Clinical Research

Relationship of Ongoing Symptom Duration Following COVID-19 İnfection to Central Sensitization

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ABSTRACT

Objective: Central sensitization (CS) is a general term for facilitated synaptic plasticity caused by neuronal dysregulation and excessive excitability in the central nervous system. CS is characterized by abnormally increased pain and hypersensitivity.
This study aimed to investigate the frequency of CS, which is important in the pathophysiology of chronic pain, and the parameters affecting CS in patients who were previously infected and survived coronavirus disease 2019 (COVID-19).
Material and Method: A total of 350 patients, who survived COVID-19 infection, classified into Groups 1 and 2. Group 1 comprised those with subacute or prolonged COVID-19 (clinical presentation occurring 4-12 weeks after acute disease onset), and Group 2 comprised those with the chronic or post-COVID-19 syndrome (clinical presentation lasting for >12 weeks after acute disease onset and cannot be explained by any alternative diagnosis). The visual analog scale was used to evaluate the current pain of patients. The depression anxiety scale, central sensitization inventory, centrality of the pain scale, and pain quality assessment scale were administered.
Results: Regarding the time elapsed since positive polymerase chain reaction results, 53.4% (n =187) and 46.6% (n =163) patients were in Groups 1 and 2, respectively. CS was detected in 11.1% of patients (n =39). The CS risk in Group 1 was 0.15 times less than that in Group 2 (p =0.001). The CS risk was 260,211 times (p <0.001), 43,361 times (p <0.001), 2429 times (p =0.048), and 51,610 times higher (p <0.001) in hospitalized patients, those requiring intensive care, those with joint pain, and those with headache, respectively.
Conclusion: Duration of symptoms following COVID-19 infection is an important factor that should not be ignored when assessing CS.

Keywords: *Central Sensitization, Subacute Prolonged COVID-19, Chronic Post-COVID-19.*

ÖZ

COVID-19 Enfeksiyonu Takiben Devam Eden Semptom Süresinin Santral Sensitizasyonla İlişkisi
Amaç: Santral sensitizasyon (SS), merkezi sinir sisteminde nöronal düzensizlik ve aşırı uyarılabilirliğin neden olduğu kolaylaştırılmış sinaptik plastisite için kullanılan genel bir terimdir. SS, hem ağrılı hem de ağrısız uyaranlara anormal derecede artan ağrı ve aşırı duyarlılık ile karakterizedir.
Bu çalışma, daha önce koronavirüs hastalığı 2019 (COVID-19) ile enfekte olmuş ve hayatta kalmış hastalarda kronik ağrı patofizyolojisinde önemli olan SS sıklığını ve SS'yi etkileyen parametreleri araştırmayı amaçladı.
Gereç ve Yöntem: COVID-19 enfeksiyonundan kurtulan 350 hasta, Grup 1 ve 2 olarak sınıflandırıldı. Grup 1; subakut veya uzamış COVID-19 (klinik tablo akut hastalık başlangıcından 4-12 hafta sonra ortaya çıkan) ve Grup 2; Kronik veya post-COVID-19 sendromu (akut hastalık başlangıcından sonra >12 hafta süren klinik tablo ve herhangi bir alternatif tanı ile açıklanamaz). Hastaların mevcut ağrılarını değerlendirmek için görsel analog skala kullanıldı. Depresyon anksiyete ölçeği, merkezi sensitizasyon envanteri, merkezi ağrı ölçeği ve ağrı kalitesi değerlendirme ölçeği (PQAS) uygulandı.
Bulgular: Hastaların %53,4'ü (n =187) Grup 1'de %46,6'sı (n =163) Grup 2 'de yer aldı. Hastaların %11,1'inde (n =39) SS saptandı. Grup 1'deki SS riski, Grup 2'dekinden 0,15 kat daha azdı (p =0,001). SS riski; hastanede yatan hastalarda 260.211 kat (p <0.001), yoğun bakım yatışı olanlarda 43.361 kat (p <0.001), eklem ağrısı olanlarda 2429 kat (p =0.048) ve baş ağrısı olanlarda 51.610 kat daha yüksekti (p <0.001).
Sonuç: COVID-19 enfeksiyonunu takiben semptom süresi, SS değerlendilirken gözardı edilmemesi gereken önemli bir faktördür.

Anahtar Sözcükler: *Santral Sensitizasyon, Subakut-Uzamış COVID-19, Kronik Post COVID-19.*

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The coronavirus disease 2019 (COVID-19) outbreak started in Wuhan, China. On March 11, 2020, the World Health Organization announced COVID-19 as a pandemic, causing social, psychological, biological, and economic problems in the majority of the population. COVID-19 has significantly altered human behavior and presented a public health concern worldwide.

The pathophysiology of COVID-19 symptoms has not yet been fully elucidated. COVID-19 is a neurotropic virus by nature and may be a source of neuropathic pain, nociceptive/nociplastic pain due to inflammatory mediators, or central functional pain (1). Some studies that investigated the effect of COVID-19 on the central nervous system suggested that the virus can cross the blood-brain barrier due to endothelial damage, which

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may explain the central involvement of this pathway. Alternatively, the central transmission may be via the olfactory bulb, referring to the high frequency of anosmia-hyposmia (2, 3).

Su et al. (3) reported that inflammation caused by cytokines, such IL-1, IL-6, and tumor necrosis factor, which play an important role in a cytokine storm, led to symptoms, such as arthralgia and myalgia with tissue damage. Sheraton et al. (4) reported that the effects on the neuromuscular system might be related to inflammation, immune-mediated mechanisms, and direct damage. Studies reported that headache, encephalitis, and epilepsy might develop because of increased inflammation, edema, or neural invasion in the central nervous system. Hypoxia, which develops because of pulmonary damage, may aggravate symptoms by increasing congestion and edema in the brain (5).

A physiological phenomenon known as CS occurs when the central nervous system neurons become hyperexcitable, leading to increased sensitivity to both noxious and non-noxious stimuli. Chronic pain is usually thought to be caused by neural plasticity in pain coding pathways and circuits. Neuronal plasticity involves central sensitization of pain-processing neurons in the brain and spinal cord, and peripheral sensitization of primary sensory neurons of the dorsal root ganglia (DRG) and trigeminal ganglia (6-8)

Central sensitization syndromes (CSS) refer to a range of medically nonspecific conditions, including fibromyalgia (FM), chronic fatigue syndrome (CFS), and irritable bowel syndrome. CS may represent a common etiology for these conditions. Additionally, CS may also be the etiology of the chronic pain experienced by patients after COVID-19.

The COVID-19 pandemic causes significant stress worldwide. A study showed that the pain sensitivity syndrome epidemic worsened people's physical and mental health. Thus, interdisciplinary approaches are urgently required to deliver optimal healthcare to this group (9-12). Another study showed that all groups, except for chest pain and dyspnea, were associated with CS in patients who were divided into clinical groups (such as fatigue, myalgia, dyspnea, headache, chest pain, orthostatic tachycardia after COVID-19 infection. A female predominance was observed in these groups (10-13). To the best of our knowledge, these persistent chronic symptoms in the post-COVID period are similar to CSS, FM, CFS, and postural orthostatic tachycardia syndrome and can often develop during the post-infection period.

This study aimed to investigate the symptoms that persisted after COVID-19 infection. The presence of CS, which plays a role in the etiology of chronic pain after COVID-19 infection, and its relationship with various parameters will be discussed.

MATERIAL AND METHOD

Of the patients admitted to the Fethi Sekin City Hospital Physiotherapy and Neurology outpatient clinic, we included 350 patients with COVID-19 infection. A neurologist and a physical therapist examined all patients. Those with any previous psychiatric diagnosis, fibromyalgia, chronic fatigue syndrome, a history of inflammatory disease, or any muscle, tendon, or soft tissue anomalies explaining the pain, underwent surgery in the last 6 months, severe heart or kidney failure were excluded from the study.

This study was conducted in accordance with the principles of the Declaration of Helsinki 2008. Ethics committee approval Firat was obtained from the University Non-Interventional Ethics Committee, and T.C. Necessary permissions were obtained from the Ministry of Health (26.04.2022-8148). All patients signed the informed consent forms. We recorded the date when polymerase chain reaction (PCR) became positive, hospitalization, and the need for intensive care. The present pain of the patients was evaluated using the visual analog scale (VAS), and accompanying symptoms were determined.

Central sensitization inventory (CSI); Initial CSI has two components. The first part contains 25 items, including pain-related, psychosocial, cognitive, and functional items. The second part includes restless legs, CFS, FM, temporomandibular joint disorder, migraine or tension headache, irritable bowel, multiple chemical sensitivities, and three disorders related to CSS (11-14).

The centrality of pain scale (COPS); COPS is a 10-item self-report questionnaire measuring how patients with chronic pain assess pain in their daily life. Each of the 10 items is graded on a five-point Likert scale. Higher scores show a more “centralized” pain (12-16)

Pain quality assessment scale (PQAS); The respondents were instructed to rate the severity of each of the 20 pain domains using 0-10 numerical rating scales, and PQAS has 16 specific pain quality questions common to patients with both neuropathic and non-neuropathic pain, in addition to 20 items measuring global pain intensity and unpleasantness (14-17).

The patients were classified into two groups based on the time elapsed after infection. Group 1 comprised patients with subacute or prolonged COVID (clinical presentation between 4-12 weeks after onset of acute disease). Group 2 comprised those with the chronic or post-COVID-19 syndrome (clinical presentation lasting >12 weeks after onset of acute disease and not explained by alternative diagnoses). We excluded those whose current symptoms and findings were explained by different diagnoses. Those with a CS scale score of ≥40 were considered positive.

Statistical analysis

Data were entered into software SPSS (Version 23) and T-test, ANOVA, Regression methods were used for data analysis. The Shapiro-Wilk test was used to evaluate the conformity to the normal distribution. Subse-

quently, the Mann-Whitney U test was used to compare data that were not normally distributed based on the paired groups. Yates correction, Pearson's Chi-square, and Fisher's exact test statistics were used to examine the relationship between categorical variables according to groups. Binary logistic regression analysis was used to analyze the independent risk factors affecting central sensitization. Analysis results were presented as mean ±standard deviation and median (minimum-maximum) for quantitative data and frequency (percent) for categorical variables. $p < 0.05$ was considered statistically significant.

RESULTS

Of the study participants, 55.7% (n =195) and 44.3% (n =155) were women and men, respectively. The groups were divided based on the time elapsed since positive PCR results, with 53.4% (n =187) and 46.5% (n =163) patients in Groups 1 and 2, respectively. Additionally, CS was detected in 11.1% (n =39), and 16.2% of the patients were hospitalized, and 4% required intensive care. The lungs were involved in 24.5% of the patients. Moreover, fatigue, headache, myalgia, and joint pain were detected in 65.2%, 29.4%, 46.8%, and 46.8% of the patients, respectively. Table 1 shows the frequency and percentage of the categorical variables.

Table 1. *Frequency and percentage values of categorical variables.*

	Frequency (n)	Percentage (%)
Sex		
Female	195	55.7
Male	155	44.3
Groups		
4–12 weeks after the onset of acute disease (Group 1)	187	53.4
>12 weeks after the onset of acute disease (Group 2)	163	46.6
Hospitalization		
Yes	57	16.2
No	293	83.8
Intensive care		
Yes	14	4
No	336	96
Pulmonary involvement		
Yes	86	24.5
No	264	75.5
Central sensitization		
Positive	39	11.1
Negative	311	88.9
Joint pain		
Yes	164	46.8
No	186	53.2
Myalgia		
Yes	164	46.8
No	186	53.2
Headache		
Yes	103	29.4
No	247	70.6
Dyspnea		
Yes	62	17.7
No	288	82.3
Gastrointestinal symptoms		
Yes	72	20.5
No	278	79.5
Palpitation		
Yes	111	31.7
No	239	68.3
Cognitive dysfunction		
Yes	102	29.1
No	248	70.9
Paresthesia		
Yes	125	35.7
No	225	64.3
Weight loss		
Yes	85	24.2
No	265	75.8

The patients were classified into two groups based on symptom duration after COVID-19 infection. Hospitalization (p =0.017), pulmonary involvement (p =0.019), fatigue (p =0.007), joint pain (p =0.013), dyspnea (p =0.038), and admission to intensive care (p =0.021) were significantly different in Group 2. Moreover, myalgia, headache, gastrointestinal symptoms, cognitive dysfunction, paresthesia, weight loss, and palpitations did not differ between the groups. Table 2 shows the comparison of categorical variables based on the groups.

Table 2. *Comparison of categorical variables according to groups.*

	Groups		
	4–12 weeks after the onset of acute disease (Group 1)	>12 weeks after the onset of acute disease (Group 2)	p
Sex			
Female	92 (49.1)	79 (48.4)	0.489*
Male	95 (50.9)	84 (51.6)	
Hospitalization			
Yes	24 (12.8)	33 (20.2)	**0.017****
No	163 (87.2)	130 (79.8)	
Intensive care			
Yes	5 (1.5)	9 (5.5)	**0.021*****
No	182 (98.5)	154(94.5)	
Pulmonary involvement			
Yes	24 (12.8)	62 (38)	**0.019***
No	163 (87.2)	101 (62)	
Fatigue			
Yes	101 (54)	127 (77.9)	**0.007***
No	86 (46)	36 (22.1)	
Joint pain			
Yes	69 (36.8)	95 (58.2)	**0.013***
No	118 (63.2)	68 (41.8)	
Myalgia			
Yes	77 (41.1)	87 (53.3)	0.985*
No	110 (58.9)	76 (46.7)	
Headache			
Yes	40 (21.3)	63 (38.6)	0.125*
No	147 (78.7)	100 (61.4)	
Dyspnea			
Yes	17 (9)	45 (27.6)	**0.038****
No	170 (91)	118 (72.4)	
Gastrointestinal symptoms			
Yes	34 (18.1)	38 (23.3)	0.523**
No	153 (81.9)	125 (76.7)	
Palpitation			
Yes	47 (25.1)	64 (39.2)	0.562*
No	140 (74.9)	99 (60.8)	
Cognitive dysfunction			
Yes	46 (24.5)	56 (34.3)	0.127
No	141 (75.5)	107 (65.7)	
Paresthesia			
Yes	65 (34.7)	60 (36.8)	0.215
No	122 (65.3)	103 (63.2)	
Weight loss			
Yes	35 (18.7)	50 (30.6)	0.325
No	152 (81.3)	113 (69.4)	
Central sensitization			
Positive	10 (5.34)	29 (17.7)	**0.001****
Negative	177 (94.6)	134 (82.3)	

** Pearson's chi-square test; ** Yates correction; *** Fisher's exact test.*

Comparison of quantitative data in both groups showed that pain severity determined by VAS, depression-anxiety scale, pain centering scale, PQAS, and CS inventory scoring were significantly higher in Group 2 (p <0.005). Table 3 shows the comparison of quantitative variables by groups.

Table 3. *Comparison of quantitative variables by groups.*

	Groups				p
	4–12 weeks after the onset of acute disease (Group 1)		>12 weeks after the onset of acute disease (Group 2)		
	Mean ±standard deviation	Median (min–max)	Mean ±standard deviation	Median (min–max)	
Age	46.37 ±12.38	43.7 (18–76)	49.48 ±15.78	48.9 (17–80)	0.102
VAS (visual analog scale)	35.24 ±19.11	50 (20–80)	47.25 ±17.83	60 (20–90)	**0.004**
Depression anxiety scale	11.7 ±3.86	8 (5–32)	12.6 ±8.45	10 (5–38)	**0.011**
Centrality of pain scale	28.00 ±9.33	26 (14–50)	16.36 ±5.31	15 (10–40)	**<0.001**
Pain quality assessment cale	51.72 ±16.67	52 (20–85)	35.10 ±12.08	30 (20–70)	**<0.001**
Central sensitization inventory	28.25 ±14.36	18 (12–42)	31.25 ±16.89	28 (18–48)	**<0.001**

Mann–Whitney U Test; Mean ±standard deviation; Median (min–max).

Univariate analysis showed that symptom duration is an independent risk factor in CS. The CS risk increases 1.105 times as symptom duration increases (p =0.003). The CS risk in Group 1 was 0.15 times less than that in Group 2 (p =0.001). The CS risk was 260,211 times (p <0.001), 43,361 times (p <0.001), 2429 times (p =0.048), and 51,610 times higher (p <0.001) in those who were hospitalized, requiring intensive care, with joint pain, and with headache, respectively. Table 4 shows the logistic regression analysis of the risk factors affecting the CS status and examination results.

Table 4. *Examination of risk factors affecting central sensitization using logistic regression analysis.*

	Univariate	
	OR (95% CI)	p
Age	1.035 (1.006–1.065)	**0.019***
Sex (Reference: Male)	1.137 (0.489–2.64)	0.766
Symptom duration	1.105 (0.968–1.261)	**0.003**
Group (Reference: lasting >12 weeks after onset of acute illness)	0.15 (0.05–0.45)	**0.001**
Hospitalization (Reference: No)	260.211 (33.337–2031.088)	**<0.001***
Intensive care (Reference: No)	43.361 (8.384–224.253)	**<0.001**
VAS	1.007 (0.982–1.032)	0.607
Depression scale	1.274 (1.182–1.373)	**<0.001***
Centrality of pain scale	1.256 (1.161–1.36)	**<0.001**
Pain quality assessment scale	1.078 (1.047–1.11)	**<0.001***
Fatigue (Reference: No)	1.422 (0.511–3.958)	0.501
Joint pain (Reference: No)	2.429 (1.007–5.856)	**0.048**
Myalgia (Reference: No)	1.984 (0.797–4.939)	0.141
Headache (Reference: No)	51.610 (11.701–227.633)	**<0.001***

** In the multivariate model, the Backward Wald method was used to include the independent variables in the model.*

DISCUSSION

The WHO defines post-COVID-19 condition as having symptoms that persist for at least two months and a history of suspected or confirmed SARS-CoV-2 infection, usually three months after COVID-19 start (18). The patients in this study had a positive COVID-19 test at least three months prior to study inclusion, however it was not specified how long the patients' symptoms had persisted.

Studies showed that symptoms (fatigue, weakness, headache, sleep disorders, cognitive dysfunction) persist after infectious diseases with the severe high inflammatory process, such as Epstein-Barr virus, West Nile virus, Zika, Chikungunya, severe acute respiratory syndrome (SARS), and Borrelia (15-17,19). Similarly, post-infection pain has been reported in SARS CoV-2 (1, 20). However, the prevalence of chronic pain after COVID-19 infection remains unknown.

Current ideas suggest that SARS-CoV-2-induced cytokines and interleukin storms may increase the sensitivity of pain pathways (21, 22). SARS-CoV-2 infection could trigger nociplastic pain responses by altering the balance between those neuromodulation systems of nociception (23). Widespread symptomatology has also been linked to inadequate immune regulatory mechanisms which may suggest a prolonged immune system impact in individuals with post-COVID pain, ultimately leading to increased sensitization (24). There is evidence that up to 60% of patients experience multiple symptoms following the acute phase of COVID-19 infection. The most common post-COVID symptoms are fatigue and dyspnea (25, 26). In the current study, fatigue, myalgia, and pain were also highly prevalent symptoms (27). There's growing evidence that post-COVID pain bears similarities to musculoskeletal characteristics (28). In the present study joint pain and myalgia were seen %46.8. The fundamental idea behind the term "nociplastic pain" is that sensitization-associated symptoms can be linked to both neuropathic pain disorders and chronic musculoskeletal pain (29).

The term "nociplastic pain" refers to pain that results from altered nociception without conclusive proof of disease or somatosensory system lesion causing pain, or proof of tissue damage activating peripheral nociceptors (30). In addition to exaggerated pain responses, nociceptive pain conditions are linked to symptoms originating from the central nervous system, including exhaustion, insomnia, memory loss, and psychological disruptions (31). Since exhaustion and memory loss are two of the most common post-COVID symptoms, all

these characteristics have been seen in people with prolonged COVID (25, 26). In the current study,%29.1 of the patients had cognitive dysfunction.

According to a recent meta-analysis, the prevalence of post-COVID pain varied between 4.6% and 18.1% at various follow-ups in the first year following the infection (27). Indeed, a sizable cohort study found that, eight months after hospitalization, up to 45% of previously hospitalized COVID-19 survivors experienced musculoskeletal post-COVID pain (32). Actually, a Delphi study attempted to determine the sensitization phenotypes of people experiencing pain following COVID-19 (33). According to that study, orthostatic intolerance, pain, fatigue, dyspnea, and gastrointestinal issues were among the symptoms linked to sensitization (33). In the present study symptoms associated with sensitization like gastrointestinal problems were seen %20.5, palpitation %31.7, and paresthesia were %35.7.

According to Ibañez et al. those with pre-existing chronic pain sensitization syndromes were more likely to experience psychological distress during the global COVID-19 pandemic (34). Actually, the available data indicates that psychological variables and stress had a major influence on how the pain was processed. A probable reason could be the dysfunction of serotonergic and noradrenergic neurons impacting somatic and psychological pain pathways (35).The finding that the CSI score was positively correlated with anxiety and depression levels is consistent with earlier research on individuals with chronic pain (36). In the present study Depression anxiety scale and vas Central sensitization inventory score were statically higher in group 2 with long covid patients, Centrality of pain scale, Pain quality assessment scale were higher in group 1.

This results support the assumption that the CSI questionnaire can exhibit a significant overlap with psychological construct as previously suggested (37). One of the main symptoms of disorders linked to central sensitization is fatigue (38, 39). This has led to the theory that patients with post-COVID-19 conditions and those with chronic pain may share a common etiology, which is central sensitization (33). Recent data indicates that a subset of patients with post-COVID-19 illness may have central sensitization. A Belgian study that used the central sensitization inventory (CSI), a self-rated questionnaire, revealed that 70% of people with post-COVID-19 condition had sensitization-associated symptomatology (40). In contrast, a Spanish study found that only 34% of patients in a group exhibiting post-COVID pain had this prevalence(41). The fact that people with post-COVID-19 condition display a number of symptoms related to the central nervous system, such as exhaustion, sleep issues, memory loss, concentration issues, or psychological disturbances, provides additional evidence in favor of the existence of central sensitization (42).Along with acute symptoms of infectious disease, they may include prolonged fatigue, sleep disturbances, nausea, headaches, and cognitive dysfunction, lasting in many cases for much longer than 6 months, and eventually, patients may satisfy the requirements for CFS or another CSS. Table 5 includes the criteria for CFS (43-47).

Table 5*. Centers for disease control and prevention diagnostic criteria for chronic fatigue syndrome (18).*

Severe fatigue for >6 months and at least four of the following symptoms:	
Headache of a new type, pattern, or severity Multijoint pain without swelling or erythema Muscle pain Postexertional malaise for >24 h Sigificant impairment in short-term memory or concentration	Sore throat Tender lymph Nodes Unrefreshing sleep

Recently, genes related to the epigenetics of FM, which is one of the CSS, are suggested to be dormant and activate the disease in long-term stressful situations, such as social, major medical, economic, or physical stressors (48-53). Following this activation, patients with CS disorders experience fatigue and an often significant symptom burden, which was detected by clinical testing due to central nervous system sensitivity to various stimuli, including vision, hearing, smell, and pain.

The etiology of symptoms persisting after COVID-19 infection may vary. This may be caused by the need for intensive care and ventilator, long hospitalization, and COVID-19. In present study, the CS in patients who were hospitalized, needed intensive care, and had lung involvement were significantly different compared who didn't need hospitalization.

Previous studies determined that the most common infections related to patients with post-COVID-19 were EBV, West Nile virus, and Borrelia spp. Additionally, they exhibit similarities to other post-infectious disorders, including those linked to the disease (53-56)

In this study, the most common symptoms were fatigue, joint pain, and myalgia. These patients may be clinically diagnosed with one of the prevalent CSS disorders if their symptoms last for 6 months without any other clear underlying cause. Data showed that the CS frequency after COVID-19 infection was 11%. However, only a few studies have investigated this subject. Bierle et al. (33) detected persistent COVID-19 symptoms in 9% (42/465) of patients with COVID-19, contributing to the definition of the post-COVID-19 syndrome. Currently, post-COVID-19 syndrome presents a wide range of symptoms in all age groups, showing that individual factors also affect this condition (51-53). Studies have reported that secondary symptoms may develop in asymptomatic patients (55). Thus, patients with CSS may possibly develop new or worsening symptoms after COVID-19 infection.

This study has some limitations. First, the current results can only be utilized by patients with mild-to-moderate COVID-19 who were hospitalized. Second, laboratory parameters were not investigated. Third, data on the presence of CSS in patients before infection were unavailable. Finally, asymptomatic–symptomatic questioning of patients in the acute period was lacking, and only a few patients were included in the study.

Conclusions

In present study, the fact that pain scales, depression scale and central sensitization scale scores were higher in patients whose symptoms persisted for more than 12 weeks after infection suggests that central sensitization should be kept in mind in the post-covid period. However, the long-term effects of COVID-19 infection should be studied in the future.

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