



Evaluation of pain, disease activity, anxiety, depression, and neuropathic pain levels after COVID-19 infection in fibromyalgia patients

Dilek Eker Büyüksireci¹ · Ayla Çağlıyan Türk¹ · Ender Erden¹ · Ebru Erden¹

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Abstract

Background Psychological stressors may cause mental disorders such as anxiety, depression, and post-traumatic stress disorders and fibromyalgia (FM) patients could be affected by these stressors.

Aim To evaluate pain, disease activity, anxiety, depression, and neuropathic pain levels after COVID-19 infection in patients with FM.

Methods According to the 2016 American College of Rheumatology (ACR) criteria, fifty-seven patients with FM alone and 77 patients with FM and recovering from COVID-19 infection were recruited to the study (group 1: patients with FM alone and group 2: patients with FM and recovering from COVID-19). Demographic and clinical characteristics were recorded. The pain level was determined by the Numerical Rating Scale (NRS), the pain regions by the Widespread Pain Index (WPI) of the 2016 ACR criteria, the severity of the symptoms by the Symptom Severity Scale (SSS) of the 2016 ACR criteria, the disease activity by the Fibromyalgia Impact Questionnaire (FIQ), the anxiety and depression levels by the Hospital Anxiety and Depression Scale (HADS), and the neuropathic pain level by Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS).

Results Age, height, weight, Body Mass Index (BMI), and the duration of FM diagnosis were similar in both groups ($p > 0.05$). NRS, FIQ, HADS depression scale, and SSS and LANSS scores were similar between group 1 and group 2 ($p > 0.05$). HADS anxiety score and WPI were significantly increased in group 2 ($p = 0.026$ and $p = 0.024$ respectively).

Conclusions Anxiety and widespread pain levels were higher in patients with FM and recovering from COVID-19 infection.

Keywords Anxiety · Depression · Disease activity · Fibromyalgia · Neuropathic pain · Pain · Post-COVID-19 infection

Introduction

Fibromyalgia (FM) is a chronic, musculoskeletal disorder and some of the symptoms are widespread pain, fatigue, cognitive dysfunction, headache, and impaired sleep quality in patients with FM [1, 2]. The prevalence of FM is 2.7% worldwide [3]. The etiology of FM has still been unknown. FM usually progresses with increasing–decreasing pain attacks [4]. Stress-increasing factors are often associated with the onset and exacerbations of the FM [5]. It has been assumed that infections may accelerate the onset of FM [6].

Due to the COVID-19 pandemic, individuals are faced with contamination of disease, fear of death, social isolation, economic problems, and difficulties accessing health services [7, 8]. These psychological stressors may cause mental disorders such as anxiety, depression, and post-traumatic stress disorders [7–9]. According to our clinical experience,

✉ Dilek Eker Büyüksireci
dilekeker55@gmail.com

Ayla Çağlıyan Türk
drayla1976@hotmail.com

Ender Erden
ender.erden@saglik.gov.tr

Ebru Erden
ebru.durmus40@gmail.com

¹ Department of Physical Medicine and Rehabilitation, Hitit University Erol Olçok Education and Research Hospital, Çorum, Turkey

we consider patients with FM to be an extremely vulnerable population in the COVID-19 pandemic. Cankurtaran et al. [10] showed that patients with FM had more increased anxiety, depression, coronavirus anxiety, and coronavirus fear levels. A study in the literature showed that patients who recovered from COVID-19 had clinical features of FM [11]. Also, in patients with FM and concomitant COVID-19 infection, more severe FM symptoms and disease activity were found [12]. In the literature, there are no studies evaluating pain, disease activity, anxiety, depression, and neuropathic pain levels after COVID-19 infection in fibromyalgia patients. So we aimed to evaluate pain, disease activity, anxiety, depression, and neuropathic pain levels after COVID-19 infection in patients with FM in our study.

Materials and methods

This study was planned as a cross-sectional study. Fifty-seven patients with FM alone and 77 patients with FM and recovering from COVID-19 infection (at least 1 month after COVID-19 infection and no more than 1 year has passed since COVID-19 infection) were recruited to the study (group 1: patients with FM alone and group 2: patients with FM and recovering from COVID-19). The number of patients was determined assuming 80 points mean difference and 16 points SD of total score at Fibromyalgia Impact Questionnaire (FIQ) with 80% power and 5% significance and 63 patients were planned to invite to the study for each group [13]. The 2016 American College of Rheumatology (ACR) criteria was used for the diagnosis of FM [14]. All patients, who applied to the physical medicine and rehabilitation outpatient clinic between January 1, 2022, and March 1, 2022, were of the ages 18–65 and had primary FM for more than 1 year. For group 2, only patients with confirmed COVID-19 infection with nasopharyngeal swab who registered in the hospital information system were included in the study.

Patients with concomitant rheumatic disease or secondary FM, neurological disease; history of other systemic diseases such as hypothyroidism/hyperthyroidism, diabetes mellitus; previous history of overt trauma; and those with COVID-19 infection within 1 month before the examination were excluded.

The demographic and clinical characteristics of the patients were recorded. In addition, the symptoms of COVID-19, whether there was a history of hospitalization, whether there was an increase in fatigue levels, and whether there was a cognitive dysfunction after COVID-19 infection, were recorded for group 2. The pain level of all patients was determined by the Numerical Rating Scale (NRS), the pain regions by the Widespread Pain Index (WPI) of the 2016 ACR criteria, the severity of the symptoms by the Symptom

Severity Scale (SSS) of the 2016 ACR criteria, the disease activity by the Fibromyalgia Impact Questionnaire (FIQ), and the anxiety and depression levels by the Hospital Anxiety and Depression Scale (HADS). In addition, the neuropathic pain level was evaluated with the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS).

Fibromyalgia Impact Questionnaire (FIQ) is composed of 10 items (physical functioning, well-being, missed work days, difficulty in work, pain, fatigue, morning tiredness, stiffness, anxiety, and depression) [15]. Evaluation is made out of a total of 100 points [16]. Low scores show low disease activity [15]. The validity and reliability of the Fibromyalgia Impact Questionnaire (FIQ) for Turkey were assessed [16].

NRS is a subjective measurement in which pain levels of participants were evaluated. It is composed of 0 (no pain) to 10 (worst pain) [17].

The Hospital Anxiety and Depression Scale (HADS) consists of 14 questions. Anxiety and depression levels are determined with this scale [18]. Higher scores show higher severity of anxiety and depression [18]. The reliability and validity of the HADS for Turkey were assessed [19]. Cutoff scores for Turkish society have been determined as 7 for anxiety and 10 for depression [19].

The Widespread Pain Index (WPI) of the 2016 ACR FM diagnostic criteria was utilized [14]. WPI is the number of body areas where the patient has experienced pain in the last 1 week [14]. Symptoms such as fatigue, waking unrefreshed, and cognitive symptoms in the last 1 week and headache, abdominal pain/cramps, and depression in the last 6 months are determined in the Symptom Severity Scale (SSS) of the 2016 ACR FM diagnostic criteria [14].

The Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS) determines the presence of neuropathic pain. It includes 5 questions for pain true and 2 items for sensory testing: allodynia and altered pin-prick threshold [20]. If the score > 12, neuropathic mechanisms are thought contributing to the patients' pain [20]. The Turkish validity and reliability of LANSS were made by Yücel et al. [21].

Approval for the study was obtained from the Committee on Human Research Ethics (Hitit University Clinical Research Ethics Committee, dated: 16.06.2021 decision number: 473). A well-written informed consent was obtained from all participants according to the principles of the Helsinki Declaration.

Statistical analyses

All data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 program for Windows. The variables were investigated using visual and analytical methods to determine whether or not

they are normally distributed. Continuous variables are expressed as mean \pm SD and categorical variables as numbers, percentages and nonparametric variables as median (25–75%). Student's *t* test was used to compare age, height, weight, BMI, FIQ, and HADS anxiety and HADS depression scores. Mann–Whitney *U* test was used to compare NRS, LANSS, WPI, and SSS scores. Chi-square test and Fisher's exact test were used to compare nominal values. Spearman's correlation coefficient was used to evaluate the linear relationship between predictive variables. A value of $p < 0.05$ was considered statistically significant.

Results

One hundred thirty-four patients with a diagnosis of fibromyalgia according to 2016 ACR classification criteria for fibromyalgia syndrome were included. All patients were female. Age, height, weight, Body Mass Index (BMI), education level, marital status, and the duration of FM diagnosis were similar in both groups (Table 1). In group 2, there

were 41 (53.2%) patients with no drugs, 18 (23.4%) patients with duloxetine, and 18 (23.4%) patients with pregabalin (Table 1). In group 1, there were 25 (43.9%) patients with no drugs, 11 (19.3%) patients with duloxetine, and 21 (36.8%) patients with pregabalin (Table 1). NRS, FIQ, HADS depression scale, SSS, and LANSS scores were similar between group 1 and group 2 (Table 1). HADS anxiety score and WPI were significantly increased in group 2 (Table 1). There were no differences in the 10 items of FIQ (physical functioning, well-being, missed work days, difficulty in work, pain, fatigue, morning tiredness, stiffness, anxiety, and depression) between group 1 and group 2 (Table 2).

Clinical features of COVID-19 disease in group 2 were summarized in Table 3. There were no significant differences in clinical features of COVID-19 disease between group 2 who was under pregabalin or duloxetine treatment and group 2 who was not under any treatment (Table 3).

HADS anxiety and depression scores were significantly higher in group 2 without medical treatment compared to group 1 without medical treatment (Table 4). There were no significant differences in NRS, FIQ, LANSS, WPI, and

Table 1 Demographic and clinical features of group 1 and group 2

	Group 1 <i>N</i> = 57	Group 2 <i>N</i> = 77	<i>P</i> value
Age (year)	43.98 \pm 8.32	46.92 \pm 8.72	0.051
Height (cm)	160.52 \pm 6.68	160.40 \pm 5.84	0.909
Weight (kg)	70.29 \pm 17	75.07 \pm 12.97	0.068
BMI (kg/m ²)	27.29 \pm 6.27	29.20 \pm 5.01	0.052
Education (<i>n</i> , %)	0 illiterate 1 (1.8%) literate	2 (2.6%) illiterate 2 (2.6%) literate	0.350
	31 (54.4%) primary school 4 (7%) middle school 10 (17.5%) high school 11 (19.3%) university	43 (55.8%) primary school 6 (7.8%) middle school 18 (23.4%) high school 6 (7.8%) university	
Marital status (<i>n</i> , %)	52 (91.2%) married	74 (96.1%) married	0.284
NRS	7 (5–8)	7 (5–8)	0.462
FIQ	56.57 \pm 23	59.18 \pm 25.59	0.492
HADS anxiety score	8.07 \pm 4.73	9.79 \pm 4.06	0.026
HADS depression score	7.52 \pm 3.85	7.97 \pm 3.42	0.480
LANSS	9 (3–12)	8 (5–13)	0.783
WPI	10 (7–13)	12 (8.5–15)	0.024
SSS	8 (6–9)	8 (7–10)	0.686
The duration of FM diagnosis (year)	4 (2–6)	3 (1.5–5)	0.436
Post-COVID-19 duration (month)		8 (5–9)	
Drugs (<i>n</i> , %)	25 (43.9%) none 11 (19.3%) duloxetine 21 (36.8%) pregabalin	41 (53.2%) none 18 (23.4%) duloxetine 18 (23.4%) pregabalin	0.237

Data are determined as median (25–75%), mean \pm standard deviation, or *n* (%). $P < 0.05$

Group 1: patients with FM alone; group 2: patients with FM and concomitant COVID-19. *BMI* Body Mass Index, *NRS* Numerical Rating Scale, *FIQ* Fibromyalgia Impact Questionnaire, *HADS* Hospital Anxiety and Depression Scale, *LANSS* the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale, *WPI* the Widespread Pain Index of the 2016 ACR FM diagnostic criteria, *SSS* Symptom Severity Scale of the 2016 ACR FM diagnostic criteria

Table 2 Comparison of 10 items (physical functioning, well-being, missed work days, difficulty in work, pain, fatigue, morning tiredness, stiffness, anxiety, and depression) of FIQ between group 1 and group 2

	Group 1 N=57	Group 2 N=77	P value
Physical functioning score	3.33 (2.70–5.98)	3.99 (2.68–5.40)	0.908
Well-being score	5.72 (2.86–8.58)	5.72 (2.86–7.15)	0.980
Missed work days score	2.86 (0–6.57)	4.29 (1.43–7.15)	0.269
Difficulty in work score	6 (3–8)	5 (2.5–8.5)	0.892
Pain score	7 (5–9)	7 (5–9)	0.801
Fatigue score	7 (5–10)	8 (6–10)	0.177
Morning tiredness	7 (4–10)	8 (5–10)	0.247
Stiffness score	7 (3–9)	6 (3.5–9)	0.895
Anxiety score	6 (3–8)	7 (4–10)	0.203
Depression score	5 (3–9)	7 (4.5–10)	0.295
Total score	56.57 ± 23	59.18 ± 25.59	0.492

SSS scores between group 2 without medical treatment and group 1 without medical treatment (Table 4). There were no significant differences in NRS, FIQ, HADS anxiety,

depression, LANSS, WPI, and SSS scores between group 2 under pregabalin or duloxetine treatment and group 1 under pregabalin or duloxetine treatment (Table 5).

Discussion

In this study, we investigated the pain, disease activity, anxiety, depression, and neuropathic pain levels after COVID-19 infection in FM patients. We found that anxiety levels and WPI were more increased in patients with FM and recovering from COVID-19 infection. We did not find any differences in pain, disease activity, and neuropathic pain between patients with FM alone and patients with FM and recovering from COVID-19 infection. Also, we found that anxiety and depression levels were higher in patients with FM and recovering from COVID-19 infection who did not take any drugs for FM compared to patients with FM alone who did not take any drugs for FM. Salaffi et al. [12] evaluated 965 patients with FM and 68 patients were followed up because of COVID-19. They found that sleep quality, fatigue/energy, pain, and stiffness scores of revised FIQ were significantly increased in patients with FM and concomitant COVID-19 (68 patients) compared to FM without concomitant COVID-19 (897 patients) [12]. They showed that FM patients are

Table 3 Clinical features of COVID-19 disease in group 2

	Group 2 N=77	Group 2 under pregabalin or duloxetine treatment N=36	Group 2 without medical treatment N=41	P* value
Presence of fever (n, %)	45 (58.4%)	22 (61.1%)	23 (56.1%)	0.817
Presence of weakness (n, %)	73 (94.4%)	35 (97.2%)	38 (92.7%)	0.618
Presence of cough (n, %)	53 (45.5%)	17 (47.2%)	18 (43.9%)	0.821
Pain (n, %)	8 (10.4%) none 19 (24.7%) low back pain 21 (27.3%) back pain 29 (37.7%) myalgia	3 (8.3%) none 8 (22.2%) low back pain 10 (27.8%) back pain 15 (41.7%) myalgia	5 (12.2%) none 11 (26.8%) low back pain 11 (26.8%) back pain 14 (34.1%) myalgia	0.865
Loss of smell (n, %)	44 (57.1%)	20 (55.6%)	24 (58.5%)	0.821
Loss of taste (n, %)	49 (63.6%)	20 (55.6%)	29 (70.7%)	0.235
Presence of headache (n, %)	57 (74%)	29 (80.6%)	28 (68.3%)	0.299
Presence of diarrhea (n, %)	15 (19.5%)	7 (19.4%)	8 (19.5%)	0.612
Hospitalization (n, %)	7 (9.1%)	4 (11.1%)	3 (7.3%)	0.699
Presence of post-COVID-19 pain (n, %)	36 (46.8%) same 37 (48.1%) increased 4 (5.2%) decreased	19 (52.8%) 15 (41.7%) increased 2 (5.6%) decreased	17 (41.5%) 22 (53.7%) increased 2 (4.9%) decreased	0.573
Presence of post-COVID-19 forgetfulness (n, %)	34 (44.2%) same 43 (55.8%) increased	19 (52.8%) 17 (47.2%) increased	15 (36.6%) 26 (63.4%) increased	0.174
Presence of post-COVID-19 sleep change (n, %)	43 (55.8%)	15 (41.7%) 21 (58.3)	19 (46.3%) 22 (53.7%)	0.819
Presence of post-COVID-19 fatigue (n, %)	54 (70.1%) increased	24 (66.7%) increased	30 (23.2%) increased	0.621

P* p value between group 2 under pregabalin or duloxetine treatment and group 2 without medical treatment

Table 4 Comparison of the pain, disease activity anxiety, depression, and neuropathic pain levels between group 2 without medical treatment and group 1 without medical treatment

	Group 2 without medical treatment N=41	Group 1 without medical treatment N=25	P value
NRS	7 (6–8)	6 (5–8)	0.066
FIQ	60.14 (44.44–71.85)	52.90 (37.14–75.43)	0.401
HADS anxiety score	10.09 ± 3.86	6.8 ± 4.05	0.002
HADS depression score	7.92 ± 3.15	6.36 ± 2.81	0.046
LANSS	11 (5–15)	10 (3.5–12.5)	0.427
WPI	12 (9–15)	8 (6.5–14.5)	0.057
SSS	8 (7–10)	8 (6–9)	0.269

more active and severe in patients with concomitant COVID-19 infection [12]. However, in their study, FM patients were not evaluated for disease activity in the post-COVID-19 infection period. Differently from their study, we evaluated the FM patients in the post-COVID-19 infection period and we found only increased anxiety levels and increased widespread pain scores in patients with FM and post-COVID-19. Similar to their study, we evaluated the clinical features of COVID-19 infection in FM patients. They found that 22.1% of patients had between 38 and 39°C body temperature and 14.7% of patients had over 39°C body temperature [12]. We had found that 58.4% of patients had over 38.3°C body temperature. They found that 58.8% of patients had cough and 72.1% of patients had headache [12]. We found that 45.5% of patients had cough and 74% of patients had headache. Additionally, we evaluated the differences in clinical features of COVID-19 infection between patients with FM and post-COVID-19 infection under pregabalin or duloxetine and patients with FM and post-COVID-19 infection without medical fibromyalgia treatment. But we did not show any differences between these two groups. So we could say that being under the medical treatment with pregabalin or duloxetine does not affect the clinical features of COVID-19 infection in FM patients.

Ursini et al. [11] investigated 616 COVID-19 infection patients. The patients were evaluated 6 ± 3 months after COVID-19 infection and 189 (30.7%) patients satisfied the ACR survey criteria for FM after COVID-19 infection

[12]. Also, they found that obesity and male gender were independent predictors for post-COVID FM. Different from this study, all patients were female in our study. So if we had included male FM patients, perhaps we could see increased disease activity in patients with male FM and post-COVID-19 patients. Prolonged bed rest, deconditioning, post-traumatic stress disorder, etc. could cause the predisposition of FM after the COVID-19 infection period [11]. In a study, the physical and mental impact of the COVID-19 outbreak was evaluated on fibromyalgia patients [22]. High levels of pain, anxiety, depression, sleep disturbances, and subjective perception of worsening were found among FM patients during the COVID-19 outbreak and lockdown measures [22]. This study shows that FM patients are a group of patients who have been significantly affected by the COVID-19 pandemic, even if they are not infected with COVID-19. In our study, only anxiety and WPI scores were found to be higher in FM patients who had COVID-19 infection. There was no difference between the two groups in terms of depression, neuropathic pain level or pain level, and disease activity. There may be no difference between the two groups, as depression, neuropathic pain level, pain level, and disease activity increased in both groups in our study due to the presence of only the COVID-19 pandemic. Because all individuals worldwide are faced with fear of contamination, fear of death, social isolation, economic problems, and difficulties accessing health services [7, 8]. FM patients may be affected much more deeply than the healthy population.

Table 5 Comparison of the pain, disease activity anxiety, depression, and neuropathic pain levels between group 2 under pregabalin or duloxetine treatment and group 1 under pregabalin or duloxetine treatment

	Group 2 under pregabalin or duloxetine treatment N=36	Group 1 under pregabalin or duloxetine treatment N=32	P value
NRS	7 (5–8.75)	7.5 (6–8)	0.588
FIQ	62.44 (39.46–76.18)	61.19 (44.75–74.15)	0.663
HADS anxiety score	9.44 ± 4.31	9.06 ± 3.05	0.738
HADS depression score	8.02 ± 3.75	8.43 ± 4.33	0.678
LANSS	7 (5–11)	8.5 (3–12)	0.554
WPI	12 (8–14)	10.5 (7.25–12.75)	0.193
SSS	8 (6.25–9)	8 (6.25–9.75)	0.633

FM patients may not have been able to implement their exercise programs due to social isolation during this pandemic, and in addition, they may not have been able to continue their medical treatment due to serious problems in accessing drugs used in FM treatment. In our study, there were 53.2% patients with no drugs in the FM and post-COVID-19 infection groups and there were 43.9% patients with no drugs in the FM patient-alone group.

In a study, the patterns of morbidity and mortality in a large cohort of patients with FM and COVID-19 were evaluated [23]. In the FM and COVID-19 groups, old age, male gender, and hypertension were found associated with hospitalization due to COVID-19, similar to the general population [23]. Only having FM was not found directly associated with COVID-19 hospitalization or mortality [23]. We did not assess the comorbidities of FM patients in our study. In FM patients, there were 7 (9.1%) hospitalized patients associated with COVID-19 in our study and there were 14.2% hospitalized patients associated with COVID-19 in their study [23]. In COVID-19 and FM cohort, the prevalence of anxiety and depression was found increased [23] similar to our study.

Cankurtaran et al. [10] showed that patients with FM were affected by psychological stress due to COVID-19. Also, symptom severity, sleep quality, and anxiety and depression levels were affected in patients with FM [10]. Additionally, they found increased COVID-19 fear and anxiety levels in patients with FM [10]. In our study, although patients with FM and post-COVID-19 infection had significantly higher anxiety levels, both groups had high anxiety levels. So, this situation can be related to fear of COVID-19 infection.

This is the first study evaluating pain, disease activity, anxiety, depression, and neuropathic pain levels after COVID-19 infection in fibromyalgia patients. Therefore, this study will make valuable contributions to the literature and daily practice while planning the management of fibromyalgia patients during the pandemic process. But there are some limitations to this study. Exclusion of male FM patients, cross-sectional study design, vaccination of some participants, and unknown exercise status of patients were some limitations of our study.

As a conclusion, anxiety and widespread pain levels were higher in patients with FM and post-COVID-19 infection. Fibromyalgia patients should be followed closely during the pandemic process, and these conditions should be considered in FM management by evaluating the pain and anxiety levels of those with COVID-19 infection.

Author contribution All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Research involving human subjects complied with all relevant national regulations and institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the Committee on Human Research Ethics (Hitit University Clinical Research Ethics Committee, dated: 16.06.2021 decision number: 473).

Informed consent Informed consent has been obtained from all individuals included in this study.

Competing interests The authors declare no competing interests.

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