Arch Rheumatol 2024;39(3):436-446
doi: 10.46497/ArchRheumatol.2024.9990

ORIGINAL ARTICLE

Neuropathic component of chronic musculoskeletal pain in patients with post-COVID-19: A cross-sectional study

Sevgi Gümüş Atalay[1], Pınar Borman[1], Ayşegül Yaman[2], Evren Yaşar[1]

[1]*Department of Physical Medicine and Rehabilitation, University of Health Sciences, Ankara City Hospital, Ankara, Türkiye*
[2]*Department of Physical Medicine and Rehabilitation, University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Türkiye*

Correspondence: Sevgi Gümüş Atalay, MD.
E-mail: sevgigumusatalay@hotmail.com

Received: October 24, 2022
Accepted: December 17, 2023
Published online: August 26, 2024

Citation: Gümüş Atalay S, Borman P, Yaman A, Yaşar E. Neuropathic component of chronic musculoskeletal pain in patients with post-coronavirus disease 2019: A cross-sectional study. Arch Rheumatol 2024;39(3):436-446. doi: 10.46497/ArchRheumatol.2024.9990.

ABSTRACT

Objectives: This study aimed to evaluate the neuropathic component of chronic musculoskeletal pain in post-coronavirus disease 2019 (COVID-19) and examine the relationship between neuropathic pain and clinical and demographic characteristics.

Patients and methods: This cross-sectional study included 163 adult patients (85 females, 78 males; mean age: 41.7±4.3 years; range, 22 to 50 years) with post-COVID-19 musculoskeletal pain between February 1, 2021, and April 30, 2021. Demographic and clinical characteristics, including age, sex, affected site, duration, and severity of post-COVID-19 musculoskeletal pain using the Visual Analog Scale (VAS), as well as a neuropathic component of pain using the Leeds assessment of neuropathic symptoms and signs (LANSS), were collected. The most common post-COVID-19 symptoms, presence of hospitalization, and length of hospital stay during active COVID-19 infection were recorded from the patient records.

Results: The mean duration and severity of pain were 7.85±1.53 months and 5.09±1.95, respectively. Half of the patients were hospitalized, and the mean length of hospital stay was 12.15±18.06 days. The most common pain sites were upper and lower back pain, followed by leg and arm pain. A total of 92 (56.4%) patients had previously received pharmacological or nonpharmacological treatment for post-COVID-19 musculoskeletal pain. Based on the LANSS (scores >12), 31 (19%) patients had neuropathic pain. There was a significant correlation between the presence of neuropathic pain and pulmonary involvement/symptoms. The presence and length of hospital stay were correlated with LANNS scores ($p<0.05$). The frequency, LANSS scores, and VAS-pain scores of the patients with and without neuropathic pain were similar between male and female patients ($p>0.05$).

Conclusion: The neuropathic component of chronic musculoskeletal pain may be common, as one-fifth of our patients had neuropathic pain as assessed by the LANNS. Therefore, the awareness of post-COVID-19 chronic neuropathic musculoskeletal pain should be increased. We believe that focusing on the identification of pain phenotypes would provide adequate and tailored chronic neuropathic musculoskeletal pain management in the post-COVID-19 period.

Keywords: Musculoskeletal pain, neuropathic pain, post-COVID-19.

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization in March 2020. It mainly presents with respiratory system signs and symptoms and affects many systems and organs, including the nervous and musculoskeletal systems.[1,2]

The global pandemic has regressed, and it is no longer considered a public health emergency of international concern; however, new challenges resulting from the effect of the disease have become apparent in the post-COVID-19 period.[1,3] The National Institute for Health and Care Excellence (NICE) defines "post-COVID-19 syndrome" or "long COVID-19" as a set of persistent physical, cognitive, or psychological symptoms that continue for more than 12 weeks after illness that are not explained by an alternative diagnosis.[4] The post-COVID-19 period is associated with painful musculoskeletal symptoms, which include myalgia, arthralgia, abdominal pain, headache, and chest pain.[5,6] Myalgia, arthralgia, Guillain-Barré syndrome, as well as myositis and rhabdomyolysis secondary to

direct muscle involvement, lead to common pain symptoms in patients infected with COVID-19.[7]

Chronic pain is one of these emerging symptoms in the post-COVID-19 period. Chronic pain is divided into three main types: nociceptive, neuropathic, and nociplastic. Nociceptive pain is defined as the pain that develops with the stimulation of primary nociceptive nerve endings after tissue damage.[8] Neuropathic pain is the pain caused by a lesion or dysfunction of the nervous system, and nociplastic pain is the pain resulting from altered nociception without tissue or somatosensory damage that causes pain and peripheral nociceptor activation.[8]

COVID-19 has a special affinity for the neural tissue both involving central and peripheral nervous systems.[9] In the literature, there is a limited number of studies regarding chronic pain experienced after COVID-19, and most of these studies are case reports or studies carried out via telephone interviews. Therefore, there is still a need for studies using face-to-face interviews.

There are several reports concerning the manifestations of neuropathic pain among COVID-19 patients, showing itself through different mechanisms and leading to direct nervous system injury or overactivation of the immune system.[10-13] There are limited data on the clinical characteristics of chronic neuropathic pain in post-COVID-19 patients in the literature.[14,15] However, it is becoming increasingly apparent that many patients who recovered from the acute phase of COVID-19 infection have persistent musculoskeletal pain symptoms, but the neuropathic component of the chronic pain has not been investigated in detail.[7,14,16] Hence, in the present study, we aimed to evaluate the typical features of chronic musculoskeletal pain, assess the neuropathic component of pain in the post-COVID-19 period, and investigate the relationship between neuropathic pain and clinical and demographic characteristics.

PATIENTS AND METHODS

This single-center, cross-sectional study was conducted at the Ankara City Hospital, Department of Physical Medicine and Rehabilitation (PMR) between February 1, 2021, and April 30, 2021. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed.[17] Inclusion criteria were as follows: age between 18 and 50 years; confirmed diagnosis of COVID-19 by a positive real-time polymerase chain reaction (PCR) testing of nasopharyngeal and oropharyngeal specimens; individuals who recovered from SARS-CoV-2 infection and who were diagnosed by real-time reverse PCR testing of nasopharyngeal/oral swab samples; the existence of musculoskeletal pain for more than three months after the COVID-19; sufficient cognitive function to understand the questions and having completed the full questionnaire. Only the patients presenting to the outpatients clinics of the PMR department were included in the study. Exclusion criteria were as follows: a preexisting history of pain or any preexisting medical comorbidity (explaining the presence of pain symptomatology); having any chronic systemic, rheumatic, neurological, or musculoskeletal diseases (e.g., diabetes, autoimmune diseases, rheumatoid arthritis, malignancy, multiple sclerosis, Guillain-Barré syndrome, or neurodegenerative diseases); having vitamin deficiencies that may cause neuropathy or chronic neuropathic pain; having any clinical condition affecting the ability to complete self-administered instruments or any diagnosed psychological disease before or after the COVID-19 infection; having an active COVID-19 infection. Additionally, patients who had chronic musculoskeletal pain before COVID-19, those diagnosed with sarcopenia, cachexia, or myositis during or after COVID-19, and patients using drugs for chronic neuropathy were excluded from the study. Since neuropathic pain is common in patients with diabetes, they were also excluded. Patients over 50 years of age were not included due to the increased incidence of chronic diseases and comorbidities in this population. Of a total of 200 patients initially assessed for inclusion, 163 (85 females, 78 males; mean age: 41.7±4.3 years; range, 22 to 50 years) were eligible (Figure 1).

Data collection and definitions

Post-COVID-19 was defined as a set of persistent physical, cognitive, or psychological symptoms

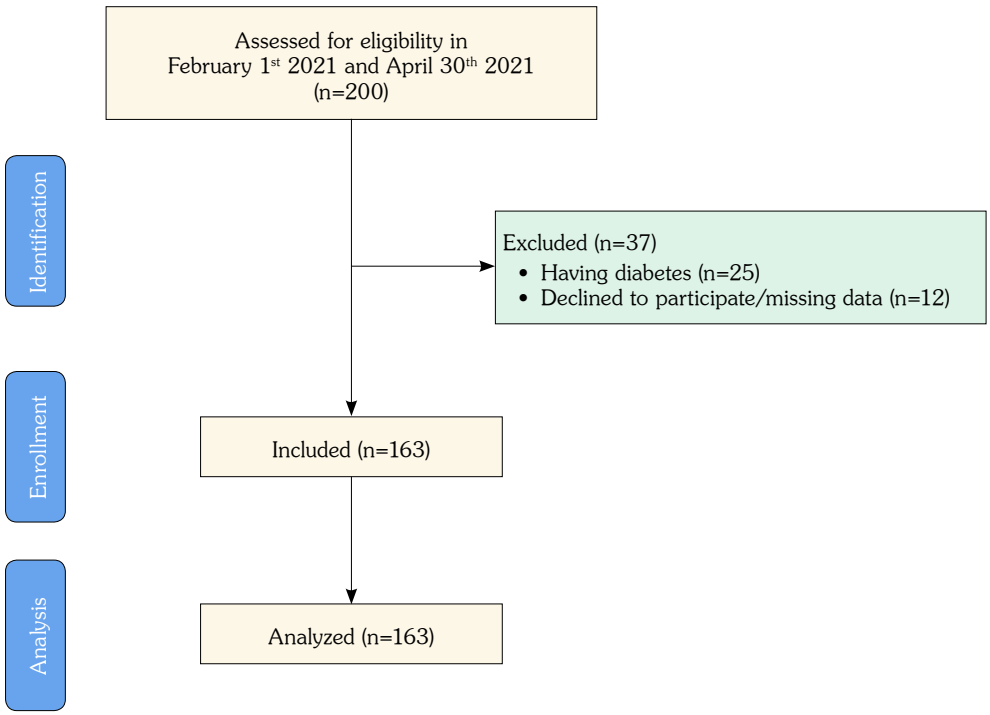

Figure 1. STROBE flow chart.
STROBE: Strengthening the reporting of observational studies in epidemiology.

that continue for more than 12 weeks after illness that are not explained by an alternative diagnosis in accordance with the NICE guidelines.[4]

Demographic data, clinical symptoms and findings, laboratory test results, and medical history and prognosis of the patients were retrieved from the medical records. A comprehensive questionnaire and patient records were used for the collection of data. All patients were questioned whether they experienced unexplained prolonged musculoskeletal pain as part of the post-COVID-19 syndrome, which they described as permanent despite their recovery from COVID-19. An evaluation was made for possible neuropathic pain based on the International Association for the Study of Pain grading system.[18]

Data regarding the period of COVID-19 infection, including the presence of hospitalization for COVID-19, length of hospital stay, chief COVID-19 symptoms during the infection (e.g., pulmonary involvement, chest pain, smell and taste impairment, dyspnea, cough, walking difficulty, and immobilization), and comorbidities were also recorded.

All patients were examined in detail by the same physicians. Laboratory tests for diagnosis and differential diagnosis included muscle enzymes and kidney and liver function tests, and the results were recorded for each patient before the enrollment. Clinical features comprising the site and duration of musculoskeletal pain, pain severity, treatment for post-COVID-19 chronic pain (pharmacological/nonpharmacological), and the number of pain medications (analgesic/nonsteroidal anti-inflammatory drugs) used for post-COVID-19 pain were assessed.

Assessment tools

Pain severity from the most painful musculoskeletal area was assessed using the Visual Analog Scale (VAS). Patients were asked how much pain they felt (at the time of measurement), where 0 indicated no pain and 10 indicated the most severe pain.[19]

The neuropathic component of musculoskeletal pain was evaluated using the Leeds assessment of neuropathic symptoms and signs (LANSS) questionnaire.[20] LANSS is a simple, time-saving, and self-administered

scale that has a specificity of 85% and a sensitivity of 80%. The first five questions assess the symptoms of pain, while the last two questions include the clinical examination performed by the patients themselves. The answers to the questions are yes or no. Each question has a different score. The total score on the scale is 24. A total score of 12 or higher

Table 1. The demographic variables and characteristics of patients with chronic musculoskeletal pain in the post-COVID-19 period (n=163)

	n	%	Mean±SD	Min-Max
Age (year)			41.7±4.3	22-50
Sex				
Female	85	52.1		
Male	78	47.9		
Body mass index (kg/m^2)			27.69±4.34	17.26-46.06
Marital status				
Married	140	85.9		
Single	23	14.1		
Education				
Primary	62	38		
Secondary-lycee	36	22.1		
University	65	39.9		
Profession				
Employee	23	14.1		
Unemployed	11	6.7		
Housewife	46	28.2		
Officer	48	29.4		
Retired	2	1.22		
Other	13	8		
Smoking				
Yes	17	10.4		
No	115	70.6		
Ex smoker	31	19		
Living with				
Partner/spouse/family	148	90.8		
No one/live alone	15	9.2		
Location of chronic musculoskeletal pain				
Upper back	67	41.1		
Low-back	49	30.1		
Leg/foot	46	28.2		
Arm/hand	39	24.5		
Neck	16	9.8		
Knee	23	14.1		
Shoulder	18	11		
Duration of pain (month)			7.85±1.53	6-18
Visual Analog Scale			5.09±1.95	1-10
Treatment for post-COVID musculoskeletal pain				
No	71	43.6		
Yes	92	56.4		
Number of drugs used for treatment COVID-19				
0	83	50.9		
1	38	23.3		
2	17	10.4		
3	13	8		
4	10	6.1		
5	2	1.2		
LANSS			5.71±5.44	0-19
Neuropathic pain determined by LANSS.				
Yes	31	19		
No	132	81		

COVID-19: Coronavirus disease 2019; SD: Standard deviation; LANSS: Leeds Assessment of Neuropathic Symptoms and Sign.

indicates neuropathic pain. Validation and reliability studies of the scale were carried out by Unal-Cevik et al.[21] in the Turkish population.

Statistical analysis

Study power and sample size calculation were performed using the G*Power version 3.1.9.2 (Franz Faul, Universitat Kiel, Kiel, Germany) based on 100% study power with *post hoc* power analysis and 3.22 effect size (d) in terms of neuropathic pain scores of groups with and without neuropathic pain (α=0.05; n1=31; n2=131).

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented as mean ± standard deviation (SD) or number and frequency, where applicable. The Kolmogorov-Smirnov test was used to indicate normal distribution. The chi-square test was used to analyze differences in categorical variables between the groups. The differences between continuous variables of two independent groups were assessed by the independent samples t-test. The Spearman correlation analysis was used to evaluate the correlation between neuropathic pain scores and clinical parameters. A linear regression analysis was used to examine the relationship between the LANSS scores, walking difficulty/immobilization, and length of hospital stays. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

The mean body mass index was 27.69±4.34 kg/m^2. The majority of the participants (85.9%) were married, living with their

Table 2. Clinical characteristics during the COVID-19 infection (n=163)

	n	%	Mean±SD	Min-Max
Hospitalization due to COVID-19				
Yes	80	49.1		
No	83	50.9		
Duration of hospitalization (days)			12.15±18.06	0-41
Smell and taste impairment				
Yes	135	82.8		
No	28	17.2		
Pulmonary involvement				
Yes	104	63.8		
No	59	36.2		
Chest pain				
Yes	65	39.9		
No	98	60.1		
Dyspnea				
Yes	67	41.1		
No	96	58.9		
Cough				
Yes	41	25.2		
No	122	74.8		
Walking difficulty/immobilization				
Yes	52	31.9		
No	111	68.1		
Chronic disease				
No	111	69.9		
Hypertension	42	25.7		
Coronary artery disease	10	6.1		
Musculoskeletal involvement during COVID-19				
Myalgia	72	44.2		
Arthralgia	45	27.6		
Guillain-Barre syndrome	3	1.84		
Acute cerebrovascular disease	1	0.61		

COVID-19: Coronavirus disease 2019; SD: Standard deviation.

families, and 39.9% graduated from high school or university. The majority of the patients were public servants (29.4%), followed by housewives (28.2%). Most of the patients (70.6%) were nonsmokers. Demographic and clinical characteristics of the patients are shown in Table 1.

The most common chronic musculoskeletal pain sites were the upper back (41.1%) and lower back (30.1%), followed by the leg (28.2%) and arm (24.5%). The mean duration of chronic pain was 7.85±1.53 months, and the mean VAS score was 5.09±1.95. More than half of the participants (56.4%) were given pharmacological treatment for post-COVID-19 musculoskeletal pain, while 43.6% of the patients did not receive any pharmacological treatment. The pain was defined as neuropathic pain in 31 (19%) patients according to the LANSS scores (≥12). Most of the patients (50.9%) received nonpharmacological treatment during the COVID-19 period. Those who received medical treatment used hydroxychloroquine (23.3%), favipiravir (10.4%), azithromycin (8%), steroids (6.1%), and tocilizumab (1.2%; Table 1).

Table 3. The demographic and clinical variables regarding presence of neuropathic pain assessed by LANNS

	Neuropathic pain (+) (n=31)		Neuropathic pain (–) (n=132)		
	n	Mean±SD	n	Mean±SD	*p*
Age (year)		43.4±13.9		41.2±14.4	0.446
Sex					0.234
Female	13		72		
Male	18		60		
Body Mass Index (kg/m²)		28.2±4.4		27.6±4.3	0.494
Education					0.532
Primary	13		49		
Secondary-lycee	9		27		
University	9		56		
Smoking					0.713
Yes	4		13		
No	20		95		
Exsmoker	7		24		
Hospitalization due to COVID-19					**0.005**
Yes	23		60		
No	8		72		
Duration of hospitalization (day)		16.5±17.2		8.8±13.2	**0.049**
Smell and taste impairment					0.111
Yes	29		106		
No	2		26		
Pulmonary involvement					**0.037**
Yes	25		79		
No	6		53		
Chest pain					**0.008**
Yes	19		46		
No	12		86		
Dyspnea					**0.042**
Yes	18		49		
No	13		83		
Cough					1.000
Yes	8		33		
No	23		99		
Walking difficulty/immobilization					**0.005**
Yes	17		35		
No	14		97		
Visual Analog Scale		5.5±1.9		5±1.9	0.215
LANSS scores		14.4+1.8		3.66+3.7	<0.001

LANSS: Leeds assessment of neuropathic symptoms and sign; COVID-19: Coronavirus disease 2019.

Half of the participants were hospitalized, and the mean length of hospital stay was 12.15±18.06 days. The rate of COVID-19 symptoms during the active infection was 82.8% for smell and taste dysfunction, 63.8% for pulmonary involvement, 39.9% for chest pain, 41.1% for dyspnea, 25.2% for cough, and 31.9% for walking difficulty/immobilization. While 69.9% of the patients did not have a chronic disease, 25.7% had hypertension, and 6.1% had coronary artery disease. The rate of musculoskeletal manifestations during COVID-19 was 44.2% for myalgia and 27.6% for arthralgia. Of the patients, 1.8% had Guillain-Barré syndrome, and 0.6% had acute cerebrovascular disease, which improved completely (Table 2).

Demographic and clinical characteristics in patients with and without chronic neuropathic pain are shown in Table 3. The rate of pulmonary involvement, pulmonary symptoms (dyspnea), walking difficulty/immobilization, hospitalization, and patients with chronic neuropathic pain had significantly longer hospital stays. Demographic variables and VAS-pain scores were comparable between the patients with and without chronic neuropathic pain.

We found a significant correlation between the presence of neuropathic pain, pulmonary involvement, pulmonary symptoms (dyspnea, chest pain), and walking difficulty/immobilization (Table 4). In addition, there was a correlation between the LANNS scores and hospitalization and length of hospital stay. According to the results of linear regression analysis, the length of hospital stay ($r=0.370$, $p<0.001$) and walking difficulty/immobilization ($r=-0.188$, $p=0.016$) were found to be effective on the LANSS score. Of these two variables, the length of hospital stay was more correlated with the LANSS score. There was a positive and statistically significant linear relationship between the length of hospital stay and the LANNS score. The number of patients with and without neuropathic pain, the mean LANSS scores, pain duration, and pain severity based on the VAS scores were comparable between male and female patients (Table 5).

Table 4. The correlation coefficients between the mean LANSS and VAS values and the demographic and clinical variables

	LANSS	VAS
Age	NS	NS
Sex	NS	NS
Body mass index	NS	NS
Education	NS	NS
Smoking	NS	NS
Hospitalization due to COVID-19 r *p*	 0.250 0.001	NS
Duration of hospitalization r *p*	 0.370 0.000	<0.001
Smell and taste impairment	NS	NS
Pulmonary involvement r *p*	 –0.188 0.016	NS
Chest pain	NS	NS
Dyspnea r *p*	 –0.184 0.019	NS
Cough	NS	NS
Walking difficulty/immobilization r *p*	 –0.311 0.000	<0.001
Duration of pain	NS	NS

LANSS: Leeds assessment of neuropathic symptoms and sign; VAS: Visual analog score; NS: Not significant.

DISCUSSION

In the current study, we evaluated the typical features of chronic musculoskeletal pain and assessed the neuropathic component of pain in the post-COVID-19 period. The results showed that 19% of the post-COVID-19 patients with chronic musculoskeletal pain had a neuropathic component, as evidenced by the LANSS scores. Clinical characteristics with the presence of neuropathic pain were identified as hospitalization, length of hospital stay, pulmonary involvement, symptoms, and walking difficulty/immobilization during the COVID-19 period. Neither any demographic characteristics nor the severity of chronic pain was found to be related to the presence of neuropathic pain.

Many musculoskeletal signs and symptoms are described during the COVID-19 infection. Currently, it is recognized that COVID-19 is linked to painful symptoms, such as myalgia, arthralgia, abdominal pain, headache, and chest

Table 5. The demographic and clinical properties and pain characteristics in regard to sex

	Female (n=85)		Male (n=78)		
	n	Mean±SD	n	Mean±SD	*p*
Age (year)		38.9±13.3		44.7±14.2	**0.010**
Body mass index (kg/m^2)		28.3±5.3		27±2.9	0.066
Education					**0.005**
Primary	42		20		
Secondary-lycee	11		25		
University	32		33		
Smoking					**<0.001**
Yes	3		14		
No	79		36		
Exsmoker	3		28		
Smell and taste impairment					0.838
Yes	71		64		
No	14		14		
Pulmonary involvement					**0.009**
Yes	46		58		
No	39		20		
Walking difficulty/immobilization					0.182
Yes	23		29		
No	62		49		
Chest pain					**0.037**
Yes	27		38		
No	58		40		
Dyspnea					0.633
Yes	33		34		
No	52		44		
Cough					0.371
Yes	24		17		
No	61		61		
Hospitalization due to COVID-19					**0.005**
Yes	34		49		
No	51		29		
Duration of hospitalization (day)		7.6±11.5		12.9±10.7	0.049
Duration of musculoskeletal pain (month)		2.9±1.4		2.8±1.7	0.916
Number of drugs used for post-COVID-19 pain		2.1±1.1		2.3±1.3	0.051
Visual analog scale		5.1±2.1		5.1±1.8	0.989
LANSS		5.04±4.9		6.4±5.9	0.107
Neuropathic pain determined by LANSS					0.234
Yes	13		18		
No	72		60		

SD: Standard deviation; LANSS: Leeds assessment of neuropathic symptoms and sign.

pain.[5] Among those reported are back and neck pains, myalgia, arthralgia, back pain, fatigue, sarcopenia, stroke, Guillain-Barré syndrome, and skeletal muscle injury.[12,15,22,23]

Myalgia has been commonly documented in COVID-19 patients, with a prevalence rate in large cohort studies ranging from 11 to 50%.[7] Among 25% of the patients infected with COVID-19, myalgia accompanied by fatigue was reported. Although myalgia is a typical symptom, the exact mechanisms of muscle involvement in COVID-19 patients have not been elucidated.[24] The pathophysiology of myalgia has been proposed to involve hematogenous spread and direct invasion of skeletal muscle by SARS-CoV-2 via the angiotensin-converting enzyme 2 receptor.[2,7,11] Arthralgia has also been reported; however, since arthralgia is often

combined with myalgia, it is difficult to specifically define the prevalence of arthralgia.[15,16,20] In a study, arthralgia, which is considered a separate symptom, was identified as a symptom of COVID-19, occurring in 2.5% of patients.[25] In our study, myalgia was present in nearly half of the patients, while arthralgia was a complaint in one-third of the patients, consistent with previous studies.

The spread curve of COVID-19 appears to be flattening worldwide, and special care is mostly needed for post-COVID-19 symptoms and complications.[4] Most of the patients completely recover from the disease, but some of them may have prolonged signs and symptoms, including musculoskeletal pain. Concomitant and postinfectious neuropathic pain has been reported by several authors separately or combined with other conditions such as Guillain-Barré syndrome, post-stroke pain, and myelitis.[7,9,14,15,26] Previous studies have indicated that 2.3% of COVID-19 patients experienced neuropathic pain, which was related to respiratory compromise.[9,25] In our study, we observed neuropathic pain in 19% of the patients based on the LANSS screening questionnaire. However, different from previous studies, this finding indicates the neuropathic component of chronic musculoskeletal pain, which was not addressed in detail in the literature. Previous reports have demonstrated that the most common sites of post-COVID-19 neuropathic pain are the arms, legs, hands, and feet, indicating a high level of VAS-pain.[10,13,16] Our results suggest that the most common sites of chronic musculoskeletal pain are the upper and lower back, as well as legs and arms, consistent with a previous study.[14]

The possibility of more severe COVID-19 or newly developed neuropathic pain following COVID-19 has not been well understood. The related factors with post-COVID-19 pain have been reported as depression, the severity of COVID-19, and azithromycin used in the active infection period.[16] Our results are consistent with preliminary data that the neuropathic pain is related to the presence and length of hospital stay and presence of pulmonary involvement and symptoms during the active infection.

Furthermore, chronic pain has been shown to be related to psychological stressors, viral infection itself, or the consequence of intensive care unit, which may present as local or widespread pain. Pain may have a link to psychological factors and mental health conditions. Patients with preexisting multimorbidity have been reported to be at a higher risk for chronic pain.[5] In our study, we were unable to evaluate depression symptoms; however, we excluded those with a history or presence of psychological diseases or using related drugs.

In the present study, a few patients had stroke and Guillain-Barré syndrome, but all of them recovered without any sequelae. Therefore, the neuropathic component of pain seems to be due to COVID-19 itself and the severity of the active disease. As it is unclear whether persistent musculoskeletal pain is a part of long COVID-19, future research may be necessary to elucidate the etiology of prolonged musculoskeletal pain.

Many drugs, including steroids, hydroxychloroquine, chloroquine, azithromycin, remdesivir, favipiravir, lopinavir/ritonavir, ivermectin, and tocilizumab, have been used in the treatment of COVID-19 patients. Side effects of these drugs have mostly been observed in the hematopoietic system, followed by the cardiovascular system and the gastrointestinal system. In addition, dizziness, headache, and thrombocytopenia are the most common diseases due to multiple use of drugs. Although chronic pain has been reported as a result of the use of these treatments, particularly on steroids, no information has been found in the current literature on neuropathic pain.[27] Most of our patients did not receive treatment for COVID-19. Those who received treatment used hydroxychloroquine, azithromycin, steroids, favipiravir, and tocilizumab.

The prevalence and clinical characteristics of chronic musculoskeletal neuropathic pain in post-COVID-19 are not well-documented.[13,16] We believe that our results would provide additional contribution to the literature regarding the incidence of neuropathic pain in patients with chronic musculoskeletal symptoms after COVID-19 infection. Considering the importance of chronic neuropathic pain, which needs to be distinguished from other components of chronic pain, clinicians should be vigilant for chronic neuropathic musculoskeletal pain to ensure adequate pain management in the post-COVID-19 period.

This study has some limitations. First, we were unable to use a scale to evaluate psychological status of the patients affected by pain sensation. However, none of our patients had psychological disease before or after COVID-19, and none of them were using drugs for the psychological status. Another limitation was the lack of electrophysiological tests for neuropathy. However, the presence of comorbidities that may be related to neuropathic conditions was ruled out based on the medical history, medical files, and clinical findings, including detailed physical examination findings and history of drugs used. In addition, previous case reports regarding post-COVID-19 neuropathic pain showed no clinical or electrophysiological evidence of large fiber involvement.[14] Third, we were unable to evaluate sleep patterns of the patients, although sleep disorders have been shown to be strongly associated with common pain disorders. On the other hand, the main strengths of the current study are that it was the first study to assess the neuropathic component of chronic musculoskeletal pain as evidenced by the LANSS and the relatively large sample size compared to previous studies. Furthermore, the nondivergent sampling strategy (cases only from the PMR outpatient clinic) may have provided additional value.

In conclusion, neuropathic pain may be common in post-COVID-19, which may be underrecognized and possibly undertreated. Clinicians should be mindful of post-COVID-19 chronic neuropathic pain and recognize the relevance of identifying the pain phenotypes. We believe that our results could provide guidance for clinicians to provide adequate and tailored chronic neuropathic musculoskeletal pain management in the post-COVID-19 period, particularly for patients hospitalized, having pulmonary involvement, and walking difficulties in the active infection period. Further multicenter, large-scale, prospective studies are warranted to address the pathophysiological mechanism of post-COVID-19 chronic neuropathic musculoskeletal pain.

Ethics Committee Approval: The study protocol was approved by the Ankara City Hospital Ethics Committee (date: 10.02.2021, no: E2-21-72). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization and design: P.B., S.GA.; Control/supervision, critical review: E.Y., A.Y., S.GA; Data collection and/or processing, writing the article: P.B., S.GA; Analysis and/or interpretation: A.Y., P.B., S.GA E.Y.; Literature review: P.B., S.GA; E.Y., A.Y.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Seyed Hosseini E, Riahi Kashani N, Nikzad H, Azadbakht J, Hassani Bafrani H, Haddad Kashani H. The novel coronavirus Disease-2019 (COVID-19): Mechanism of action, detection and recent therapeutic strategies. Virology 2020;551:1-9. doi: 10.1016/j.virol.2020.08.011.
2. Correia AO, Feitosa PWG, Moreira JLS, Nogueira SÁR, Fonseca RB, Nobre MEP. Neurological manifestations of COVID-19 and other coronaviruses: A systematic review. Neurol Psychiatry Brain Res 2020;37:27-32. doi: 10.1016/j.npbr.2020.05.008.
3. Novak P, Mukerji SS, Alabsi HS, Systrom D, Marciano SP, Felsenstein D, et al. Multisystem involvement in post-acute sequelae of Coronavirus Disease 19. Ann Neurol 2022;91:367-79. doi: 10.1002/ana.26286.
4. Venkatesan P. NICE guideline on long COVID. Lancet Respir Med 2021;9:129. doi: 10.1016/S2213-2600(21)00031-X.
5. Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: Implications for rehabilitation. Br J Anaesth 2020;125:436-40. doi: 10.1016/j.bja.2020.05.021.
6. Kubota GT, Moisset X. What lies behind and beyond acute COVID-19 pain? Eur J Pain 2022;26:282-3. doi: 10.1002/ejp.1889.
7. Paliwal VK, Garg RK, Gupta A, Tejan N. Neuromuscular presentations in patients with COVID-19. Neurol Sci 2020;41:3039-56. doi: 10.1007/s10072-020-04708-8.
8. Trouvin AP, Perrot S. New concepts of pain. Best Pract Res Clin Rheumatol 2019;33:101415. doi: 10.1016/j.berh.2019.04.007.
9. Aksan F, Nelson EA, Swedish KA. A COVID-19 patient with intense burning pain. J Neurovirol 2020;26:800-1. doi: 10.1007/s13365-020-00887-4.

10. Widyadharma IPE, Sari NNSP, Pradnyaswari KE, Yuwana KT, Adikarya IPGD, Tertia C, et al. Pain as clinical manifestations of COVID-19 infection and its management in the pandemic era: A literature review. Egypt J Neurol Psychiatr Neurosurg 2020;56:121. doi: 10.1186/s41983-020-00258-0.
11. D V, Sharma A, Kumar A, Flora SJS. Neurological manifestations in COVID-19 patients: A meta-analysis. ACS Chem Neurosci 2021;12:2776-97. doi: 10.1021/acschemneuro.1c00353.
12. Jena D, Sahoo J, Barman A, Dalai A, Patel S. Neuropathic pain in hospitalized patients with COVID-19: A prospective case series. Arch Rehabil Res Clin Transl 2022;4:100188. doi: 10.1016/j.arrct.2022.100188.
13. Attal N, Martinez V, Bouhassira D. Potential for increased prevalence of neuropathic pain after the COVID-19 pandemic. Pain Rep 2021;6:e884. doi: 10.1097/PR9.0000000000000884.
14. McWilliam M, Samuel M, Alkufri FH. Neuropathic pain post-COVID-19: A case report. BMJ Case Rep 2021;14:e243459. doi: 10.1136/bcr-2021-243459.
15. Bittencourt JV, Reis FJJ, Nogueira LAC. Pain in COVID-19 patients: A call to action for physical therapists to provide pain management after an episode of COVID-19. Braz J Phys Ther 2021;25:367-8. doi: 10.1016/j.bjpt.2021.06.003.
16. Magdy R, Eid RA, Fathy W, Abdel-Aziz MM, Ibrahim RE, Yehia A, et al. Characteristics and risk factors of persistent neuropathic pain in recovered COVID-19 patients. Pain Med 2022;23:774-81. doi: 10.1093/pm/pnab341.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Int J Surg 2014;12:1495-9. doi: 10.1016/j.ijsu.2014.07.013.
18. Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, et al. Neuropathic pain: An updated grading system for research and clinical practice. Pain 2016;157:1599-606. doi: 10.1097/j.pain.0000000000000492.
19. Turk D, Melzack R, editors. Handbook of pain assessment. 2nd ed. New York: The Guilford Press; 1992.
20. Bennett M. The LANSS pain scale: The Leeds assessment of neuropathic symptoms and signs. Pain 2001;92:147-57. doi: 10.1016/s0304-3959(00)00482-6.
21. Unal-Cevik I, Sarioglu-Ay S, Evcik D. A comparison of the DN4 and LANSS questionnaires in the assessment of neuropathic pain: Validity and reliability of the Turkish version of DN4. J Pain 2010;11:1129-35. doi: 10.1016/j.jpain.2010.02.003.
22. Meyer-Frießem CH, Gierthmühlen J, Baron R, Sommer C, Üçeyler N, Enax-Krumova EK. Pain during and after COVID-19 in Germany and worldwide: A narrative review of current knowledge. Pain Rep 2021;6:e893. doi: 10.1097/PR9.0000000000000893.
23. McFarland AJ, Yousuf MS, Shiers S, Price TJ. Neurobiology of SARS-CoV-2 interactions with the peripheral nervous system: Implications for COVID-19 and pain. Pain Rep 2021;6:e885. doi: 10.1097/PR9.0000000000000885.
24. Ciaffi J, Meliconi R, Ruscitti P, Berardicurti O, Giacomelli R, Ursini F. Rheumatic manifestations of COVID-19: A systematic review and meta-analysis. BMC Rheumatol 2020;4:65. doi: 10.1186/s41927-020-00165-0.
25. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of hospitalized patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77:683-90. doi: 10.1001/jamaneurol.2020.1127.
26. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barré syndrome associated with SARS-CoV-2. N Engl J Med 2020;382:2574-6. doi: 10.1056/NEJMc2009191.
27. Kumar D, Trivedi N. Disease-drug and drug-drug interaction in COVID-19: Risk and assessment. Biomed Pharmacother 2021;139:111642. doi: 10.1016/j.biopha.2021.111642.