

Musculoskeletal system symptoms in patients with COVID-19 and the impact of these symptoms on quality of life

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Abstract.

BACKGROUND: Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and also affects the musculoskeletal system.

OBJECTIVE: This study was conducted to investigate the musculoskeletal symptoms, type of pain and effect on quality of life in patients presenting with pain after COVID-19.

METHODS: This prospective, descriptive study included 97 patients aged 18 years or older who were diagnosed with COVID-19 based on a positive polymerase chain reaction test result, with or without musculoskeletal pain prior to COVID-19 infection. Patients who applied to the post-COVID-19 outpatient clinic with the complaint of pain at least 1 month and maximum 1 year after the diagnosis of COVID-19 were included. Patients' demographic characteristics and musculoskeletal examination findings were evaluated. The patients were examined, and the questionnaire forms were completed. The pain was assessed using the visual analog scale (VAS), the Douleur-Neuropathique-4 (DN-4) questionnaire, while the quality of life was assessed using the Short Form-36 (SF-36) survey. Patients were divided into groups in terms of gender, age, body mass index. Shapiro-Wilk's test, the independent samples t-test and the Mann-Whitney U test were used for statistical analyses.

RESULTS: The mean age of the patients was 46.5 ± 13.5 years, 30 of them were male. Pain increased in patients with pre-COVID-19 arthralgia and myalgia ($p < 0.001$). Post-COVID-19 VAS was significantly higher than pre-COVID-19 VAS (7 ± 1.2 vs. 3.2 ± 1.9 , $p < 0.05$). Pre-COVID-19 patients with myalgia had significantly worse SF-36 physical function, social function, pain, general health perception ($p < 0.05$). The mean scores of females in the SF-36 physical function, pain were significantly worse than males ($p < 0.05$). According to DN-4, 41 (42.3%) patients had neuropathic pain. There was moderate negative correlation between VAS, DN-4 and SF-36 ($p < 0.05$).

CONCLUSIONS: Arthralgia, myalgia, and neuropathic pain, all of which negatively affect the quality of life, are often observed in the patients infected with COVID-19.

Keywords: COVID-19, arthralgia, myalgia, neuropathic pain, short form-36

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1. Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a new type of coronavirus that emerged on December 31st, 2019, in Wuhan, China and was first isolated on January 7th, 2020. The World Health Organization (WHO) declared COVID-19 a pandemic on March 11th, 2020 [1]. COVID-19 is transmitted via droplets and contact. In addition to other body systems, COVID-19 affects the musculoskeletal system with widely varying symptoms, including fever, cough, fatigue, headache, myalgia, and shortness of breath [2]. As of December 11th, 2022, over 645 million confirmed COVID-19 cases and over 6.6 million COVID-19-related deaths had been reported globally [3].

COVID-19 affects the musculoskeletal system in various ways. SARS-CoV-2 enters the cells via the angiotensin-converting enzyme 2 (ACE2) receptors using the transmembrane protease, a serine 2 (TMPRSS2) enzyme. In addition to the respiratory system, ACE2 receptors are also found in the tissues of other systems. COVID-19 gives rise to pathological changes in the musculoskeletal system, i.e., the muscle tissue, the synovium, and cortical bone, which include these receptors [4,5]. Cytokines and pro-inflammatory molecules released after COVID-19 infection also cause damage to the musculoskeletal system [2,6]. At least one rheumatic and musculoskeletal symptom was reportedly observed in 74.6% and 43.2% of the COVID-19 patients during three-month and six-month follow-up periods, respectively [7]. On the other hand, studies that investigated either arthralgia or myalgia in COVID-19 patients reported the rate of patients with myalgia between 13.1% and 60.7% and the rate of patients with arthralgia between 5.7% and 43.6% [8–13]. Additionally, neuropathic pain and paresthesia were reported in 21% and 33% of COVID-19 patients, respectively [14,15].

Complaints such as fatigue, myalgia, shortness of breath, hot flashes, headache, tachycardia, chest tightness, and anxiety continue even after the acute phase of COVID-19. These prolonged complaints have been evaluated as the symptoms of the post-COVID syndrome and have reportedly affected the patients both physically and psychologically, causing them difficulties in daily life activities, a situation that negatively affects not only the patients but also their social environment [16,17].

More detailed data for musculoskeletal symptoms will increase our understanding of the effects of

COVID-19 and lead to more efficient and better care for those recovering from COVID-19. In this context, the objective of this study is to assess the musculoskeletal symptoms seen in patients who received outpatient or inpatient treatment due to COVID-19 and to determine the impact of these symptoms on the quality of life. The changes observed in these symptoms in COVID-19 patients who already had these symptoms before they were infected with COVID-19 were also investigated, given the limited studies on this subject.

2. Materials and methods

The population of this prospective, descriptive, gender-neutral study included 110 patients aged 18 years and over with or without musculoskeletal pain before COVID-19 infection, who applied to a post-COVID clinic, were diagnosed with COVID-19 based on the positive result of the polymerase chain reaction test using a nasopharyngeal sample, were treated as inpatients or outpatients between May and August 2021, and met the WHO termination criteria for isolation. Ten patients aged over 75 years old and three patients who developed acute cerebrovascular disease following COVID-19 were excluded from the study. In the end, the study sample consisted of 97 patients (Fig. 1).

The study protocol was approved by the Clinical Research Committee of Hitit University (Approval No.: 418, Approval Date: 10/03/2021). The study was conducted in accordance with the principles set forth in the Declaration of Helsinki. Written informed consent was obtained from all patients before the study.

Patients aged between 18 and 75 years, who presented to the post-COVID-19 outpatient clinic with pain, were referred to the Physical Medicine and Rehabilitation outpatient clinic. Inclusion criteria encompassed individuals who had a documented COVID-19 infection within the past year, had been diagnosed with COVID-19 for at least 1 month, and met the aforementioned age range. Exclusion criteria comprised patients who received intensive care unit treatment during their COVID-19 infection, had a history of cerebrovascular disease, exhibited cognitive impairment, suffered from rheumatological disease, joint contracture, neurological disease, or were pregnant women. Patients' demographic data (age, gender, body mass index [BMI], educational status, marital status, occupation), comorbidities (hypertension, diabetes mellitus, thyroid disease, heart disease, respiratory disease, malignancy, and others), smoking status, presence of lung involvement in

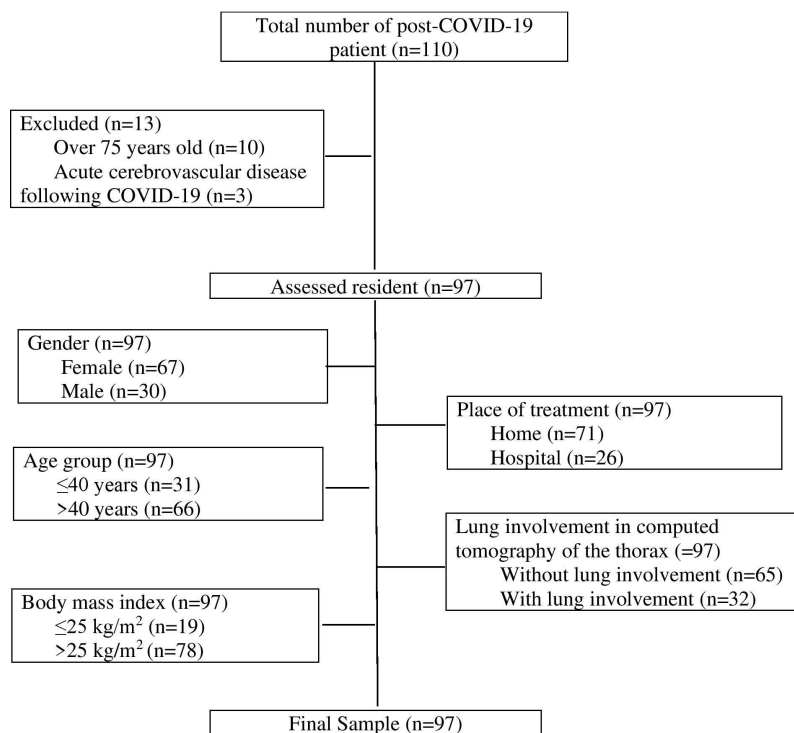


Fig. 1. Flowchart for the inclusion of the patients and patient grouping.

computed tomography of the thorax, length of hospital stay, steroid use, and time from COVID-19 diagnosis to assessment (duration of the disease) were recorded. Patients' muscle pain, joint pain, the type of pain (nociceptive pain, neuropathic pain) they experienced, and changes in pain intensity compared to before COVID-19 were assessed, and superficial sensory examinations (touch, pain-temperature) were performed. In our study, patients underwent examination and completed questionnaire forms upon their presentation to the outpatient clinic.

The pain experienced by patients was assessed using the visual analog scale (VAS). VAS is a standard pain assessment tool used in daily clinical practice. Patients assess their pain by assigning a score between 0 (no pain) and 10 (unbearable pain). A VAS score of 1 to 3 indicates mild pain, 4 to 6 moderate pain, and 7 to 10 severe pain [18].

Patients' neuropathic pain assessment was carried out using the Douleur Neuropathique 4 (DN-4) questionnaire. The DN-4 questionnaire, which was developed by the French Neuropathic Pain Group, assesses the symptoms and findings related to neuropathic pain in four subscales and ten items. The first two subscales focus on anamnesis, and the remaining two focus on the clinical examination findings. The first subscale queries

the character of the pain (burning sensation, sensation of painful cold, electric shock sensation) in three items. The second subscale queries paresthesia/dysesthesia (tingling, pins-and-needles, numbness, itching sensations) in the body site with pain in four items. The third subscale queries the sensory deficit (hypoesthesia to touch, hypoesthesia to pinprick) in the body site where the pain is located in two items. Finally, the fourth subscale queries whether brushing inflicts or aggravates pain in one item. Items are answered as either 'yes' (1 point) or 'no' (0 points). Patients with a total score of 4 or more are considered to have neuropathic pain [19]. The Turkish adaptation, validity, and reliability studies of the DN-4 questionnaire were carried out by Cevik et al. [20].

The patients' quality of life and functional status were evaluated using the Short Form-36 (SF-36) survey. This self-assessment survey evaluates the quality of life in the last four weeks by focusing on the physical, social, and spiritual components of health without concentrating on a specific age or disease group. The survey consists of 36 items that are measured in eight subscales: physical function subscale (10 items), social function subscale (2 items), role limitations due to physical problems subscale (4 items), role limitations due to emotional problems subscale (3 items), mental

health subscale (5 items), vitality subscale (4 items), pain subscale (2 items), and general perception of health subscale (5 items). The total score that can be obtained from each subscale ranges from 0 to 100. The higher the score, the higher the quality of life [21]. The Turkish adaptation, validity, and reliability studies of the SF-36 survey were carried out by Koçyiğit et al. [22].

Age, gender, obesity, lung involvement, and hospitalization have been cited as factors that affect the severity of COVID-19 [23], which may also have an effect on pain. The patients included in the study group were divided into various subgroups according to gender, place of treatment (home/hospital), age group (≤ 40 years/ > 40 years), presence of lung involvement in computed tomography of the thorax, and BMI (≤ 25 kg/m²/ > 25 kg/m²).

2.1. Statistical analysis

Power analysis and sample size calculation were carried out using PASS 11.0 (Power Analysis and Sample Size Software, NCSS LLC, Kaysville, UT, USA). Accordingly, the power of the study with a sample size of 77 COVID-19 patients was calculated as 95% ($\alpha = 0.05/\text{Beta} = 0.048/\text{chi-square } 13.13 / W = 0.41$) to detect an effect size (W) of 0.4130 using one as the degree of freedom in chi-square test with a significance level (α) of 0.05000 [24].

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) software package. Descriptive statistics obtained from the collected data were expressed as mean and standard deviation values in the case of continuous variables determined to conform to the normal distribution, as median and interquartile range values in the case of continuous variables determined not to conform to the normal distribution, and as frequency (n) and percentage (%) values in the case of categorical variables. Normal distribution characteristics of the continuous variables were analyzed using Shapiro-Wilk's test. Comparisons of two independent groups were made using the independent samples t -test and the Mann-Whitney U test in the case of normally distributed and non-normally distributed continuous variables, respectively. Additionally, categorical variables were compared using Pearson's chi-square test or Fisher's exact test for proportion. Pearson's and Spearman's correlation analyses were used to examine the relationship between normally distributed continuous and unspecified variables, respectively. All significance tests were 2-tailed. The probability (p) statistics of < 0.05 were deemed to indicate statistical significance.

Table 1
Demographic and clinical characteristics of the patients ($n = 97$)

Parameters	
Age (years)	46.5 \pm 13.5 (18–75)
Gender (female/male)	67 (69)/30 (31)
BMI (kg/m ²)	29.0 \pm 4.9 (16–39)
Educational status	
Illiterate	3 (3.1)
Primary school	50 (51.5)
Middle school	15 (15.5)
High school	18 (18.6)
College/university	11 (11.3)
Smoking	13 (13.8)
Disease duration (months)	4.0 \pm 2.2 (1–10)
Place of treatment (home/hospital)	71 (73.2)/26 (26.8)
Length of hospital stay (days)	3.1 \pm 7.4 (0–60)
Steroid use	18 (18.6)
Lung involvement	32 (33)
Myalgia before COVID-19	49 (50.5)
Myalgia after COVID-19	96 (99)
Arthralgia before COVID-19	40 (41.2)
Arthralgia after COVID-19	77 (79.4)
New arthralgia developed after COVID-19	37 (38.1)
New myalgia developed after COVID-19	47 (48.5)
Type of pain before COVID-19	
Nociceptive/neuropathic	35 (36.1)/14 (14.4)
Type of pain after COVID-19	
Nociceptive/neuropathic	50 (51.5)/47 (48.5)
Increase in pre-COVID pain intensity	49 (100)
Abnormal sensory examination findings	18 (18.6)
VAS score after COVID-19	6.9 \pm 1.5 (2–10)
DN4 score after COVID-19	3.5 \pm 2.4 (0–9)
Neuropathic pain confirmed with DN4 after COVID-19	41 (42.3)
SF-36 subscale scores after COVID-19	
Physical function	60.4 \pm 20.7 (5–100)
Physical role limitation	35.8 \pm 36.4 (0–100)
Emotional role limitation	36.4 \pm 37.6 (0–100)
Vitality	36.9 \pm 16.3 (5–90)
Mental health	49.2 \pm 16.4 (8–92)
Social function	53.1 \pm 25.0 (0–100)
Pain	34.3 \pm 21.3 (0–80)
General perception of health	40.3 \pm 17.5 (0–75)

BMI: body mass index, DN4: Douleur Neuropathique 4 questionnaire, SF-36: Short Form-36 survey, VAS: visual analog scale. The data are expressed as mean \pm standard deviation, (range) or n , (%). Significant p values are written in bold.

3. Results

The mean age of the 97 patients included in the study, of whom 67 (69.1%) were males, was 46.5 \pm 13.5 years. The mean disease duration was 4.0 \pm 2.2 months. Thirty-two (33%) patients had lung involvement, 18 (18.6%) received steroid treatment, and 26 (26.8%) were treated as inpatients. Myalgia started after COVID-19 infection in 47 of the 96 (99%) patients who had myalgia, and arthralgia started after COVID-19 infection in 37 (38.1%) of the 77 (79.4%) patients who had arthralgia among the patients who applied to the

Table 2

Location of arthralgia and myalgia of patients ($n = 97$)

Parameters	
Location of arthralgia before COVID-19	
Shoulder	17 (17.5)
Elbow	11 (11.3)
Wrist	8 (8.2)
Hip	6 (6.2)
Knee	24 (24.7)
Foot/ankle	5 (5.2)
Location of arthralgia after COVID-19	
Shoulder	43 (44.3)
Elbow	26 (26.8)
Wrist	21 (21.9)
Hip	22 (22.7)
Knee	39 (40.2)
Foot/ankle	13 (13.4)
Location of myalgia before COVID-19	
Neck-back-lumbar	27 (27.8)
Front trunk	2 (2.1)
Arm	22 (22.7)
Forearm	22 (22.7)
Thigh	15 (15.5)
Calf	20 (20.6)
Location of myalgia after COVID-19	
Neck-back-lumbar	59 (60.8)
Front trunk	16 (16.5)
Arm	43 (44.3)
Forearm	37 (38.1)
Thigh	32 (33.0)
Calf	44 (45.4)

The data are expressed as n , (%).

post-COVID clinic due to musculoskeletal pain after COVID-19 infection. The pain intensity in 49 patients who had myalgia and/or arthralgia before the COVID-19 infection increased after the infection. The mean score patients obtained from the DN-4 questionnaire was 3.5 ± 2.4 . According to the DN-4 questionnaire scores, 41 (42.3%) patients had neuropathic pain. The mean post-COVID-19 VAS score of patients with or without musculoskeletal pain before COVID-19 infection was 6.9 ± 1.5 . Patients' demographic and clinical characteristics, musculoskeletal findings, DN-4 questionnaire, VAS, and SF-36 survey scores are given in Table 1.

Sixty percent of the patients were homemakers, and 17% were working actively. Eighty-one percent of the patients were married, and 14.4% were living alone. The most common comorbidities were hypertension (24.7%), diabetes mellitus (14.4%), respiratory disease (10.3%), thyroid disease (8.2%), heart disease (5.2%), and malignancy (2.1%). In addition, 45 (46.4%) patients had no comorbidities, 33 (34%) had only one comorbidity, 14 (14.4%) had two comorbidities, and 5 (5.2%) had three or more comorbidities.

The most common site of arthralgia in patients with arthralgia before the COVID-19 infection was the knee

(24.7%), whereas the most common site of arthralgia after the COVID-19 infection was the shoulder (44.3%). On the other hand, both the most common locations of myalgia before COVID-19 infection and after COVID-19 infection were neck/back/lumbar (27.7% and 60.8%, respectively) (Table 2).

The mean VAS scores of the patients who had musculoskeletal pain were 3.2 ± 1.9 and 7 ± 1.2 before and after the COVID-19 infection, respectively, indicating a significant increase in pain ($p < 0.001$).

There were 49 patients with myalgia and 40 with arthralgia before the COVID-19 infection. The comparisons between the patients with and without arthralgia and myalgia before COVID-19 are given in Table 3.

Gender-based comparisons of the patients revealed that the mean VAS score of females, as well as the number of female patients who developed myalgia after COVID-19, were significantly higher than those of males ($p < 0.05$ for both cases). On the other hand, the number of male smokers and the mean scores of males from the physical function and pain subscales of the SF-36 survey were significantly higher than those of females ($p < 0.05$ for all cases) (Table 4).

Additionally, age-based comparisons of the patients revealed that the mean BMI, number of comorbidities, number of patients with comorbidities, number of patients treated as inpatients, and the mean length of hospital stay were significantly higher in patients > 40 years old than in patients ≤ 40 years old ($p < 0.05$ for all cases) (Table 4).

BMI-based comparisons of the patients revealed that the mean age, number of patients with comorbidities, and number of patients using steroids were significantly higher in patients with a BMI of $> 25 \text{ kg/m}^2$ than in patients with a BMI of $\leq 25 \text{ kg/m}^2$ ($p < 0.05$ for all cases) (Table 4).

In terms of the place of treatment, the mean age, mean BMI, number of comorbidities, number of patients with comorbidities, number of patients using steroids, and the number of patients with lung involvement were significantly higher in patients who were treated as inpatients than in patients who were treated as outpatients ($p < 0.05$ for all cases). On the other hand, the mean disease duration was significantly longer in patients treated as outpatients than in patients treated as inpatients ($p = 0.02$) (Table 5).

Additionally, the mean BMI, number of comorbidities, number of patients with comorbidities, number of patients treated as inpatients, mean length of hospital stay, number of patients using steroids, and the mean score of the vitality subscale of the SF-36 survey were

Table 3
Comparison of the demographic and clinical data of the patients according to arthralgia before COVID-19 and myalgia before COVID-19

Variable	Arthralgia before COVID-19 (n = 57)		Myalgia before COVID-19 (n = 97)		p
	Not developed (n = 57)	Developed (n = 40)	Not developed (n = 48)	Developed (n = 49)	
Age (years)	44.9 ± 13.5	48.7 ± 13.2	44.7 ± 13.6	48.2 ± 13.2	0.171
Gender (female/male)	37 (64.9)/20 (35.1)	30 (75)/10 (25)	28 (58.3)/20 (41.7)	39 (79.6)/10 (20.4)	0.024
BMI (kg/m ²)	28.9 ± 4.8	29.2 ± 5.3	28.8 ± 5.3	29.2 ± 4.8	0.605
Number of comorbidities	0.7 ± 0.8	0.9 ± 0.9	0.6 ± 0.7	0.9 ± 1.0	0.324
Disease duration (months)	4 (3–5.3)	3 (2–5)	4 (2–5.4)	3.5 (2.1–5)	0.635
Length of hospital stay (days)	3.3 ± 8.7	2.9 ± 5.2	1.9 ± 3.6	4.3 ± 9.8	0.249
Place of treatment (home/hospital)	42 (73.7)/15 (26.3)	29 (72.5)/11 (27.5)	37 (77.1)/11 (22.9)	34 (69.4)/15 (30.6)	0.392
Smoking	8 (14)	5 (12.5)	9 (18.8)	4 (8.2)	0.126
Comorbidities	29 (50.9)	23 (57.5)	25 (52.1)	27 (55.1)	0.766
Steroid use	11 (19.3)	7 (17.5)	8 (16.7)	10 (20.4)	0.636
Lung involvement	19 (33.3)	13 (32.5)	15 (31.3)	17 (34.7)	0.718
Arthralgia	37 (35.1)	40 (100)	30 (62.5)	47 (95.9)	< 0.001
Myalgia	57 (100)	39 (97.5)	47 (97.9)	49 (100)	0.495
Arthralgia developed after COVID-19	37 (64.9)	0 (0)	25 (52.1)	12 (24.5)	0.005
Myalgia developed after COVID-19	43 (75.4)	4 (10)	47 (97.9)	0 (0)	< 0.001
VAS score	7 (6–8)	7 (6–8)	7 (6–8)	7 (6–8)	0.656
DN-4 score	3 (2–5)	3 (2–5)	2 (2–4)	4 (2–5.5)	0.023
Neuropathic pain confirmed with DN-4	24 (42.1)	17 (42.5)	16 (33.3)	25 (51)	0.078
SF-36 subscale scores					
Physical function	63.1 ± 21.8	56.6 ± 18.8	70 (55–80)	55 (42.5–72.5)	0.003
Physical role limitation	25 (0–75)	25 (0–50)	25 (0–75)	25 (0–50)	0.151
Emotional role limitation	33.3 (0–66.7)	33.3 (0–58.4)	33.3 (0–91.7)	33.3 (0–66.7)	0.646
Vitality	40 (30–50)	35 (20–45)	38.6 ± 14.6	35.4 ± 17.9	0.323
Mental health	50.5 ± 15.4	47 ± 17.7	52 ± 16.3	46.2 ± 16.1	0.082
Social function	55 ± 24.7	50.3 ± 25.7	58.9 ± 26.0	47.4 ± 23.0	0.024
Pain	35 (22.5–45)	22.5 (10.6–46.9)	37.5 (33.1–47.5)	22.5 (10–45)	0.003
General perception of health	40 (35–55)	40 (26.3–48.8)	43.9 ± 18.4	36.9 ± 16.2	0.047

BMI: body mass index, DN4: Douleur Neuropathique 4 questionnaire, SF-36: Short Form-36 survey, VAS: visual analog scale. The data are expressed as mean ± standard deviation, median and interquartile range or n, (%). Significant p values are written in bold.

Table 4
Comparison of the demographic and clinical data of the patients according to gender, age group and body mass index

Variables	Gender		Age group		Body mass index	
	Female (n = 67)	Male (n = 30)	≤ 40 years old (n = 31)	> 40 years old (n = 66)	≤ 25 BMI (n = 19)	> 25 BMI (n = 78)
Age (years)	45.3 ± 14.2 *	49.1 ± 11.4 *	30.8 ± 7.6	53.8 ± 8.3	33.6 ± 13.7	49.6 ± 11.5
Gender (female/male)			24 (77.4)	43 (65.2)	14 (73.7)	53 (67.9)
			7 (22.6)	23 (34.8)	5 (26.3)	25 (32.1)
BMI (kg/m ²)	28.8 ± 5.0	29.6 ± 4.9	25.7 ± 5.0	30.5 ± 4.2	21.7 ± 2.4	30.8 ± 3.7
Number of comorbidities	0.7 ± 0.9	0.8 ± 0.7	0.4 ± 0.6	1.0 ± 0.9	0.5 ± 0.8	0.9 ± 1
Disease duration (months)	4 (2-5)	3.8 (2.9-5.9)	3.5 (2-4.5)	4 (2-5)	3 (2-5.5)	4 (2-5)
Length of hospital stay (days)	2.8 ± 8.2	3.6 ± 5.3	1.0 ± 2.8	4.1 ± 8.6	1.2 ± 3.5	3.6 ± 28.1
Place of treatment						
Home	52 (77.6)	19 (63.3)	27 (87.1)	44 (66.7)	17 (89.5)	54 (69.2)
Hospital	15 (22.4)	11 (36.7)	4 (12.9)	22 (33.3)	2 (10.5)	24 (30.8)
Smoking	2 (3.0)	11 (36.7)	2 (6.5)	11 (16.7)	2 (10.5)	11 (14.1)
Comorbidities	32 (47.8)	20 (66.7)	12 (38.7)	40 (60.6)	6 (31.6)	46 (59)
Steroid use	11 (16.4)	7 (23.3)	3 (9.7)	15 (22.7)	19 (100)	18 (23.1)
Lung involvement	19 (28.4)	13 (43.3)	6 (19.4)	26 (39.4)	3 (15.8)	29 (37.2)
Arthralgia	55 (82.1)	22 (73.3)	21 (67.7)	56 (84.8)	13 (68.4)	64 (82.1)
Myalgia	66 (98.5)	30 (100)	30 (96.8)	66 (100)	18 (94.7)	78 (100)
Arthralgia developed after COVID-19	25 (37.3)	12 (40.0)	8 (25.8)	29 (43.9)	4 (21.1)	33 (42.3)
Myalgia developed after COVID-19	27 (40.3)	20 (66.7)	14 (45.2)	33 (50.0)	10 (52.6)	37 (47.4)
VAS score	7 (6-8)	6 (5-7)	7 (6-9)	7 (6-8)	6 (6-7)	7 (6-8)
DN4 score	3 (2-5)	3 (2-5)	4 (2-5)	3 (2-5)	6 (6-7)	3 (2-5)
Neuropathic pain confirmed with DN4	29 (43.3)	12 (40.0)	17 (54.8)	24 (36.4)	8 (42.1)	33 (42.3)
SF-36 subscale scores						
Physical function	56.4 ± 19.8	69.2 ± 20.3	60 (50-75)	65 (45-75)	65 (50-75)	65 (45-70)
Physical role limitation	25 (0-75)	25 (0-81.3)	25 (0-75)	25 (0-56.3)	25 (0-75)	25 (0-75)
Emotional role limitation	33.3 (0-66.7)	33.3 (0-75)	33.3 (0-66.7)	33 (0-66.7)	33.3 (0-66.7)	33.3 (0-66.7)
Vitality	35.4 ± 16.9	40.5 ± 14.5	35.4 ± 18.0	37.6 ± 15.6	37.1 ± 16.8	36.9 ± 16.4
Mental health	47.7 ± 16.7	52.0 ± 15.3	47.8 ± 16.7	49.6 ± 16.3	48.8 ± 19.5	49.1 ± 15.7
Social function	51.5 ± 23.7	56.7 ± 27.7	50 (37.5-75)	62.5 (37.5-75)	62.5 (37.5-75)	50 (37.5-75)
Pain	29.8 ± 20.0	44.4 ± 21.1	35 (20-47.5)	35 (22.5-45)	35 (22-45)	35 (22.5-47.5)
General perception of health	38.0 ± 18.1	45.5 ± 18.2	41.6 ± 18.9	39.7 ± 17.0	45 (25-50)	40 (33.7-55)

BMI: body mass index, DN4: Douleur Neuropathique 4 questionnaire, SF-36: Short Form-36 survey, VAS: visual analog scale. The data are expressed as mean ± standard deviation, median and interquartile range or n, (%). Significant p values are written in bold.

Table 5
Comparison of the demographic and clinical data of the patients according to place of treatment and lung involvement

Variable	Place of treatment (n = 97)			Lung involvement (n = 97)		
	Home (n = 71)	Hospital (n = 26)	p	Without lung involvement (n = 65)	With lung involvement (n = 32)	p
Age (years)	44.7 ± 13.8	51.3 ± 11.1	0.031	44.6 ± 13.9	50.2 ± 11.9	0.057
Gender (female/male)	52 (73.2)/19 (26.8)	15 (57.6)/11 (42.4)	0.142	48 (73.8)/17 (26.2)	19 (59.4)/13 (40.6)	0.147
BMI (kg/m ²)	28.3 ± 4.9	31.0 ± 4.6	0.022	28.0 ± 4.8	31.7 ± 4.7	0.003
Number of comorbidities	0.6 ± 0.8	1.2 ± 0.8	0.001	0.5 ± 0.8	1.2 ± 0.8	0.001
Disease duration (months)	4 (2.5–5)	2 (1.5–4.5)	0.027	4 (2.5–5.3)	4 (2–4.5)	0.099
Length of hospital stay (days)	NA	11.6 ± 10.4	NA	0.1 ± 0.6	9.3 ± 10.0	0.001
Place of treatment (home/hospital)	*	*	*	64 (98.5)/1 (1.5)	7 (21.9)/25 (78.1)	< 0.001
Smoking	9 (12.7)	4 (15.4)	0.729	8 (12.3)	5 (15.6)	0.652
Comorbidities	30 (42.3)	22 (84.6)	< 0.001	26 (40.0)	26 (81.2)	< 0.001
Steroid use	1 (1.4)	17 (65.4)	< 0.001	0 (0)	18 (56.2)	< 0.001
Lung involvement	7 (9.9)	25 (96.2)	< 0.001	*	*	*
Arthralgia	55 (82.1)	22 (73.3)	0.576	50 (76.9)	27 (84.4)	0.394
Myalgia	70 (98.6)	26 (100)	1.000	64 (98.5)	32 (100)	0.481
Arthralgia developed after COVID-19	26 (36.6)	11 (42.3)	0.642	23 (35.4)	14 (43.8)	0.425
Myalgia developed after COVID-19	36 (50.7)	11 (42.3)	0.464	32 (49.2)	15 (46.9)	0.827
VAS score	7 (6–8)	7 (6–7)	0.240	7 (6–8)	7 (6–8)	0.716
DN4 score	3 (2–5)	3 (1–4.3)	0.350	3 (2–5)	3 (1.3–4)	0.325
Neuropathic pain confirmed with DN4	30 (42.3)	11 (42.3)	0.996	37 (56.9)	13 (40.6)	0.818
SF-36 subscale scores						
Physical function	59.2 ± 20.9	63.6 ± 20.3	0.355	65 (47.5–75)	62.5 (45–75)	0.796
Physical role limitation	25 (0–75)	25 (0–56.3)	0.666	25 (0–75)	25 (0–50)	0.379
Emotional role limitation	33.3 (0–66.7)	33.3 (0–66.7)	0.781	33.3 (0–66.7)	33.3 (0–66.7)	0.961
Vitality	35 (20–45)	40 (33.7–55)	0.091	35 (20–45)	40 (35–55)	0.030
Mental health	47.7 ± 16.4	52.1 ± 16.1	0.265	48.0 ± 16.8	51.3 ± 15.4	0.335
Social function	62.5 (37.5–75)	50 (25–62)	0.466	62.5 (37.5–75)	50 (25–62.5)	0.072
Pain	35 (22.5–45)	40 (22.5–57.5)	0.253	35 (22.3–45)	35 (22.5–56.9)	0.424
General perception of health	40 (25–55)	40 (33.8–50)	0.815	40.2 ± 18.7	40.4 ± 15.1	0.957

BMI: body mass index, DN4: Douleur Neuropathique 4 questionnaire, SF-36: Short Form-36 survey, VAS: visual analog scale. The data are expressed as mean ± standard deviation, median and interquartile range or n, (%). Significant p values are written in bold.

Table 6
Correlation of patients with various variables

	Age	BMI	After COVID-19 VAS	Before COVID-19 VAS	DN-4	Physical function	Physical role limitation	Emotional role limitation	Vitality	Mental health	Social function	Pain	General perception of health
Age	<i>r</i> 1												
BMI	<i>p</i> 0.458	1											
After COVID-19 VAS	<i>r</i> <0.001	0.107	1										
Before COVID-19 VAS	<i>p</i> 0.916	0.295		1									
DN-4	<i>r</i> -0.440	-0.048	0.240		1								
Physical function	<i>p</i> 0.670	0.644	0.018			1							
Physical role limitation	<i>r</i> -0.106	-0.023	0.214	0.201			1						
Emotional role limitation	<i>r</i> 0.301	0.826	0.018	0.049				1					
Vitality	<i>r</i> -0.097	-0.177	-0.390	-0.238					1				
Mental health	<i>p</i> 0.347	0.083	<0.001	0.019						1			
Social function	<i>r</i> 0.105	0.013	-0.385	-0.154							1		
Pain	<i>p</i> 0.307	0.899	<0.001	0.132								1	
General perception of health	<i>r</i> 0.035	0.028	-0.227	-0.070									1
	<i>p</i> 0.736	0.785	0.026	0.494									
	<i>r</i> 0.062	-0.005	-0.216	-0.291									
	<i>p</i> 0.544	0.959	0.035	0.004									
	<i>r</i> 0.135	-0.029	-0.207	-0.335									
	<i>p</i> 0.187	0.776	0.042	0.001									
	<i>r</i> -0.036	-0.165	-0.353	-0.240									
	<i>p</i> 0.729	0.107	<0.001	0.018									
	<i>r</i> 0.066	0.052	-0.416	-0.331									
	<i>p</i> 0.519	0.614	<0.001	0.001									
	<i>r</i> -0.012	-0.215	-0.419	-0.236									
	<i>p</i> 0.910	0.035	<0.001	0.020									

BMI: body mass index, DN4: Douleur Neuropathique 4 questionnaire, VAS: visual analog scale. Significant p values are written in bold.

significantly higher in patients who had lung involvement in the computed tomography of the thorax than in patients who did not ($p < 0.05$ for all cases) (Table 5).

There was a moderate correlation between BMI and the length of hospitalization in days in the positive direction ($r_s = 0.334$, $p = 0.001$). There was a moderate correlation between BMI and SF-36 general perception of health subscale scores in the negative direction ($r_s = -0.215$, $p = 0.035$). There was a positive correlation between the VAS scores and DN-4 questionnaire scores after the COVID-19 infection and the VAS scores before the COVID-19 infection, and a negative correlation between the SF-36 physical function, social functionality, pain, and general perception of health subscale scores ($p < 0.05$). There was a moderate correlation between the VAS score and SF-36 physical function, social functionality, pain, and vitality subscales scores after the COVID-19 infection in the negative direction ($p < 0.05$). Additionally, there was a moderate correlation between the DN-4 questionnaire scores and all SF-36 subscale scores in the negative direction ($r_s = -0.351$, $r_s = -0.350$, $r_s = -0.396$, and $r_s = -0.381$ respectively, $p < 0.001$) (Table 6).

4. Discussion

This study featured the musculoskeletal symptoms and their effects on the quality of life in 97 patients who applied to the post-COVID treatment unit due to pain and were treated for COVID-19. In the post-COVID period, myalgia was observed in 48 (49.5%) and arthralgia in 37 (38.1%) patients with no previous pain. Forty-seven (49.5%) patients described numbness, burning, and tingling. In addition, neuropathic pain was identified in 41 (42.3%) patients based on the DN4 questionnaire scores. The pain intensity in all 49 patients with myalgia and/or arthralgia before COVID-19 increased after the infection. In addition, the patients included in the study scored significantly lower than the general Turkish population in all subscales of the SF-36 survey, indicating significantly poorer quality of life [25]. There was a significant relationship between the presence of pain before and after the COVID-19 infection and neuropathic pain. In addition, the quality of life decreased with the increase in pain and BMI values.

Several studies have examined the relationship between COVID-19 and musculoskeletal symptoms [23, 26]. In a review of 35 studies on COVID-19, 18 reported that the most common musculoskeletal symptoms were arthralgia and myalgia [27]. Studies that in-

vestigated both arthralgia and myalgia in COVID-19 patients reported the rate of patients with both arthralgia and myalgia between 27.8% and 30% of the COVID-19 patients [10,15]. In Bakilan et al.'s study [13] conducted with 280 post-acute COVID-19 patients 12 weeks after COVID-19 infection, it was determined that 240 (85.7%) patients had at least one musculoskeletal system symptom that either developed anew or aggravated with COVID-19 infection, whereas that 40 (14.3%) patients did not have any musculoskeletal symptom that developed anew or aggravated with COVID-19 infection. In the said study, 60.7% and 43.6% of the patients had myalgia and arthralgia, respectively. In addition, it was determined that muscle and joint pain developed anew or aggravated in 51.1% and 36.1% of the COVID-19 patients, respectively. In comparison, in this study, 96 (99%) and 77 (79.4%) patients had myalgia and arthralgia 4.0 \pm 2.2 months after COVID-19 infection, respectively. Of these patients, 47 (48.5%) and 37 (38.1%) developed myalgia and arthralgia after the COVID-19 infection. In addition, it was determined that pain intensity aggravated after the COVID-19 infection in patients who had pain before the COVID-19 infection. The higher myalgia and arthralgia rates found in this study compared to the rates reported in the literature might be attributed to the fact that the sample of this study solely consisted of patients who presented with musculoskeletal pain after COVID-19.

During the infection, muscle fibers in ischemic muscle experience an increase in sarcoplasmic reticulum proteins such as creatine kinase, lactate, alanine aminotransferase, and aspartate aminotransferase. Simultaneously, there is a decrease in pH and oxygen levels. Among the proinflammatory molecules produced by COVID-19 infection that affect musculoskeletal tissues, interleukin-6, interleukin-1 β , interleukin-10, interleukin-17, interferon- γ , tumor necrosis factor- α , C-reactive protein, soluble receptor for advanced glycation end products, receptor activator of nuclear factor-B ligand, vascular endothelial growth factor, and macrophage colony-stimulating factor are found in high levels in the serum of infected patients. These molecules induce fiber proteolysis and reduce protein synthesis. Notably, interleukin-6 serves as a significant marker for the severity of COVID-19 infection. Furthermore, COVID-19, with its increased inflammatory mediators, exacerbates and accelerates the progression of osteoarthritis in terms of joint and cartilage deterioration [28].

Studies have reported back pain as the most common (6.8%–43%) complication in the spine after COVID-

19 infection [8,10,29–32]. The VAS scores in these patients with pain ranged between 4.8 and 7.2. Bakilan et al. [13] reported that 70.1% of the 280 post-acute COVID-19 patients had spinal pain, which was mostly observed in the back (30.4%), followed by the waist (16.1%), and the neck (11.4%), and that joint pain was mostly observed in the knee (12.1%) followed by the shoulder (5.7%). In a cohort study covering 1.5 to 3 months after COVID-19 diagnosis with a positive PCR test, Oguz-Akarsu et al. [30] determined that 159 (71.6%) of the 222 patients had pain and that the most common type of pain was back pain (41.8%), followed by widespread pain (36.4%) and extremity pain (21.8%). In another study conducted with 1712 COVID-19 patients, the most common site of pain was the head, followed by the neck, back, lower back, and shoulder [33]. Mils et al. reported that pain was detected in half of the patients with COVID-19 infection and that it was most commonly (27%) observed in the lower extremities, followed by the lumbar region (19%), and the upper extremities (13%) [34]. In comparison, the most common (60.8%) site for muscle pain after COVID-19 infection in patients included in this study was the neck-back-waist region, followed by the calves (45.4%) and the arms (44.3%), while the most common (44.3%) site for the joint pain after COVID-19 infection was the shoulder followed by the knee (40.2%). The mean VAS score of these patients after COVID-19 infection was 6.9 ± 1.5 . In addition, an increase in pain intensity was detected in all 49 patients who had pain before the COVID-19 infection. Pain intensity was higher among female patients.

The prevalence of neuropathic pain in patients with COVID-19 infection reported in the literature varies between 0.4% and 25% [14,29,30,35,36], whereas the prevalence of paresthesia varies between 6% and 33% [15,37]. Miller et al. [36] detected peripheral nerve injury in the upper extremity in 15 of the 114 COVID-19 patients hospitalized in the prone position and treated in the intensive care unit for an average of 32.5 days. The electroneuromyographic assessment revealed neuropathic pain, and motor weakness in all the said 15 patients on, indicating high-grade nerve damage. In another study conducted with 135 COVID-19 patients, sensory impairment was detected in 20 (14.8%) patients, while 29 (25%) patients described numbness, burning, and tingling [38]. In a study conducted with 29 patients that were followed up for an average of 24 days in the intensive care unit for COVID-19 infection, the incidence of neuropathic pain within 4–6 weeks after discharge was reported as 21% [14]. In comparison,

in this study, sensory dysfunction was detected in 18 (18.6%) patients, neuropathic pain was detected in 41 (42.2%) patients based on the scores obtained from the DN-4 questionnaire, and 47 (48.5%) patients described numbness, burning, and tingling after the COVID-19 infection. Accordingly, it was determined that the pain before COVID-19 was associated with neuropathic pain.

It has been well-established in the literature that the quality of life of patients with COVID-19 is adversely affected [23,38–41]. A study reported that the quality of life was adversely affected even approximately seven months after the infection in 52.2% of COVID-19 patients. In another study, it was determined that all COVID-19 subgroups scored lower than the general population in the SF-36 survey in the 3rd month after discharge [42,43]. In a systematic review by Malik et al., including twelve studies that assessed the quality of life in COVID-19 patients using the European Quality of Life 5 Dimensions and 5 Levels Scale (EQ-5D-5L), the prevalence of mobility, personal care, usual quality, pain/discomfort, and anxiety/depression was 36%, 8%, 28%, 42%, and 38%, respectively [39]. In a study that assessed the quality of life in 323 healthcare workers using the Sheehan Disability Scale, it was determined that work life, social life, and life at home were adversely affected due to the ongoing symptoms of COVID-19 infection in 26%, 15%, and 12% of the workers, respectively [40]. Menges et al. reported that at least one dimension of quality of life, i.e., pain/discomfort in 39% and anxiety/depression in 31% of the patients, was adversely affected in 225 (52.2%) of the 431 patients after an average of 7.2 months after they were diagnosed with COVID-19 [42]. In another study, 110 COVID-19 patients scored significantly lower in all subscales of the SF-36 survey an average of 83 days after they were discharged from the hospital compared to the age-matched general population [43]. In a study that compared patients who received and did not receive corticosteroids during COVID-19 infection in terms of quality of life, it was determined that the patients who received corticosteroids obtained significantly better results from the 'physical pain' and 'mental health' subscales of the SF-36 survey and that corticosteroids reduced long-term symptoms and improved quality of life [39]. Rass et al. [38] determined using the SF-36 that the quality of life of 28 (31%) of the 90 COVID-19 patients deteriorated three months after COVID-19 infection. Of these 28 patients, six and 16 obtained significantly lower scores from the physical and mental components of SF-36, respectively. The remaining six received significantly lower scores from both mental

and physical components. In comparison, the patients included in this study scored significantly lower compared to the general Turkish population in all subscales of the SF-36 survey [25]. On the other hand, there was no significant difference between the subgroups created according to the place of treatment and age in terms of quality of life. In addition to the rate of hospitalization and steroid use, the vitality subscale score was higher among the patients with lung involvement. Additionally, female COVID-19 patients had significantly lower SF-36 physical function and pain subscale scores. Lastly, the presence of pain severity and neuropathic pain both before and after the COVID-19 infection were found to be associated with quality of life.

It is important to consider that pain may manifest in the musculoskeletal system following a COVID-19 infection, or pre-existing pain may intensify. Patients should be thoroughly evaluated in this regard. Seeking pain treatment in specialized clinics holds significance in improving patients' quality of life. The presence of neuropathic pain is valuable for clinicians and researchers as it aids in determining the neural involvement of the viral agent.

The relatively limited sample size is the primary limitation of this study. In addition, given that the study sample consisted only of patients who applied to the post-COVID clinic with at least one complaint of myalgia or arthralgia, the study results cannot be generalized to all post-acute COVID-19 patients. Lastly, the treatment and laboratory data of the patients, except for steroid use data as well as long-term musculoskeletal system and quality of life outcomes of the patients, were lacking.

5. Conclusion

Arthralgia, myalgia, and neuropathic pain, which negatively affect the quality of life, were detected in approximately one-third of the patients after COVID-19 infection. Therefore, it is recommended to query COVID-19 patients, especially those whose pain increased after COVID-19 infection, in terms of musculoskeletal symptoms and neuropathic pain in particular, in order to manage the respective symptoms and outcomes.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Informed consent

An informed consent form was included at the beginning of the survey, which presented the necessary information and recorded the participant's willingness to participate in the study.

Author contributions

All named authors have made an active contribution to the conception design, analysis, interpretation of the data, drafting of the paper and have critically reviewed its content. All authors read and approved the final version submitted for publication.

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