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Original Article

Pain types and risk factors in post-COVID-19

Ayşegül Ketenci[1], Mert Zure[2], Fatma Merih Akpınar[3], Yelda Soluk Özdemir[4], Özlem Balbaloğlu[5], Mazlum Serdar Akaltun[6], Ender Erden[7], Ayla Çağlıyan Türk[7], Merve Damla Korkmaz[2], Burcu Metin Ökmen[8], Özlem Altındağ[6], Feray Soyupek[9], Elif Yakşi[10], Dilşad Sindel[3], Nalan Sezgin[11], Kübra Ustaömer[12], Fatma Nur Kesiktaş[4], Didem Dere[4], Şevket Güneş[13], Cansın Medin Ceylan[4], Birkan Sonel Tur[14], Deniz Evcik[15]

[1]Department of Physical Medicine and Rehabilitation, Koç University Hospital, Istanbul, Türkiye
[2]Department of Physical Therapy and Rehabilitation, Istanbul Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Türkiye
[3]Department of Physical Medicine and Rehabilitation, Istanbul University Istanbul Faculty of Medicine, Istanbul, Türkiye
[4]Department of Physical Therapy and Rehabilitation, Istanbul Physical Medicine and Rehabilitation Training and Research Hospital, Istanbul, Türkiye
[5]Department of Physical Medicine and Rehabilitation, Yozgat Bozok University Faculty of Medicine, Yozgat, Türkiye
[6]Department of Physical Medicine and Rehabilitation, Gaziantep University Research Hospital, Gaziantep, Türkiye
[7]Department of Physical Medicine and Rehabilitation, Hitit University Faculty of Medicine, Çorum, Türkiye
[8]Department of Physical Medicine and Rehabilitation, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye
[9]Department of Physical Medicine and Rehabilitation, Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye
[10]Department of Physical Medicine and Rehabilitation, Abant Izzet Baysal University Faculty of Medicine, Bolu, Türkiye
[11]Department of Physical Medicine and Rehabilitation, Medikent Hospital, Lüleburgaz, Türkiye
[12]Department of Physical Medicine and Rehabilitation, Tekirdağ Namık Kemal University Faculty of Medicine, Tekirdağ, Türkiye
[13]Department of Physical Therapy and Rehabilitation, Istanbul Sancaktepe Ilhan Varank Training and Research Hospital, Istanbul, Türkiye
[14]Department of Physical Medicine and Rehabilitation, Ankara University Faculty of Medicine, Ankara, Türkiye
[15]Department of Physical Medicine and Rehabilitation, Güven Hospital, Ankara, Türkiye

ABSTRACT

Objectives: This study aims to accurately evaluate pain lasting longer than three months and falls under the category of chronic pain and to determine the risk factors to follow up and treat properly and to develop appropriate diagnostic and treatment algorithms.

Patients and methods: Between March 2021 and December 2021, a total of 437 patients (162 males, 275 females; mean age: 44±14.6 years; range, 12 to 82 years) who were referred to the participating centers due to pain complaints and were diagnosed with post-COVID-19 condition according to the criteria defined by the World Health Organization (WHO) were included in the study. The patients were divided into three groups as nociceptive pain, neuropathic pain, and central sensitization, based on the physician's clinical evaluation and the Self-Report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and Central Sensitization Inventory scores.

Results: The most common diagnosis was nociceptive pain followed by central sensitization. Patients with nociceptive pain had less pain. It was found that not exercising regularly, having a chronic disease and being a woman were risk factors for central sensitization, having thyroid disease before COVID-19, and defining the current pain as very severe were risk factors for neuropathic pain.

Conclusion: In the evaluation of post-COVID-19 pain, neuropathic pain and central sensitization should be also considered in addition to nociceptive pain and the severity of pain, systemic diseases and physical activity should be questioned.

Keywords: Central sensitization, neuropathic pain, nociceptive pain, pain, physical activity, post-COVID-19 conditions.

It is known that some patients develop permanent symptoms after infectious diseases. Epstein-Barr virus, West Nile virus, Zika, Chikungunya, severe acute respiratory syndrome (SARS), and Borrelia spp. are some examples for these types of infectious diseases. These permanent symptoms may include chronic fatigue, non-restorative sleep, nausea, headache, and cognitive dysfunction. The symptoms persist for more than six months in most cases, and patients meet the criteria for chronic fatigue syndrome or another central sensitization syndrome in which the perception of the intensity of sensory stimuli is increased.[1]

Corresponding author: Fatma Merih Akpınar, MD. İstanbul Üniversitesi İstanbul Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, 34093 Fatih, İstanbul, Türkiye
E-mail: merih.akpinar@istanbul.edu.tr

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During the novel coronavirus disease-2019 (COVID-19) pandemic, it has been reported that, in nearly 25% of individuals who had COVID-19, symptoms continued for a month after the illness and, in 10%, the symptoms lasted longer than 12 weeks.[2,3] This post-COVID-19 condition which was defined by different terms, such as but not limited to post-COVID-19, long COVID-19, or long-hauler COVID-19, became an umbrella term to identify a complex multisystem disease occurring immediately or shortly after recovery, regardless of the severity of COVID-19.[4] Although it is characterized by long-term sequelae, it presents with many symptoms such as severe fatigue, muscle weakness, mild fever, impaired concentration, memory loss, mood changes, sleep disorders, headache, pins and needles in the arms and legs, episodes of diarrhea and vomiting, loss of taste and smell, sore throat and difficulty swallowing, new-onset diabetes and hypertension, skin rash, shortness of breath, chest pain, and palpitations.[3,5] It is twice as often in women, but around the age of 60 the frequency becomes equal.[2] With the increase in the frequency of this clinical picture, the World Health Organization (WHO) defined post-COVID-19 condition as the presence or development of new symptoms three months after the initial COVID-19 infection with the symptoms lasting for at least two months. The symptoms should not be explained by an alternative diagnosis and reinfection with SARS-coronavirus 2 (SARS-CoV-2) should also be excluded. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which usually have an impact on everyday functioning.[6] In post-COVID-19 condition, symptoms often affect activities of daily living, may be new onset following recovery or persistent from an acute episode of COVID-19, and may fluctuate or relapse over time.[6,7]

In the United Kingdom, post-COVID-19 syndrome has been described in more than one million individuals, while there are no clear data from other countries, yet.[4] In Türkiye, 17,042,722 individuals have had COVID-19 as of March 2023 and the exact number of post-COVID-19 patients is unknown. Pain is one of the most common and debilitating symptoms in post-COVID-19 condition.[8] It is important to identify the pain characteristics to treat musculoskeletal pain effectively, which is increasingly common.

A recent study reported that the prevalence of musculoskeletal pain was 45.1% among COVID-19 patients discharged from the hospital eight months ago. Most of the patients had new-onset musculoskeletal post-COVID-19 pain. The risk factors for developing post-COVID-19 pain related to musculoskeletal system were defined as being female, having a history of musculoskeletal pain, having myalgia and headache as symptoms of COVID-19 in the acute phase, and number of days spent in hospital. However, they included only hospitalized patients like most of the studies on post-COVID-19 pain in the literature.[8] In their cross-sectional population-based study, Peter et al.[9] reported that post-COVID-19 condition was more common in those with two and more symptoms, who needed medical support during the acute phase of COVID-19 infection, and in female, those with obesity, and older patients. Oğuz-Akarsu et al.[10] investigated the main pain syndromes in 222 patients about 1.5 to 3 months after polymerase chain reaction (PCR) test positivity via telephone survey and 159 patients reported at least one type of pain syndrome with a prevalence of 71.6%. A total of 49.6% of the patients reported myalgia, 49.1% headache, 24.8% neuropathic pain symptoms, and 13.5% polyarthralgia. In a narrative review, approximately 10% of COVID-19 patients reported complaints of musculoskeletal-related post-COVID-19 pain, such as myalgia (5.6 to 18.2%), arthralgia (4.6 to 12.1%), and chest pain (7.8 to 23.6%), at different follow-up periods within the first year. They also noted that there was a decrease in the prevalence of post-COVID-19 pain from symptom onset to 30 days, an increase after 60 days, and a second decrease was observed >180 days after infection.[11] However, there are no data in the literature on whether the characteristics of the pain in patients diagnosed with post-COVID-19 condition are nociceptive or neuropathic.

In the present study, we aimed to accurately evaluate pain lasting longer than three months and falls under the category of chronic pain and to determine the risk factors to follow up and treat properly and to develop appropriate diagnostic and treatment algorithms.

PATIENTS AND METHODS

This multi-center, cross-sectional study was conducted at 15 centers, Department of Physical Medicine and Rehabilitation (PMR) outpatient clinics between March 2021 and December 2021. A total of 776 patients who were admitted with a complaint of pain lasting longer than three months after surviving from COVID-19 and received the diagnosis of post-COVID-19 syndrome were included in the

study. The study was conducted with 22 researchers from 15 centers (9 university hospitals, 4 training and research hospitals, 2 private health institutions).

Among patients who applied to the PMR outpatient clinics, those who met the following criteria were included: patients aged 18 years or over; having the symptoms of COVID-19 and being diagnosed with COVID-19 by PCR test; patients who survived COVID-19 in the past three months before the pain started, worsened, and/or changed features; and those diagnosed with post-COVID-19. Finally, a total of 437 patients (162 males, 275 females; mean age: 44±14.6 years; range, 12 to 82 years) were recruited.

Detailed history including demographic features, if and where the patient received treatment for COVID-19 (i.e., home, hospital, intensive care unit), comorbidities that may increase pain (such as steroid use, malignancy, osteoporosis, inflammatory diseases, diabetes, hyperthyroidism), medications taken during COVID-19 and those still being taken, physical activity level (exercise level and activity level at home), the onset of pain, previous pain experience, characteristics of pain, how the patient define the pain, location and, precipitating factors of pain. Musculoskeletal and neurological examinations were performed in all patients.

Pain intensity including nociceptive pain was evaluated using the Numerical Rating Scale (NRS) by the patient rating the pain from 0 (no pain) to 10 (worst pain) (at rest, at night and while moving). Neuropathic pain was assessed by the Self-Report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) scale and central sensitization was measured using the Central Sensitization Inventory (CSI). Those with major anxiety and depression were excluded from the study after completing the Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS).

Thereafter, PMR physicians were asked to make a clinical preliminary diagnosis choosing from one of the predefined options, which were central sensitization, nociceptive pain, and neuropathic pain. These clinical preliminary diagnoses were based on the detailed anamnesis, clinical examinations, and the physicians' clinical experience in musculoskeletal diseases, also supported by the questionnaires described below. Nociceptive pain is a diagnosis made according to anamnesis and clinical examination. Neuropathic pain accompanied by sensory deficit and/or motor weakness was evaluated as neuropathic pain, whereas pain inconsistent with nerve traces with allodynia was evaluated as central sensitization. Patients in more than one group were excluded from the study to determine the characteristics of each group.

Scales

Self-Report Leeds Assessment of Neuropathic Symptoms and Signs

The S-LANSS was preferred in the evaluation, as its validity and reliability in Turkish has been demonstrated and the physicians participating in the study had experience with this scale. The S-LANSS is a self-assessment scale comprising of a seven-item pain scale developed by Bennett et al.[12] for identifying and characterization of pain. The S-LANSS scale helps to differentiate neuropathic pain from nociceptive pain. A patient with a score of 12 or higher is diagnosed as having neuropathic pain. The Turkish version of the scale was developed

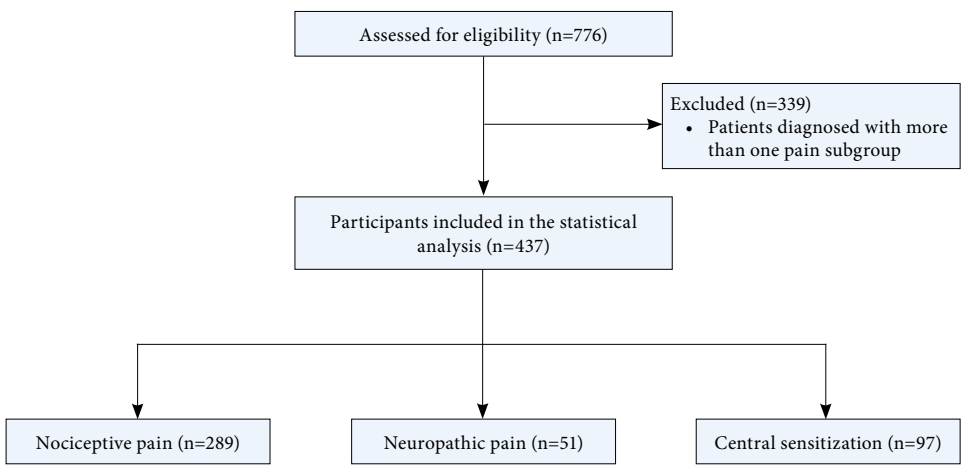

Figure 1. Study flowchart.

and the validity and reliability study was performed by Koç et al.[13]

Central Sensitization Inventory

The CSI is a scale consisting of 25 questions and evaluated over 5 points. A score of 40 or more out of 100 points indicates central sensitization. The CSI is a patient-reported screening tool used to identify and quantify central sensitization/central sensitization syndromes-related symptomology (sensitivity: 81%, specificity: 75%).[14] The Turkish translation and the validity and reliability study were performed by Düzce Keleş et al.[15] The diagnosis of central sensitization was made according to the International Association for the Study of Pain (IASP) 2014 criteria.[16]

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The normality of the results was determined by the Shapiro-Wilk and Kolmogorov-Smirnov tests. The Fisher exact (in low sample sizes) and chi-square tests were used to determine the ratio or correlation differences between categorical variables. To show the behavioral differences of the group averages, the Kruskal-Wallis test (number of groups=3) was used, when the assumptions of normality and homogeneity were not met. Relative risk (RR) ratios of parameters were calculated by using multivariate multinomial logistic regression analysis. A *p* value of <0.05 was considered statistically significant.

RESULTS

A total of 66.13% of the patients were diagnosed with nociceptive, 11.67% with neuropathic, and 22.20% with central sensitization (Figure 1). Demographic properties of the patients are given in Table 1 and 2. According to these statistical analyses, the ratio of males in the central sensitization group was lower compared to the other groups (p<0.001). Also, the rate of regular exercise in the central sensitization group was lower compared to the other groups (p=0.006). The nociceptive pain rate among housewives was significantly lower compared to white collar workers, blue collar workers, public servants, healthcare workers, freelance workers, students, retirees, and unemployed participants, while the central sensitization rate was notably higher (p<0.001).

TABLE 1
Demographic properties of the patients

	Nociceptive pain (n=289)			Neuropathic pain (n=51)			Central sensitization (n=97)						
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	p†	p^1	p^2	p^3
Body mass index (kg/m^2)	26.96±4.6	26.54	15.94-48.07	27.93±4.85	28.13	19.03-38.06	27.62±4.95	27.41	18.59-46.47	0.286	0.537	0.839	1
Time after COVID-19 (month)	5.61±3.44	5	0-18	5.8±3.37	5	1-14	5.78±3.72	5	1-25	0.943	1	1	1
Age (year)	42.7±14.63	43	14-75	44.73±14.98	47	20-82	45.19±15.14	47	12-74	0.337	1	0.468	1

SD: Standard deviation; COVID-19: Novel coronavirus disease-2019; † Kruskal-Wallis test; p^1: Nociceptive pain vs. neuropathic pain; p^2: Nociceptive pain *vs.* central sensitization; p^3: Neuropathic pain *vs.* central sensitization.

TABLE 2
Demographic properties of the patients

	Nociceptive pain (n=289)		Neuropathic pain (n=51)		Central sensitization (n=97)					
	n	%	n	%	n	%	*p*	p^1	p^2	p^3
Sex							**<0.001***	1	**0.0015**	**0.0015**
Male	125	43.3	22	43.1	15†	15.5				
Female	164	56.7	29	56.9	82‡	84.5				
Smoking							0.099**	1	0.231	0.104
Quit	21	7.3	4	7.8	2	2.1				
Yes	49	17.0	12	23.5	12	12.4				
No	219	75.8	35	68.6	83	85.6				
Physical activity level							**0.006****	1	**0.0435**	**0.0165**
Regular exercise	27†	9.3	6†	11.8	1‡	1.0				
House chores	139	48.1	24	47.1	61	62.9				
Daily walking	46	15.9	12	23.5	12	12.4				
Sedentary	77	26.6	9	17.6	23	23.7				
Where the patient was during COVID-19	242	83.7	46	90.2	83	85.6	0.139**	0.831	0.16	1
Home	44	15.2	4	7.8	10	10.3				
Hospital	3	1.0	1	2.0	4	4.1				
ICU										

COVID-19: Novel coronavirus disease-2019; ICU: Intensive Care Unit; * Pearson's Chi-squared test; ** Fisher exact test; † Statistically lower values; ‡ Statistically higher values; p^1: Nociceptive pain *vs.* neuropathic pain; p^2: Nociceptive pain *vs.* central sensitization; p^3: Neuropathic pain *vs.* central sensitization.

TABLE 3
Relationships between comorbidities and diagnoses

	Nociceptive pain (n=289)		Neuropathic pain (n=51)		Central sensitization (n=97)					
	n	%	n	%	n	%	*p*	p^1	p^2	p^3
Previously known chronic disease							**<0.001***	0.471	**0.0015**	0.69
Present	98‡	33.9	23	45.1	55†	56.7				
Absent	191†	66.1	28	54.9	42‡	43.3				
Hypertension							**0.014***	1	**0.039**	0.122
Present	50	17.3	7	13.7	29†	29.9				
Absent	239	82.7	44	86.3	68‡	70.1				
Diabetes							**0.003****	**0.036**	**0.0435**	1
Present	15‡	5.2	8	15.7	13	13.4				
Absent	274†	94.8	43	84.3	84	86.6				
Thyroid disease							**0.001****	**0.024**	**0.012**	1
Present	10‡	3.5	7	13.7	11	11.3				
Absent	279†	96.5	44	86.3	86	88.7				
COPD							0.436**	1	1	1
Present	14	4.8	4	7.8	7	7.2				
Absent	275	95.2	47	92.2	90	92.8				
Coronary artery disease							0.22**	1	1	0.498
Present	17	5.9	1	2.0	9	9.3				
Absent	272	94.1	50	98.0	88	90.7				
Rheumatoid arthritis							0.638**	1	1	1
Present	3	1.0	0	0.0	2	2.1				
Absent	286	99.0	51	100.0	95	97.9				
Corticosteroid use during COVID-19							0.427**	1	1	1
Doesn't know	19	6.6	6	11.8	8	8.2				
Yes	54	18.8	9	17.6	24	24.7				
No	214	74.6	36	70.6	65	67.0				

COPD: Chronic obstructive pulmonary disease; COVID-19: Novel coronavirus disease-2019; * Pearson's Chi-squared test; ** Fisher exact test; † Statistically higher values; ‡ Statistically lower values; p^1: Nociceptive pain *vs.* neuropathic pain; p^2: Nociceptive pain *vs.* central sensitization; p^3: Neuropathic pain *vs.* central sensitization.

Considering the presence of comorbid conditions between the groups, previously known chronic diseases were more common in the central sensitization group than in the nociceptive pain group (p=0.0015), with hypertension being the differentiating factor between these groups (p=0.039). Diabetes and thyroid diseases were less common in patients with nociceptive pain compared to other groups (Table 3).

When pain characteristics defined by patients were evaluated in all the groups, chronic pain before COVID-19 was less frequent in nociceptive pain group compared to other groups (p<0.001). Pins and needles sensation was less frequent in central

TABLE 4
Pain characteristics defined by patients

	Nociceptive pain (n=289)		Neuropathic pain (n=51)		Central sensitization (n=97)					
	n	%	n	%	n	%	*p*	p^1	p^2	p^3
Pain before COVID-19							**<0.001***	**0.018**	**0.0015**	1
Present	125‡	43.3	33	64.7	67†	69.1				
Absent	164†	56.7	18	35.3	30‡	30.9				
Headache							0.126*	0.176	1	0.242
Present	63	21.8	5	9.8	22	22.7				
Absent	226	78.2	46	90.2	75	77.3				
Pain at night							0.057**	0.414	0.114	1
Present	32	11.1	2	3.9	4	4.1				
Absent	256	88.9	49	96.1	93	95.9				
Aching							0.858*	1	1	1
Present	80	27.7	16	31.4	28	28.9				
Absent	209	72.3	35	68.6	69	71.1				
Burning							0.26*	0.531	0.891	1
Present	35	12.1	10	19.6	16	16.5				
Absent	254	87.9	41	80.4	81	83.5				
Pins and needles							**0.044***	0.265	0.63	**0.042**
Present	72	24.9	19†	37.3	18‡	18.6				
Absent	217	75.1	32‡	62.7	79†	81.4				
Sharp							0.235**	0.471	1	0.912
Present	12	4.2	5	9.8	5	5.2				
Absent	277	95.8	46	90.2	92	94.8				
Twinge							0.972*	1	1	1
Present	80	27.7	14	27.5	28	28.9				
Absent	209	72.3	37	72.5	69	71.1				
Whiny pain							0.418*	1	0.717	1
Present	41	14.2	7	13.7	19	19.6				
Absent	248	85.8	44	86.3	78	80.4				
Stabbing pain							0.076*	0.0975	1	0.558
Present	38	13.1	13	25.5	15	15.5				
Absent	251	86.9	38	74.5	82	84.5				
Very severe pain							**0.003***	**0.009**	0.618	0.28
Present	33‡	11.4	15†	29.4	16	16.5				
Absent	256†	88.6	36‡	70.6	81	83.5				
Pain with movement							0.658**	1	1	1
Present	7	2.4	1	2.0	4	4.1				
Absent	282	97.6	50	98.0	93	95.9				
Pain at rest							0.309**	1	0.468	1
Present	21	7.3	2	4.0	3	3.1				
Absent	268	92.7	48	96.0	94	96.9				

COVID-19: Novel coronavirus disease-2019; * Pearson's Chi-squared test; ** Fisher exact test; † Statistically higher values; ‡ Statistically lower values; p^1: Nociceptive pain *vs.* neuropathic pain; p^2: Nociceptive pain *vs.* central sensitization; p^3: Neuropathic pain *vs.* central sensitization.

TABLE 5
Multinomial logistic regression analysis

Parameters	Beta		*p*		Relative risk	
	Neuropathic pain	Central sensitization	Neuropathic pain	Central sensitization	Neuropathic pain	Central sensitization
Intercept	-2.750	**-1.461**	**<0.001**	<0.001	0.064	0.232
Doing regular exercise	-0.518	2.109	0.301	**0.042**	0.596	8.238
Female gender	-0.299	1.292	0.371	**<0.001**	0.741	3.640
Previously known chronic disease	0.034	0.757	0.923	**0.005**	1.035	2.133
Thyroid disease	1.436	0.334	**0.016**	0.502	4.204	1.396
Chronic pain before COVID-19	0.885	0.692	**0.009**	**0.009**	2.423	1.997
Experiencing very severe pain	1.196	0.395	**0.001**	0.265	3.306	1.485

COVID-19: Novel coronavirus disease-2019.

sensitization group than in neuropathic pain group (p=0.042). Neuropathic pain group described the pain perceived as "very severe" more frequently compared to nociceptive pain group (p=0.009) (Table 4).

In the risk analysis, individuals who were engaged in regular exercise had a significantly lower likelihood of experiencing central sensitization compared to nociceptive pain, with a reduction factor of 8,238. Additionally, being female was associated with a 3.64-fold increase in this risk. For individuals who already had a chronic disease and, then, developed pain following COVID-19, the chances of this pain arising from central sensitization were found to be 2,133 times greater than alternative explanations. Furthermore, in patients with thyroid conditions, the likelihood of experiencing neuropathic pain was notably elevated, being 4,204 times higher than the likelihood of nociceptive pain. The RR of neuropathic pain compared to nociceptive pain in post-COVID-19 patients who described their pain as severe was 3,306.

DISCUSSION

Post-COVID-19 condition has increased the number of chronic pain patients seen by physicians, particularly those interested in pain management. Although the frequency of chronic nociceptive pain in those who had chronic pain before the pandemic who could not schedule their follow-up and whose physical activity decreased due to the pandemic circumstances, usually increased; post-COVID-19 joint pain or widespread pain is more severe and reduces the quality of life apart from this chronic nociceptive pain.

In a commentary written by Fiala et al.,[17] long-lasting testicular pain, chronic pain, headache, and chest pain were defined as atypical findings of post-COVID-19, and these were mostly seen in hospitalized patients and the elderly. The fact that 83% of the patients, who applied to our outpatient clinics with chronic severe pain, experienced the acute disease phase at home rather than in the hospital, showed that chronic pain was not directly related to the severity of the disease.

In a recent review, Attal et al.[18] predicted that neuropathic pain may develop within weeks or months in some patients, or more severe neurological complications, exacerbation of neuropathic pain or worsening of neurological status may occur in some patients with chronic neuropathic pain exposed to SARS-CoV-2, considering the neurological complications of COVID-19.

Goudman et al.[19] found the central sensitization scale scores within pathological range in 70.26% of 491 COVID-19 patients, in whom they evaluated with the CSI filled out on social media. They reported that 64.76% of this patient group was classified with a high level of central sensitization-related symptom severity and they were more limited functionally. The one-to-one evaluation of patients by physiatrists and patients' presenting to the outpatient clinic with the complaints of pain were the main differences of our study from the study of Goudman et al.[19] A total of 22.2% of our 437 patients with pain complaints had central sensitization. In our study, female sex, physical activity level, and presence of previously known chronic disease were determined to be the risk factors for central sensitization.

Magdy et al.,[20] on the other hand, evaluated neuropathic pain with Douleur Neuropathique 4 questions (DN-4) and compared 45 patients diagnosed with post-COVID-19 neuropathic pain with 45 patients without neuropathic pain after COVID-19. The authors reported that moderate-to-severe illness, use of azithromycin, and presence of depression were independent risk factors for post-COVID-19 neuropathic pain. In our study, most of our patients with pain had mild disease and were not hospitalized, and they did not use any specific medication. Therefore, considering post-COVID-19 neuropathic pain and/or central sensitization only in patients with severe disease and depression is not consistent with our results.

The fact that the patients are predominantly in the central sensitization and nociceptive pain groups would be a diagnostic option for patients who do not initiate rapid treatment, considering the pain as anxiety related to the disease experienced. The frequent occurrence of nociceptive pain can be attributed to muscle involvement due to immobilization or the virus itself. Therefore, in patients who are not thought to have central sensitization and have nociceptive pain, an active exercise program should be started. On the other hand, in patients with central sensitization, appropriate medical treatments and education programs should be considered in the early period, and the patient's anxiety about pain should be minimized.

The high number of patients included in the study, evaluation of the patients by experienced physical medicine and rehabilitation specialists and completing the scales under supervision are the strengths of this study.

The main limitations are that it provides less information about elderly patients due to the mean age of 44 years, most of the patients were female, and it was planned as a cross-sectional study. There are no objective criteria for defining pain subgroups in clinical practice. These definitions are one of the most difficult areas for specialists dealing with pain. Therefore, our pain subgroup classification was based on detailed anamnesis, clinical examination and supported by questionnaires. Also, we did not include electrodiagnostic tests in our study, since neuropathic pain can still be considered clinically, even electrophysiological studies do not support the diagnosis. Objectivation of pain in pain assessment is another one of the most difficult areas for specialists dealing with pain and still has not been fully achieved. However, in our study, we attempted to reduce this risk by excluding those with major anxiety and depression using BDI and HADS.

In conclusion, nociceptive pain should be considered primarily in post-COVID-19 pain, more care should be taken in those with previously known chronic disease, thyroid disease, female patients, who describe severe pain and less physical activity. Treatment should be started early; patients should be followed closely in terms of neuropathic pain and central sensitization and countries should develop diagnostic and treatment algorithms as soon as possible.

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