify subgroups of
40
41 81 women with FMS by using cluster analysis, an unsupervised learning methodology
42
43 82 whose pursuit is to find typical profiles within a dataset without the need of *a priori*
44
45 83 hypotheses provided by the clinician. Additionally, from a clinical viewpoint, it appears
46
47 84 important that subgrouping is built on the most useful and representative data of a
48
49 85 particular condition.
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52
53 86 Previous studies have identified subgroups of women with FMS according to
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55 87 different features. Pain-related, related-disability, cognitive, or psychological aspects
56
57 88 (i.e., anxiety and depressive levels) have been previously used in several studies trying to
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3 89 identify subgroups of patients with FMS [5-10]. All these studies identified subgroups of
4
5 90 patients combining higher/lower sensitivity with/without psychological stress [5-10].
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7
8 91 Similarly, Giesecke et al. [11] and Luciano et al. [12], by using the tender point construct,
9
10 92 described different groups of FMS patients, one exhibiting high tenderness but not
11
12 93 psychological/cognitive factors and other with high psychological/cognitive factors but
13
14 94 conditioning the severity of tenderness [11,12].

15
16
17 95 Petzke et al. found that tender point construct is influenced by personal distress
18
19 96 whereas random assessment of pressure pain sensitivity is not [13]. Considering that one
20
21 97 of the most common features of FMS is pressure pain hyperalgesia (expressed as
22
23 98 decreased pressure pain thresholds), it is important to determine that most of published
24
25 99 studies did not include this neuro-physical outcome evaluating the altered nociceptive
26
27
28 100 pain processing in their analyses [5-12]. Interestingly, subgrouping of patients according
29
30 101 to their sensitization level (evaluated with quantitative sensory tests) has been found in
31
32 102 patients with chronic musculoskeletal pain such as painful knee osteoarthritis [14] or
33
34 103 chronic whiplash associated-disorders [15]. Two studies have used quantitative sensory
35
36 104 tests for classifying women with FMS. Hurtig et al. [16] evaluated thermal pain thresholds
37
38 105 for classifying sensitive vs. non-sensitive patients in a small sample (n=29). de Souza et
39
40 106 al. [17] evaluated sensitivity to pressure pain but they used the Fibromyalgia Impact
41
42 107 Questionnaire for the subclassification of patients. Based on this “a priori”
43
44 108 subclassification, no differences in sensitivity to pressure pain were observed [17].

45
46
47 109 Since an ideal theoretical framework of FMS integrates reciprocal interactions
48
49 110 between biology (clinical, sensory and physical aspects) and behaviors (psychological
50
51 111 and cognitive aspects) [18], we expanded here previous studies by including pain-related,
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53 112 related-disability, sensory, neuro-physiological, cognitive, psychological health-related,
54
55 113 and physical features in the current cluster analysis. The objective of this study was to
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3 114 determine groups (clusters) of women with FMS differing in pain-related (clinical),
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5 115 related-disability, sensory, neuro-physiological, cognitive, health-related, psychological
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7 116 or physical features to further identify different profiles of patients susceptible of
8
9 117 potentially different therapeutic interventions.
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15 119 **Methods**

16 17 120 **Participants**

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20 121 A group of 113 (mean age: 52.5±11 years) women with FMS was voluntarily
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22 122 recruited from a Fibromyalgia Association located in Madrid (Spain). To be eligible to
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24 123 participate, women should have a diagnosis of fibromyalgia syndrome by their medical
25
26 124 doctor/rheumatologist according to the 2010 American College of Rheumatology [19].
27
28 125 These criteria showed sensitivity and specificity values of 88.3 and 91.8, respectively, in
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30 126 a Spanish population of women with FMS [19]. Exclusion criteria included no previous
31
32 127 whiplash injury, surgeries, neuropathic pain conditions, underlying medical conditions,
33
34 128 or current use of medication affecting muscle tone or perception (except symptomatic use
35
36 129 of non-steroidal anti-inflammatory drugs if needed). The data collection protocol was
37
38 130 supervised and approved by the Local Ethics Committee of Universidad Rey Juan Carlos
39
40 131 and all participants signed the written informed consent before participating in the study.
41
42 132 Although the findings and data analyzed in this article are completely new and not
43
44 133 previously published elsewhere, the participants forming the sample used in this study
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46 134 are the same used in a previous article published by this research group [20].
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52 135 **Pain and Disability**

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54 136 For measuring the patient's pain intensity perception, the Numerical Pain Rate
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56 137 Scale (NPRS) was used. This tool consists of a 11-point scale where 0 means no pain and
57
58 138 10 means the worst pain imaginable. The mean of three measurements (mean pain
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3 139 intensity at rest, worst pain intensity at rest, and their mean pain intensity experienced
4
5 140 during daily living activities) was calculated and used for analyses [21]. In the cluster
6
7 141 analysis, we pooled the average value between the mean pain intensity and the worst pain
8
9 142 intensity at rest due to the presence of multicollinearity between these variables.

10
11
12 143 On the other hand, the Central Sensitization Inventory (CSI) (which is a self-
13
14 144 reported questionnaire evaluating 25 symptoms associated to sensitization) was used for
15
16 145 assessing sensitization-associated symptoms. Each item is scored in a 5-points Likert
17
18 146 scale. Therefore, final scores range from 0 to 100, where greater scores indicate worse
19
20 147 severity. According with Neblett et al. [22], a minimum score of 40 points is needed to
21
22 148 consider an altered nociceptive pain processing.

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24
25 149 Finally, the Fibromyalgia Impact Questionnaire (FIQ) was used for determining
26
27 150 the impact of FMS in patients' pain-related disability. This questionnaire is made up of
28
29 151 10 subscales assessing the daily-tasks function, number of days feeling good during the
30
31 152 last seven days, the interference of FMS with their work activity, intensity of pain, fatigue,
32
33 153 night resting, stiffness, anxiety, and depression [23]. Scores range from 0 to 100 points,
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35 154 where greater scores involve greater related-disability and symptoms-severity [23].
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41 156 **Neuropathic Pain**

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44 157 For assessing neuropathic pain components, we used two questionnaires with
45
46 158 acceptable sensitivity, specificity and positive predictive accuracy, internal consistency
47
48 159 and validity [24,25]: The Self-Administered Leeds Assessment of Neuropathic
49
50 160 Symptoms and Signs (S-LANSS) and the PainDETECT questionnaire.

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52
53 161 The S-LANSS is a tool used to confirm whether patients experience symptoms to
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55 162 be considered of predominantly or non-predominantly neuropathic origin [24]. The score
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3 163 ranges from 0 to 24, where those patients obtaining ≥ 12 points are susceptible of
4
5 164 neuropathic pain [24].

6
7 165 Additionally, the PainDETECT self-reported questionnaire was used for
8
9 166 measuring the presence of a neuropathic pain. This questionnaire consists of nine items
10
11 167 (seven pain-symptom items, one pain-course, and one pain-irradiation) completed into
12
13 168 different scales. The total score ranges from 0 to 38, where higher scores indicate higher
14
15 169 levels of neuropathic pain. The PainDETECT assesses if a neuropathic pain component
16
17 170 if unlikely (< 12 points), ambiguous (12-18 points), or likely (> 18 points) [25].

171 **Psychological Health**

172 The Hospital Anxiety and Depression Scale (HADS) was used to evaluate the
173 levels of anxiety (HADS-A, 7-items, 0-21 points) and depression (HADS-D, 7-items, 0-
174 21 points). A higher score is associated with higher depressive and anxiety levels [26].
175 Although a cut-off score of ≥ 8 points on each scale has shown good sensitivity and
176 specificity [27], we considered the cut-off scores recommended for Spanish population
177 (HADS-A ≥ 12 points; HADS-D ≥ 10 points) suggestive of clinical anxiety and depressive
178 symptoms, respectively [28].

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

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187

188 **Pressure Pain Thresholds**

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

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

199 **Cognitive Variables**

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

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

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3 212 Finally, the Pain Catastrophizing Scale (PCS) was used to assess pain
4
5 213 catastrophizing responses (e.g., rumination, magnification and despair aspects) in
6
7 214 individuals with pain [33]. It consists of 13 items answered into a 5-point Likert scale
8
9 215 ranging from 0 (“never”) to 4 (“always”), leading to a total score ranging from 0 to 52
10
11 216 points, where higher scores reflect higher levels of pain catastrophizing [33].
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15 217 **Quality of life**

16
17 218 The Fibromyalgia Health Assessment Questionnaire (FHAQ) is a disease-specific
18
19 219 tool used for assessing functional ability in FMS throughout 8 items scoring from 0 to 3
20
21 220 points [33]. Its score is calculated as the mean of the eight items, where lower scores
22
23 221 reflect less difficulties during their daily functional activities [34].
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25
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27 222 The paper-based five-level version of EQ-5D-5L questionnaire was used to
28
29 223 determine health-related quality of life [35]. The EQ-5D-5L consists of five health-related
30
31 224 dimensions evaluated from 1 (no problem) to 5 (severe problems). Responses are
32
33 225 converted into a single index number between 0 (health state judged to be equivalent to
34
35 226 death) and 1 (optimal health status) by applying crosswalk index values for Spain life
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37 227 [36].
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41 228 **Physical Condition**

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43 229 The Timed Up and Go (TUG) was used as a physical test for evaluating predictive
44
45 230 info to identify patients with high risk of falls. Patients are placed in sitting position in an
46
47 231 armchair and is asked to stand up without the use of the arms, to walk at a comfortable
48
49 232 and safe speed up to a line placed at 3m from the chair, to turn back to the chair, and sit
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51 233 down again. The TUG has shown to be a reliable physical fitness test for assessing
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53 234 agility/dynamic balance in women with FMS [37].
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237 **Data Analysis**

238 *Preprocessing and Imputation*

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

250

251 *K-means clustering*

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

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3 260 Other clustering algorithms (gaussian mixture, hierarchical clustering, and
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5 261 spectral clustering) as well as different numbers of clusters k ($k=1,2,3,4,5,6$) were tested
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7 262 and compared in terms of Silhouette coefficient, Calinski-Harabasz index, and Davies-
8
9 263 Bouldin index. K-means algorithm with $k=2$ clusters was found to dominate over the rest
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11 264 for all metrics, except for the David-Bouldin score, for which k-means with $k=3$ was
12
13 265 optimal. This is shown in **Figure 1**.

17 266 *Statistical Analysis of the Clusters*

19 267 Once the data was separated into two clusters by means of the k-means algorithm,
20
21 268 the mean and standard deviation of each feature was determined for each of the clusters,
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23 269 and the Student t-test (corrected with Holmes-Bonferroni for multiple comparisons) was
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25 270 employed to determine if, within a particular feature, the distributions of the two clusters
26
27 271 were significantly different. The statistical significance was established at a 0.05 level.
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34 273 **Results**

36 274 From 127 women with FMS screened for eligibility criteria, 14 (19%) were
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38 275 excluded due to previous surgery ($n=8$), previous whiplash ($n=4$), and pregnancy ($n=2$).
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40 276 A total of 113 women (mean age: 52.5 ± 11 years) satisfied all eligibility criteria, agreed
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42 277 to participate, and signed the informed consent. All participants took non-steroidal anti-
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44 278 inflammatory drugs regularly when the pain was intense; however, they were asked for
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46 279 avoid taking any medication from at least 24 hours before the examination.
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50 280 The cluster analysis revealed two clusters with different distributions in the
51
52 281 variables as visualized within **Figure 2**. To analyze the differences of each cluster, means
53
54 282 and standard deviations of each variable for each cluster were computed and compared
55
56 283 (**Table 1**). Both clusters showed similar PPTs at all locations, except for differences in
57
58 284 the greater trochanter where women within cluster 0 exhibited lower values than those
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3 285 within cluster 1 ($P=0.002$). On the contrary, women in the first cluster (number 0)
4
5 286 exhibited worse pain-related, related-disability, cognitive, health-related, psychological
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7 287 and physical features when compared with women in the second cluster (number 1).
8
9 288 Overall, women of cluster 0 showed higher intensity of pain and related-disability, more
10
11 289 sensitization associated symptoms, more neuropathic pain symptomatology, more
12
13 290 kinesiophobia, hypervigilance and catastrophism levels, worse sleep quality, higher
14
15 291 anxiety/depressive levels, lower health-related quality of life, and worse physical function
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17 292 than those women of cluster 1 (see **Table 1**).
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24 294 **Discussion**

27 295 Although there are published results exploring the association between multiple
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29 296 psychological, histological, hormonal, physical, neurophysiological, clinical factors in
30
31 297 female patients with FMS by using network analyses, Bayesian analyses and structural
32
33 298 equation models [20,41-50], this study provides a clustering algorithm that identified two
34
35 299 subgroups of women with FMS. In general, women with FMS showed similar widespread
36
37 300 pressure pain sensitivity, but they were different, from a statistical viewpoint, in patient-
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39 301 reported outcome measures, e.g., pain, related-disability, cognitive, psychological, health
40
41 302 -related, and physical features.

45 303 The first finding revealed by the current analysis is that the presence of widespread
46
47 304 pressure pain sensitivity seems to be a common finding in women with FMS since both
48
49 305 clusters had similar widespread PPTs. The fact that women with FMS exhibit excitability
50
51 306 of the nervous system is well accepted in the literature [51]. Sensitivity to pressure pain
52
53 307 is a clinical manifestation of altered nociceptive processing, but it should be considered
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55 308 that PPT is a quantitative sensory test used for evaluating the patient's response against a
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57 309 stimulus and it is influenced by patient's subjective perception and also expectations [52].
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3 310 It should be expected that pressure pain hyperalgesia would be related to the presence of
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5 311 sensitization-associated symptoms, assessed by the CSI, or with pain intensity, however,
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7 312 these assumptions were not supported. In fact, previous studies did not find an association
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9
10 313 between PPTs and the CSI in other chronic pain conditions [53,54]. Similarly, PPTs are
11
12 314 not linearly associated with pain or related disability [55]. These findings were also seen
13
14 315 in our study where both clusters of women with FMS exhibited similar PPTs, but different
15
16 316 CSI scores and pain and related-disability features. It is possible that PPTs represent the
17
18 317 mechanism construct whereas sensory-related and related-disability represents a clinical
19
20 318 construct of the pain spectrum.

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23
24 319 We did not identify a “more sensitive” subgroup of women with FMS based on
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26 320 PPTs. In agreement with our results, de Souza et al. [17] also identified two groups of
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28 321 women with FMS based on the FIQ, but without differences in sensitivity to pressure
29
30 322 pain. However, other studies identified groups of patients with FMS with more or less
31
32 323 sensitivity and with/without psychological stress [5-12]. These studies classified patients
33
34 324 based on the tender point count, pain intensity or related-disability, but they did not
35
36 325 evaluate PPTs. These discrepancies could be explained by the fact that pain or tender
37
38 326 point construct are highly influenced by personal distress whereas PPTs did not [13].
39
40 327 However, our analysis also identified a potential “sensitive group” (cluster 0) considering
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42 328 pain and related-disability outcomes. In fact, the sensitive group had higher sensitization-
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44 329 associated symptomatology, in agreement with a recent study showing that sensitization
45
46 330 was associated with higher pain intensity [56]. Current results would suggest that patient-
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48 331 reported outcome measures (e.g., CSI or pain-related variables) could be better for
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50 332 classifying sensitive women with FMS instead of neurophysiological outcomes (e.g.,
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52 333 PPTs).
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3 334 Our cluster analysis revealed that the subgroup of women with FMS with higher
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5 335 pain sensitization and related-disability also exhibited higher anxiety/depressive levels,
6
7 336 poor sleep quality, and more kinesiophobia, hypervigilance and catastrophism levels. The
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9 337 association between emotional disorders and sensitization is not new in individuals with
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11 338 chronic pain since mood disorders had a significant impact on pain sensitivity [57,58].
12
13 339 Similarly, poor sleep quality is also a risk factor for developing widespread chronic pain
14
15 340 and fatigue [59]. In such scenario, cognitive factors e.g., kinesiophobia or catastrophism
16
17 341 also mediate the association between pain and sensitization [60,61]. In fact, Angarita-
18
19 342 Osorio et al. found that emotional (e.g., higher depressive symptoms) and cognitive (more
20
21 343 pain catastrophizing level) factors are associated with higher pain and disability scores in
22
23 344 women with FMS [62]. Our analysis also revealed that the group of women with FMS
24
25 345 (cluster 0) with higher pain-related and related-disability also exhibited worse health-
26
27 346 related and physical outcomes, in agreement with Angarita-Osorio et al. [62]. Based on
28
29 347 previous and current research, it seems that there is a subgroup of women with FMS
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31 348 exhibiting more sensory, emotional, cognitive, and physical impairments.

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37 349 Previous and current results support the hypothesis that FMS resembles a nociplastic
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39 350 pain condition [63]. Early identification of higher levels of sensitization could play a
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41 351 relevant role as a prognostic factor for treatment since sensitization of the central nervous
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43 352 system is associated with poorer treatment outcomes in individuals with musculoskeletal
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45 353 pain [64]. The hypothesis that a subgroup of FMS should be classified as a nociplastic
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47 354 condition supports why exercise programs, a therapeutic strategy able to reduce pain
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49 355 sensitivity throughout adaptations in the central nervous system [65], usually shows the
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51 356 highest level of evidence for the management of FMS [66]. In fact, it has been recently
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53 357 discussed that pain mechanisms underpinning each patient must be considered for proper
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55 358 prescription of exercise programs in people with nociplastic conditions such as FMS [67].
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3 359 The fact that FMS can be considered as a nociplastic condition does not exclude
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5 360 the presence of neuropathic pain features in FMS since mixed pain phenotypes are also
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7 361 considered [63]. In fact, evidence supports the presence of small fiber neuropathy in FMS
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9 362 patients compatible with the presence of a neuropathic pain component [64-66]. Further,
10
11 363 the use of self-reported questionnaires e.g., the S-LANSS and PainDETECT also supports
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13 364 that some patients with FMS exhibit neuropathic pain features [67,68]. Current analysis
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15 365 revealed that cluster 0, the “sensitive group”, also showed higher scores in the S-LANSS
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17 366 and PainDETECT, suggesting a higher neuropathic component in this subgroup of FMS
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19 367 women. Nevertheless, the lack of identification of structural lesions in the somatosensory
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21 368 system in FMS does not permit to classify FMS as neuropathic pain condition [69], and
22
23 369 probably these patients would exhibit neuropathic pain features which should be treated
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25 370 if identified.

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27 371 These results, based on clustering algorithms, have two main implications for
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29 372 clinical practice. First, identification of this subgroup of women with FMS showing worse
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31 373 sensory, psychological, cognitive, health-related and higher sensitization symptomatology
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33 374 may suggest different underlying mechanisms. It is accepted that prolonged nociception
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35 375 from peripheral tissues is a primary triggering factor for centralized sensitization [68].
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37 376 The presence of higher pain levels and sensitization-associated symptoms could lead to a
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39 377 long-lasting nociceptive barrage to the nervous system contributing to this process. In
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41 378 fact, the magnitude of the peripheral input is a relevant factor to consider in FMS [69],
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43 379 although the topic of peripheral/central sensitization in chronic pain is questioned and
44
45 380 both mechanisms are connected. It is also possible that these women with FMS exhibit
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47 381 different brainstem processing [70], explaining the observed differences in sensitization
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49 382 and emotional/cognitive variables. These hypotheses should be investigated in future
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51 383 studies.
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3 384 The second clinical application pointed out to patient-centered treatment strategies.
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5 385 First, the role of sensory-related intensity supports the relevance of early treatment of pain
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7 386 in women with FMS to decrease sensitization symptomatology and related-disability. In
8
9 387 fact, several strategies are advocated for decreasing pain intensity in FMS. Nevertheless,
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11 388 it is important to consider that anxiety plays a promoting role for pain amplification.
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13 389 Accordingly, physical therapy should be combined with psychological interventions for
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15 390 managing these aspects [71], particularly in the group of FMS women with emotional
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17 391 disturbances (cluster 0). Therefore, clinicians should consider into which group of those
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19 392 identified in the current study falls each patient for better applying the most appropriate
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21 393 treatment approach, e.g., physical therapy, cognitive behavior, anxiety management, pain
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23 394 education, or exercise programs [72]. This clinical reasoning agrees with a meta-analysis
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25 395 supporting that treatment interventions for individuals with FMS should be individualized
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27 396 according to the predominant mechanism [73].
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33 397 Finally, this study presents some potential limitations. First, just women with FMS
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35 398 were included. Current subgrouping cannot be extrapolated to FMS males. Second, we
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37 399 only tested widespread pressure pain sensitivity as a clinical feature of sensitization. It
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39 400 would be interesting to investigate other sensitization outcomes, e.g., thermal or electrical
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41 401 thresholds, conditioning pain modulation or nociceptive flexor reflex, to assess potential
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43 402 differences between the identified clusters. Third, it should be recognized that most of the
44
45 403 variables included in the current study are subjective and can be affected by expectations
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47 404 and patient's perception. Finally, the last topic to consider is that cluster analyses had
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49 405 identified two subgroups of women with FMS where some variables can overlap. In fact,
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51 406 although statistically significant, some clinical variables overlap between both clusters as
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53 407 it can be observed within Figure 2. In fact, the graphical representation of the variables
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55 408 revealed that the identified clusters represent the distribution of symptom severity among
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3 409 the current cohort of women with FMS. This interpretation would suggest that FMS could
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5 410 also represent a continuum process. In fact, the consideration of FMS as a nociplastic
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7 411 condition would support this clinical assumption since some patients exhibit a more
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9 412 physical presentation whereas others a more psychological presentation.
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414 **Conclusions**

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17 415 The application of a cluster analysis has identified two groups of women with
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19 416 FMS differing in sensory, psychological, cognitive and health-related features but not in
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21 417 pressure pain hyperalgesia. This analysis supports that widespread sensitivity to pressure
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23 418 pain seems to be a common feature of this condition, but one group (e.g., the “sensitive”
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25 419 or “impaired” group) exhibits worse sensory, psychological, cognitive or health-related
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27 420 features than the other. Current results suggest that this subgroup of women with FMS
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29 421 may need to be treated differently.
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3 694 **Legend of Figures**
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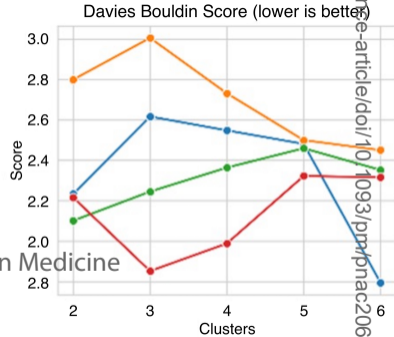
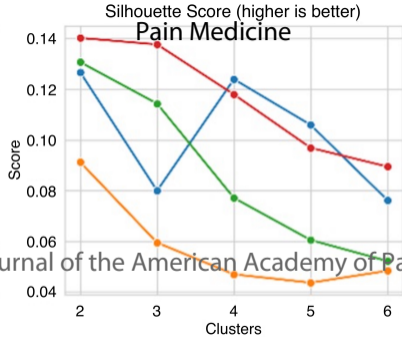
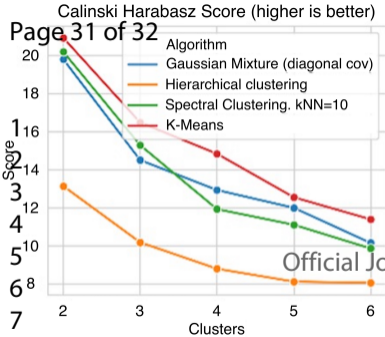
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6 695 **Figure 1.** Score comparison (left to right: Calinski-Harabasz index, Silhouette
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8 696 coefficient, and Davies-Bouldin index) for different number of clusters (2 to 6) and
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10 697 different clustering algorithms (red: K-Means; green: Spectral clustering with 10
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12 698 neighbors; orange: Hierarchical clustering; blue: Gaussian Mixture).
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15 699 **Figure 2.** Cluster analysis showing the different distributions in the variables assessed
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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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