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Post-COVID-19 pain syndrome: a descriptive study in Turkish population

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Background: The new type of corona virus has a wide range of symptoms. Some people who have COVID-19 can experience long-term effects from their infection, known as post-COVID conditions. The authors aimed to investigate prolonged musculoskeletal pain as a symptom of the post-COVID-19 condition.
Methods: This is a descriptive study on the patients who were diagnosed with COVID-19 in a university hospital, between March 2020 and March 2021. Patient records and an extensive questionnaire were used to obtain relevant demographic and clinical characteristics, including hospitalization history, comorbidities, smoking history, duration of the pain, the area of pain, and the presence of accompanying neuropathic symptoms.
Results: Of the diagnosed patients, 501 agreed to participate in the study. Among the participants, 318 had musculoskeletal pain during COVID-19 infection, and 69 of them reported prolonged pain symptoms as part of their a post-COVID condition which could not be attributed to any other cause. The mean duration of pain was 4.38 ± 1.73 months, and the mean pain level was 7.2 ± 4.3. Neuropathic pain symptoms such as burning sensation (n = 16, 23.2%), numbness (n = 15, 21.7%), tingling (n = 10, 14.5%), stinging (n = 4, 5.8%), freezing (n = 1, 1.4%) were accompanied in patients with prolonged musculoskeletal pain.
Conclusions: Patients with COVID-19 may develop prolonged musculoskeletal pain. In some patients, neuropathic pain accompanies it. Awareness of prolonged post-COVID-19 pain is crucial for its early detection and management.

Key Words: Chronic Pain; Complications; COVID-19; Musculoskeletal Pain; Neuralgia; Post-Acute COVID-19 Syndrome; Post-Infectious Disorders; Survey and Questionnaires.

INTRODUCTION

A new type of coronavirus disease, which was first detected in the city of Wuhan in China's Hubei province and named as COVID-19, spread rapidly all over the world [1]. The World Health Organization declared a pandemic in March 2020, reporting that there were more than 118,000 patients with COVID-19 in 114 countries and that the disease had spread worldwide [2]. Although the spread of the virus and its mortality have decreased with the discovery and application of vaccines, the pandemic process continues.

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The Guideline published by the National Institute for Health and Care Excellence (NICE) proposes the following classification: acute COVID-19 (symptoms for up to 4 weeks), ongoing symptomatic COVID-19 (symptoms from 4 to 12 weeks), and post-COVID (symptoms developed during or after an infection and continuing for more than 12 weeks) [3]. The NICE Guideline has also defined 'long COVID' as signs and symptoms that developed during or following COVID-19 and which continue for more than 4 weeks but are not explained by alternative diagnoses; and that term would comprise both subgroups, ongoing symptomatic COVID and post-COVID syndrome [3].

Post-COVID syndrome is thought to be due to a persistent hyperinflammatory process attributable to several mechanisms such as continued viral activity in the host viral reservoir, long-term consequences of tissue tropism, and inadequate antibody response [4–6]. Neuromuscular syndromes that develop after COVID-19 infection are also a part of this process. Regional pain seen after COVID-19 infection may develop due to the direct invasion of nerve and muscle tissue by various mechanisms [7–10].

Acute and chronic pain are different clinical entities. Acute pain is provoked by a specific condition, and serves a useful biologic purpose, while chronic pain, in contrast, has been considered a disease state [11]. The transition from acute to chronic pain appears to occur in discrete pathophysiological steps [11–13]. Chronic pain is defined as pain that persists past the normal healing time and hence lacks the acute warning function of physiological nociception; usually lasting or recurring for more than 3 months [12]. Chronic pain creates an important personal and socioeconomic burden due to the disability, emotional imbalances, and social loss it causes. Therefore, early diagnosis and treatment is critically important. Chronic pain is divided into three types: nociceptive, neuropathic, and nociplastic pain. Pain that develops with the stimulation of primary nociceptive nerve endings after tissue damage is called nociceptive pain, while pain caused by lesion or dysfunction of the nervous system is neuropathic pain, and pain resulting from altered nociception without tissue or somatosensory damage causing peripheral nociceptor activation is regarded as nociplastic pain [13].

In this study, the authors aimed to investigate prolonged musculoskeletal pain as a symptom of post-COVID-19 condition which could not be attributed to any other cause, in accordance with the definition of long COVID in the NICE Guideline. The main goal is to describe the characteristics of patients with prolonged pain after COVID-19 and to raise awareness among clinicians.

MATERIALS AND METHODS

1. Sample

This study was carried out on patients with a diagnosis of COVID-19 at Istanbul Medipol University Esenler Hospital during the pandemic period, between March 2020 and March 2021.

Inclusion criteria were a confirmed diagnosis of COVID-19 (positive diagnosis of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] with real-time reverse transcription polymerase chain reaction and/or positive SARS-CoV-2 antibodies testing), age ≥ 18 years, having verbal and written consent. Exclusion criteria were age < 18 years, and/or having speech disability.

This study was approved by the Istanbul Medipol University Faculty of Medicine Clinical Research Ethics Committee (Approval number: E-10840098-772.02-2620). Participants were informed about the study by telephone and their verbal and written consent was obtained.

2. Survey instrument

Patient records and an extensive questionnaire were used to obtain relevant demographic and clinical characteristics, including hospitalization history, comorbidities, smoking history, duration of the pain, the area of pain, and the presence of concomitant neuropathic symptoms. All participants were questioned as to whether they had prolonged musculoskeletal pain that the authors defined as persistent pain, despite recovery from COVID-19, as part of their a post-COVID syndrome which could neither be attributed to any other cause nor explained by alternative diagnoses. To determine the level of pain, the numeric visual analog scale (VAS) was used. Each patient was asked to indicate his/her overall perceived pain intensity along a 10 cm horizontal line. This rating provides a ten-point scale for the subjective report of pain [14].

Primary outcomes: incidence and duration of prolonged musculoskeletal pain as part of a post-COVID syndrome.

Secondary outcomes: Type and severity of pain (mean VAS scores) in patients with prolonged pain after COVID-19 and incidence of concomitant neuropathic pain with prolonged pain after COVID-19.

3. Statistical analysis

Quantitative data was analyzed using central tendency and measures of variability, mean and standard deviation. Fisher's exact test and the chi-squared test were used to identify differences in ratios or relationships between categorical variables when the compared groups are in-

dependent and not correlated. The Mann–Whitney *U*-test was used to compare differences between two independent groups when the dependent variable was either ordinal or continuous, but not normally distributed. Statistical significance was determined as $P < 0.05$. Statistical analyzes were provided with the IBM SPSS version 21.0 (IBM Co., Armonk, NY) package program.

RESULTS

A total of 756 patients were diagnosed with COVID-19 in our hospital, and 631 of them could be contacted by phone. Among these, 501 agreed to participate in the study. The mean age of these participants was 39.0 ± 14.5 years; 257 (51.3%) of the participants were male and 244 (48.7%) were female. Among the participants, 318 of them had musculoskeletal pain during COVID-19 infection, and 69 of them reported prolonged pain symptoms as part of their post-COVID experience, which could neither be attributed to any other cause nor explained by alternative diagnoses (**Fig. 1**).

There was no significant difference between the group developing prolonged pain and the other group in terms of demographic data (**Table 1**). The mean duration of pain was 4.38 ± 1.73 months, and the mean VAS score was 7.2 ± 4.3. Pain was mostly reported in the neck, neck/arm, back, and waist regions. Of those with prolonged pain, 29 (42.0%) were male and 40 (58.0%) were female, with no significant differences being found between the sexes. The incidence of overall comorbidity or the presence of one or more additional conditions such as asthma, hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, and epilepsy co-occurring with the primary condition (COVID-19) was higher in the patients with prolonged pain ($P = 0.017$). There were no patients with a history of psychiatric illness in either group.

During the acute phase of the disease, loss of taste and smell, and headache symptoms were more common during COVID-19 infection (**Table 2**) ($P = 0.017$, $P = 0.003$). Incidence of fatigue was higher in patients with prolonged pain ($P = 0.021$). Incidence of concomitant neuropathic pain symptoms such as burning sensation, numbness, tingling, stinging, and freezing sensation were also observed to be higher in patients with prolonged pain. The rate of regional pain accompanying at least one neuropathic pain symptom was 29.0% (n = 20). Considering all participants,

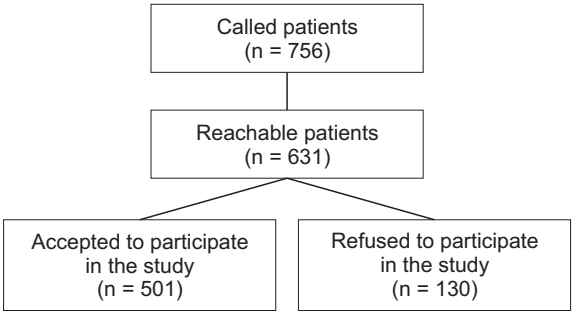

Fig. 1. Study flowchart.

Table 2. Comparison of the symptoms seen during COVID-19 infection between the patients with and without prolonged pain

Symptoms	With prolonged pain (n = 69)	Without prolonged pain (n = 432)	*P* value
Loss of taste and smell	52 (75.4)	257 (59.5)	0.017[a]
Fever	25 (36.2)	174 (40.3)	0.613
Cough	38 (55.1)	192 (44.4)	0.130
Fatigue	52 (75.4)	259 (60.0)	0.021[a]
Muscle pain	62 (89.9)	256 (59.3)	< 0.001[b]
Headache	50 (72.5)	227 (52.5)	0.003[a]

Values are presented as number (%).
[a]Pearson chi-squared test.
[b]Fisher's exact test.

Table 1. Demographic characteristics of patients with and without prolonged pain

Characteristics of patients	With prolonged pain (n = 69)	Without prolonged pain (n = 432)	*P* value
Age (yr)	41.4 ± 12.3	38.6 ± 14.8	0.090
Sex			
Male	29 (42.0)	228 (52.8)	0.126
Female	40 (58.0)	204 (47.2)	
Body mass index (kg/m^2)	28.1 ± 5.3	26.9 ± 4.9	0.084
Height (cm)	168.0 ± 9.4	169.1 ± 9.1	0.202
Weight (kg)	79.2 ± 16.2	77.2 ± 16.1	0.432
Hospitalization	6 (8.7)	24 (5.6)	0.283
Smoking	14 (20.3)	90 (20.8)	> 0.999
Comorbidity[b]	29 (42.0)	117 (27.1)	0.017[a]

Values are presented as mean ± standard deviation or number (%).
[a]Mann–Whitney *U*-test, Pearson chi-squared test; Statistical significance was determined as $P < 0.05$.
[b]A comorbidity is any coexisting chronic health condition.

Table 3. Concomitant neuropathic pain symptoms in the patients with prolonged pain

Symptoms	Patients (n = 69)
Burning	16 (23.2)
Numbness	15 (21.7)
Tingling	10 (14.5)
Stinging	4 (5.8)
Freezing sensation	1 (1.4)
Hypoesthesia	3 (4.3)

Values are presented as number (%).

this rate was 4%. The most common concomitant neuropathic symptoms were burning 23.2% (n = 16), numbness 21.7% (n = 15), and tingling 14.5% (n = 10) (**Table 3**).

DISCUSSION

This study brings to the light the role of prolonged pain as a common symptom as part of the post-COVID-19 syndrome. Through the acute phase of illness, pain was reported by the majority of patients; however, this study highlights the 13.8% of participants who reported prolonged pain as part of their chronic symptomology. This pain was shown most commonly to be bilateral, without dermatomal spread, and localized to the neck and lumbar regions with a mean duration of pain of 4.3 months. Along with increased reports of pain intensity, higher rates of additional comorbidity were observed within the prolonged pain group as well.

COVID-19 infections have had a profound impact on healthcare utilization across the spectrum including lengthy hospital courses, intensive care treatment, and rehabilitation needs often associated with various pulmonary and cardiac processes. The neuromuscular pathways also play a role in pain-related processes and in addition to invading the neuromuscular system by using the angiotensin converting enzyme-2 (ACE-2) and transmembrane protein serine-2 (TMPRSS-2) entry gates, the virus also initiates an immune-mediated inflammatory response with its molecular similarity mechanism [9]. This can lead to various neuromuscular symptoms including myalgia, which is a frequently accompanying symptom in patients with COVID-19 [15–17].

In a study conducted on 1,420 European patients, the incidence of myalgia and fatigue was reported more frequently in the elderly than in the young [18]. In another study, it was reported that myalgia continued for an average of 23 days after the end of viral shedding [19]. In the patients from this study, 63.4% reported myalgia during the active phase which eventually led to chronic pain in 13.7% of the overall patients.

Viral infections may cause neuromuscular findings by affecting the central and peripheral nervous system [17]. Many viruses, including the Epstein-Barr virus, varicella zoster virus (VZV), human immunodeficiency virus (HIV), cytomegalovirus, influenza A, and enteroviruses, have been associated with neurological complications [20]. Herpes zoster infection develops due to a decrease in cellular immunity after the VZV remains latent in the ganglia for a long time. The painful clinical picture seen after this infection is called postherpetic neuralgia [20]. In herpes zoster cases, unilateral vesicular lesions on the skin and long-lasting neuropathic pain are present [20]. Pain is limited to a particular dermatome. It may occur at a rate of 6%–10% within 3 months after herpes zoster [20]. Initially, neuropathic pain develops due to acute tissue and neuronal damage [21]. After the event has healed, pain may continue due to nerve damage [21]. Spontaneous C-nociceptor activity was observed in these cases [21]. Another virus that can infect the nervous system is HIV [20]. The clinical picture here develops as a result of the immune similarity mechanism between viral proteins and nerve fibers. Neuropathic pain is usually accompanied by burning and mechanical allodynia. Acute flaccid myelitis associated with enteroviruses may develop and chronic neuropathic pain may occur in these patients. Neurological complications such as ischemic stroke, encephalitis, myopathies, neuropathies, and Guillain–Barre syndrome have been reported after other coronaviruses, such as SARS-CoV-1 and Middle East respiratory coronavirus syndrome (MERS CoV) [20]. However, no cases of chronic pain have been reported associated with MERS CoV in the available literature. Attal et al. [20] predicted that early diagnosis and treatment strategies should be developed in this regard, in which neuropathic pain may develop in the early period or within weeks related to COVID-19, considering the data examined after previous viral infections.

Initially, the coronavirus enters cells via ACE-2 and cellular TMPRSS-2 [5,7]. ACE-2 receptors are commonly found in neuronal cells [7]. At the same time, the virus can enter nerve tissue from vascular endothelial cells using the TMPRSS-2 pathway [7,8]. In the peripheral nervous system, there is an autoimmune response to the myelin sheath or Schwann cells [9]. Looking at the pathophysiology of muscle cell involvement, it is assumed that the virus can enter the cell directly using the ACE-2 pathway [9]. Another mechanism in muscle cell involvement is the accumulation of immune complexes and the release of cytokines that cause myositis, which may be further complicated by the similarity between viral antigens and human muscle cells [9]. Another problem in COVID-19 patients is vascular problems due to hypercoagulability and immobilization. The cytokines associated with COVID-19 increase

the risk of thrombosis by causing endothelial dysfunction. Inhibition of the nitric oxide enzyme release from endothelial cells impairs vasodilation ability [10]. This, in turn, can cause tissue hypoxia, initiating nociceptive pain in the muscles. At the same time, somatosensory damage caused by thrombosis of the vasa nervorum feeding the nerve may cause neuropathic pain. Regional pains seen after COVID-19 infection may develop due to the direct invasion of nerve and muscle tissue by the viscera, immune complex accumulation, and immune similarity mechanism, or it may develop due to tissue hypoxia secondary to increased hypercoagulability because of endothelial damage.

In early series, it had been reported that up to 2.3% of patients hospitalized for COVID-19 infection might develop probable neuropathic pain [9]. Aksan et al. [22] described a case who was followed up in the hospital with the diagnosis of COVID-19 and developed severe pain in the neck and back (C1-L5) involving the trapezius and paraspinal region with burning and increased sensitivity characterized as allodynia on the second day of his hospitalization. The patient did not respond to a nonsteroidal anti-inflammatory drug during treatment, but he did benefit from gabapentin treatment, which is typically used to target neuropathic pain.

In the cases of chronic pain after COVID-19 infection that the authors described, there is no specific dermatomal spread. The pain is bilateral, seen in the neck, back, and lumbar region innervated by a wide array of spinal nerves. In some cases, neck pain is accompanied by pain in the arms. This is not a pattern described in previously seen viral neuropathic pain in the available literature. The majority of chronic pain in the patients in this study is of a nociceptive character, but was accompanied by neuropathic pain findings in 29.0% (n = 20) of subjects. When all COVID-19 cases were considered, the rate of accompanying at least one neuropathic pain symptom was 4% overall.

Odor-taste disorders are also among the neurological symptoms associated with COVID-19 [22,23]. It is assumed that the virus uses the olfactory pathway as its gateway to the brain. Postmortem autopsies showed inflammation and perivascular leukocyte infiltration in the olfactory bulb [23,24]. Agyeman et al. [23] reported an anosmia/ageusia rate of between 38%–42% in patients with COVID-19. In this study, 61.7% (n = 309) of patients had anosmia/ageusia symptoms. At the same time, the incidence of anosmia/ageusia was higher in the patient group with persistent post-COVID myalgia (75.4%).

Headache is the most common neurological symptom associated with COVID-19. Although the pathogenesis of the headache seen in COVID-19 has not yet been fully explained, virus-related proinflammatory mediators and cytokines may cause headache, and it is likely that trigeminal nerve endings in the nasal cavity may be directly invaded by the virus, or vasoconstrictor and oxidative stress due to endothelial damage may affect the trigeminal nerve and cause headache [25,26]. In a meta-analysis, the frequency of headache was reported to be 10.9% [27]. Uygun et al. [28] reported that the headache seen in COVID-19 patients was bilateral, resistant to analgesics, associated with anosmia/ageusia and gastrointestinal complaints, and was more common among them, contrary to expectations. In this study, headache was seen in 55.3% of patients. Again, the headache symptom (72.5%) was found more frequently in patients with prolonged regional pain compared to others.

This study has some limitations. It is a cross-sectional study based on self-report scales. The cases were interviewed by telephone, and therefore outpatient examination was not performed, and the classification of pain could not be made exactly. Patients with psychiatric comorbidities were excluded in the study, and one of the limitations of the current study is the lack of a scale that evaluates the patient's psychological state; further studies with the assessment of the long-term psychological effects of chronic pain or psychological-related post-COVID conditions (posttraumatic stress disorder, anxiety, depression, insomnia) are needed.

Various rehabilitation programs have been implemented for survivors of COVID-19 in many parts of the world. In addition to respiratory and cardiac rehabilitation, exercise programs to increase physical performance and stress management will significantly increase quality of life. The impact and efficacy of these programs would likely also have significant clinical relevance from the perspective of improving quality of life for patients and better optimizing resource allocation.

To the best of the authors' knowledge, the current study is the first to describe prolonged pain after COVID-19 in the Turkish population. Neuromuscular symptoms associated with COVID-19 may appear immediately at the time of infection or in the weeks following the acute infection. It was found that the pain seen in COVID-19 did not spread dermatomally but showed bilateral and regional pain characteristics stimulated by many spinal nerves. The rate of accompanying comorbidity, headache, anosmia/ageusia were also found to be increased in patients with chronic pain.

Therefore, in general practice, all patients with COVID-19 should be carefully monitored for possible neuromuscular syndromes. Untreated chronic pain is a risk factor for various conditions including anxiety disorders, sleep disorders, fatigue, impaired memory, and poor executive dysfunction. Timely and effective management of pain, including pharmacological management and physical therapy, has an important role in management of post-

COVID-19 syndrome. It is suggested that primary healthcare, physical therapy, and rehabilitation services should work in coordination.

The primary emphasis of this study is that clinicians should increase alertness that patients presenting with localized pain in the neck, back, or lumbar region, without dermatomal dissemination and/or accompanied by neuropathic symptoms, may be experiencing symptoms associated with COVID-19. Secondly, by raising awareness among physicians and patients that prolonged pain may develop in COVID-19 patients, physical and psychological disability and loss to the workforce that may occur in cases of possible chronic pain will be prevented.

DATA AVAILABILITY

Data files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/APLORE.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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