North Clin Istanb 2023;10(3):359–366
doi: 10.14744/nci.2022.31932

ORIGINAL ARTICLE PT&R

Neuropathic pain in patients with post-COVID-19

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ABSTRACT

OBJECTIVE: In this study, we aimed to determine the continuing pain during the post-COVID-19 period the frequency of neuropathic pain in these patients, and the factors affecting the frequency.

METHODS: A total of 209 participants were included in the study who had COVID-19 disease (PCR-positive) aged 18–75 years. The demographic characteristics and COVID-19 severity data were recorded by questioning the patients. The musculoskeletal pain was also assessed using Visual Analog Scale (VAS) and the extended Nordic musculoskeletal system questionnaire (NMQ-E). In addition, the neuropathic components of pain were evaluated using the Leeds Assessment of neuropathic symptoms and Signs (LANSS) pain scale and the Pain-DETECT questionnaire (PDQ).

RESULTS: The mean time elapsed since COVID-19 was 5.76±2.95 months (min, 1; max, 12). Six patients (2.9%) had neuropathic pain according to the LANSS score, and 12 patients (5.7%) according to the PDQ score. The NMQ-E indicated that the most pain was detected in the back (20.1%), low back (15.3%), and knee (11.5%) regions during the post-COVID-19 period. According to both neuropathic pain scales; low back pain (p=0.001/0.001) and knee pain (p=0.001/0.01) were more common in patients with PDQ/LANSS neuropathic pain. Logistic regression analysis showed that there were significant associations between neuropathic pain and acute COVID-19 VAS score.

CONCLUSION: This study demonstrated that musculoskeletal pain was prominent mostly in the back, low back, and knee during the post-COVID-19 period. The incidence of neuropathic pain was 2.9%–5.7% depending on the evaluation parameters. Neuropathic pain is a finding that should be considered during the post-COVID-19 period.

Keywords: COVID-19; pain; post-COVID-19; neuropathic pain.

Cite this article as: *Comruk EB, Buyukavci R, Comruk E, Akturk S, Ersoy Y. Neuropathic pain in patients with post-COVID-19. North Clin Istanb 2023;10(3):359–366.*

Coronavirus disease 2019 (COVID-19), the major pandemic of the current century, which is caused by a new type of coronavirus named SARS-CoV-2, was first identified in December 2019 [1]. Although the lungs are mainly affected by COVID-19, symptoms outside the respiratory system are also noted. This is thought to be because angiotensin-converting enzyme-2 (ACE-2), the main SARS-CoV-2 input receptor is commonly expressed in a variety of tissues [2–5].

Human coronaviruses are thought to be neuro-invasive and possibly carried via axonal transport. They have been associated with common neurological symptoms, such as encephalitis, anosmia, acute flask paralysis, and Guillan–Barré syndrome [6]. Similar to other respiratory viruses, SARS-COV-2 can infest the skeletal muscle, vascular smooth muscle, and brain through the bloodstream or through retrograde axonal transport. However, clear evidence of ACE-2 receptor expression in the brain is still insufficient, and the potential mechanism of neuroinvasion remains unclear [7].

Received: May 31, 2022 *Accepted:* June 22, 2022 *Online:* June 22, 2023

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Pain is one of the most common symptoms of COVID-19. In the acute period, the other most commonly reported symptoms are muscle pain, joint pain, headache, and abdominal pain. Neuropathic pain due to COVID-19 is less common. In the post-COVID period, the most frequent symptoms are fatigue, dyspnea, and musculoskeletal pains [8]. The presence of neuropathic pain symptoms besides peripheral pain led clinical researchers to investigate associated pain characteristics. The exact mechanisms by which SARS-CoV-2 infects the peripheral nervous system are unknown. A study suggested that nociceptors expressing ACE-2 mRNA may form free nerve endings in the skin and luminal organs [9].

Complaints of neuropathic pain due to COVID-19 started as case reports and then continued to be reported as case series [10–12]. In this study, we aimed to determine the incidence of neuropathic pain and the factors affecting it in the post-COVID-19 period.

MATERIALS AND METHODS

The study was designed as a cross-sectional observational study. The study was performed in accordance with the Helsinki Declaration and approved by the Inonu University Scientific Research Ethics Committee (no: 2021/1682). The exclusion criteria were as follows: previous experience of neuropathic pain, taking medication for neuropathic pain, having diagnoses that are frequently accompanied by neuropathic pain (polyneuropathy, stroke, multiple sclerosis, and diabetes mellitus), and patients without COVID-19 (PCR-negative). Written informed consent was obtained from all the participants. Participants under the supervision of a physician filled out the questionnaires.

Patients with COVID-19 (PCR-positive) aged between 18 and 75 years were included in the study. The demographic data of the patients were recorded. Data on symptoms during the active COVID-19 period, the form of treatment (inpatient or outpatient care or intensive care hospitalization), and the post-infection period were recorded by asking the patient. The pain level of the patients was evaluated using the Visual Analog Scale (VAS) during the active COVID-19 period, in the last month, and the last week. The extended Nordic musculoskeletal system questionnaire (NMQ-E) was used to measure and compare musculoskeletal pain. To evaluate the neuropathic pain within the musculoskeletal system, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and pain-DETECT questionnaire (PDQ) Neuropathic Pain were used.

Highlight key points

- Musculoskeletal pain was most prevalent in the back, lower back, and knee in the post-COVID period.
- The frequency of neuropathic pain was significantly high in the post- COVID period.
- 3-Neuropathic pain is a finding that should be considered during the post-COVID-19 period.

NMQ-E

NMQ-E is a questionnaire that is used to measure musculoskeletal symptoms. NMQ-E provides reliable information about the onset, prevalence, and impact of musculoskeletal pain in nine body regions (neck, shoulders, back, elbows, wrists/hands, low back, hips/thighs, knees, and ankles/feet) and can be self-administered or interviewer-administered. In the test, people are questioned whether they experienced pain or discomfort that will prevent daily activity in the past 12 months, in the past 4 weeks, and during the evaluation. Answers are marked as yes/no [13].

PDQ

PDQ is a scale consisting of 13 questions with a maximum score of 38. Alkan et al. [14] proved the validity and reliability of the scale in Turkish patients. We considered <12 points as negative and ≥12 as suspicious/positive in our study.

LANSS

The LANSS pain scale is a scale consisting of seven items. Five of the sections evaluate pain symptoms. The other two are for sensory examinations, including allodynia and pin and needle sensation testing. The answers to the questions are yes/no. The total scale ranges from 0 to 24. Scores of ≥12 indicate neuropathic pain. Yucel et al. [15] proved the validity and reliability of the LANSS pain scale in Turkish patients.

Statistical Analysis

Statistical analysis was performed using the SPSS version 22 program (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA). Descriptive data for categorical variables were presented as the number (n) and percentage (%) and continuous variables as the mean±standard deviation. The normal distribution of continuous variables was tested using the Kolmogorov–Smirnov test. Differences in categorical variables

Table 1. Demographic characteristics of the patients

	All patients	
	n	%
Age (years)	37.5±12	
Sex (female/male)	119/90	
Patient follow-up		
Outpatient	194	92.8
Inpatient	13	6.2
Intensive care	2	1
COVID-19 symptoms		
Asymptomatic	10	4.8
Pain	161	77
Arthralgia	117	56
Myalgia	141	67.5
Weakness	143	68.4
Fever	80	38.3
Dyspnea	46	22
Cough	76	36.4
Chest pain	36	17.2
Nausea	24	11.5
Vomiting	15	7.2
Diarrhea	32	15.3
Headache	124	59.3
Thromboembolism	4	1.9
Skin complications	13	6.2
Loss of taste or smell	106	5.7
Depression	3	1.4

COVID-19: Coronavirus disease 2019.

between groups were compared using the Chi-square test (Pearson Chi-square). The Mann–Whitney U-test was performed to compare differences between two independent groups. The Spearman correlation test was performed to measure the degree of association between continuous variables. Linear logistic regression tests were used. $P<0.05$ was considered statistically significant.

RESULTS

Two hundred and nine participants were included in the study, including 119 (56.9%) women and 90 (43.1%) men. The participants had a mean age of 37.5±12.0 (min, 19; max, 74) years. The mean post-COVID-19 period was 5.76±2.95 (min, 1; max, 12) months.

Table 2. VAS scores of the patients

	Mean±SD	Min–Max
VAS score during active COVID-19 period	5.44±3.06	0–10
VAS score in the past month	1.16±1.99	0–8
VAS score in the past week	1.09±1.99	0–9

VAS: Visual Analog Scale; SD: Standard deviation; Min: Minimum; Max: Maximum.

Table 3. LANSS scores of the patients and the correlation of PDQ scores to other parameters

	LANSS score	PDQ score
Age (years)		
r	0.067	0.131
p	0.336	0.059
VAS score during active COVID-19		
r	**0.239**	**0.292**
p	**0.001***	**0.001***
VAS score in the past month		
r	**0.415**	**0.559**
p	**0.001***	**0.001***
VAS score in the past week		
r	**0.438**	**0.580**
p	**0.001***	**0.001***
Post-COVID-19 period (months)		
r	-0.076	-0.121
p	0.275	0.080

LANSS: Leeds assessment of neuropathic symptoms and signs; PDQ: Pain-DETECT questionnaire; VAS: Visual Analog Scale; r=Spearman Correlation test; p=Statistically significant; COVID-19: Coronavirus disease 2019; *: Statistically significant.

Only 10 (4.8%) patients were asymptomatic during the active COVID-19 period. Fatigue (68.4%) and myalgia (67.5%) were the most common COVID-19 symptoms. Headache (59.3%), loss of smell and taste (50.7%), thromboembolism (1.9%), and depression (1.4%) were the most prevalent neurological symptoms. Overall, 194 (92.8%) patients were treated as outpatients, 13 (6.2%) were inpatients, and 2 (1%) were in intensive care (Table 1).

In 41 (19.6%) patients, musculoskeletal pain was prominent during the post-COVID-19 period. The most frequent regions in which musculoskeletal pain was experienced were the back (20.1%), lower back (15.3%), and knee (11.5%).

Table 4. Significant variables of neuropathic pain (PDQ/LANSS) using logistic regression analysis

	Beta	Wald	OR	95% CI		p
				Lower	Upper	
VAS score during active COVID-19						
PDQ	0.550	7.363	1.734	1.165	2.580	0.007*
LANSS	0.654	4.573	1.924	1.056	3.504	0.032*
VAS score in the past month						
PDQ	0.215	0.752	0.807	0.494	1.311	0.386
LANSS	0.437	1.489	1.549	0.767	3.127	0.222
VAS score in the past week						
PDQ	0.490	4.365	1.632	1.031	2.585	0.057
LANSS	-0.220	0.322	0.802	0.375	1.716	0.570

OR: Odd ratios; CI: Confidence interval; COVID-19: Coronavirus disease 2019; VAS: Visual Analog Scale; LANSS: Leeds assessment of neuropathic symptoms and signs; PDQ: Pain-DETECT questionnaire p=Statistically significant; *: Statistically significant.

The mean VAS score of the patients was 5.44±3.06 during the active COVID-19 period, 1.16±1.99 during the past month, and 1.09±1.99 during and past week (Table 2). Further, 6 patients (2.9%) had neuropathic pain according to the LANSS scale, and 12 patients (5.7%) according to the PDQ.

Correlation analysis demonstrated that there was a significant positive correlation between both the LANSS score and PDQ score and the VAS score in the active COVID-19 period, VAS score in the past month, and VAS score in the past week (Table 3). Linear logistic regression analysis revealed that the VAS score during the acute COVID-19 period could successfully predict the presence of neuropathic pain compared with both LANSS and PDQ scores ($p<0.05$) (Table 4).

There was no significant difference in the presence of neuropathic pain according to PDQ and LANSS categories between headache, thromboembolism, loss of smell and taste, and depression ($p>0.05$) (Table 5).

Pain-DETECT demonstrated that patients with neuropathic pain had significantly higher rates of disorders in the past month in their neck ($p=0.012$), back ($p=0.01$), hand/wrist ($p=0.014$), low back ($p<0.001$), knee ($p<0.001$), and foot/ankle ($p=0.014$). According to LANSS, those with neuropathic pain showed higher rates of disorders in the low back ($p<0.001$) and knee ($p=0.014$) (Table 6).

DISCUSSION

There are recent but limited studies on the incidence and risks of neuropathic pain after SARS-CoV-2 infection. In this study, we aimed to determine the incidence of neuropathic pain and the factors affecting it in the continuing pain during the post-COVID-19 period. According to our results, musculoskeletal pain continued most frequently in the back, low back, and knee after the COVID-19 infection. In addition, although it varies depending on the evaluation parameters, the incidence of neuropathic pain in the post-COVID-19 period was 2.9%–5.7%. The most important risk factors for neuropathic pain during the post-COVID-19 period were pain intensity during acute COVID-19 infection and continuing pain in the lower back and knee during the post-COVID-19 period.

As is known, viral infections can have a direct impact on the peripheral or central nervous system or induce a post-viral immune syndrome [16, 17]. The binding of SARS-CoV-2 to skeletal muscle cells, vascular smooth muscle cells, and ACE-2 receptors in the brain causes a decrease in ACE-2 receptor levels and is responsible for ACE-2-mediated neurotoxicity, neuroinflammation, and neurodegeneration [18–20]. Garvin et al. [21] suggested that SARS-CoV-2 increases ACE-2 levels while decreasing ACE levels in lung cells, which in turn may be responsible for the "bradykinin storm" that can cause pain in COVID-19. Consequently, besides cough and dyspnea, symptoms, and signs such as

Table 5. Comparison of participants with and without central nervous system involvement according to the presence of neuropathic pain (according to PDQ and LANSS)

	PDQ			LANSS		
	Negative (%)	Suspect/positive (%)	p*	No (%)	Yes (%)	p*
Headache						0.710
Yes (n=124)	92.7	7.3	0.367	96.8	3.2	
No (n=85)	96.5	3.5		97.6	2.4	
Thromboembolism						0.728
Yes (n=4)	100	0	0.618	100	0	
No (n=205)	94.1	5.9		97.1	2.9	
Loss of taste or smell						0.441
Yes (n=106)	93.4	6.6	0.587	98.1	1.9	
No (n=103)	95.1	4.9		96.1	3.9	
Depression						0.764
Yes (n=3)	100	0	0.667	100	0	
No (n=206)	94.2	5.89		97.1	2.9	

LANSS: Leeds assessment of neuropathic symptoms and signs; PDQ: Pain-DETECT questionnaire; *: Chi-square analysis was performed: p=Statistically significant.

Table 6. NMQ-E: Patients' experience of pain in the last month? (F-subtitle) (according to PDQ and LANSS)

	PDQ			LANSS		
	Negative (%)	Suspicious/positive (%)	p*	No (%)	Yes (%)	p*
Neck	7.1	33.3	**0.012**	8.4	16.7	0.476
Shoulder	4.6	16.7	0.124	4.9	16.7	0.280
Back	16.2	50	**0.01**	17.7	33.3	0.299
Elbow	1	8.3	0.163	1.5	0	0.764
Hand/wrist	3.6	25	**0.014**	4.9	0	0.577
Low back	8.6	66.7	**<0.001**	9.4	100	**<0.001**
Hips/thighs	3	16.7	0.070	3.9	0	0.620
Knee	7.6	50	**<0.001**	8.9	50	**0.014**
Foot/ankle	3.6	25	**0.014**	4.4	16.7	0.258

NMQ-E: Extended nordic musculoskeletal system questionnaire; LANSS: Leeds assessment of neuropathic symptoms and signs; PDQ: Pain-detect questionnaire; *: Chi-square analysis was performed: p=Statistically significant.

fever, fatigue, myalgia, and arthralgia may be observed in patients with COVID-19 [22]. Recent pharmacological studies have investigated the effect of bradykinin on neuropathic pain mechanisms [23]. Bradykinin is the key regulator of neuro-immune signaling, and it modulates the migration of neural stem cells and neurogenic differentiation [24]. It has been demonstrated that the activation of this signaling pathway is induced by various cytokines [25]. Our results support that the severity of pain caused by the virus in the acute period is a neuropathic pain predictors in the post-COVID-19 period.

The virus has a direct or indirect impact on the nervous system. The exact mechanism of action of SARS-CoV-2 on the peripheral nervous system is unknown. Shiers et al. [9] found that a nociceptor subpopulation

of human dorsal root ganglion neurons expresses ACE-2 mRNA. It has been suggested that SARS-CoV-2 may gain access to the nervous system through entry into neurons that form free nerve endings at the skin and luminal organs. In a retrospective study, neurological findings of 214 patients with COVID-19 hospitalized in Wuhan, China, were analyzed. Neuropathic pain was detected in only 5 (2.3%) of 78 (36.4%) patients who had neurological findings. However, no objective parameters were used in the evaluation of neuropathic pain [6]. In a larger cohort, Romero-Sanchez et al. [26] in their patient-based study detected more neurological symptoms than the study in Wuhan. In this study, the neurological findings were detected in 57.4% of all cases. However, neuropathic pain was not analyzed separately, although peripheral neurological symptoms were included in the study. Aksan et al. [11] reported a new case of SARS-CoV-2-related neuropathic pain and allodynia in which the diagnosis was made after drug treatments. Correia et al. [8] analyzed seven studies in their review. Headache was found to be the most prevalent accompanying neurological finding. Dizziness, altered consciousness, vomiting, and epileptic crises were the other prominent symptoms. Importantly, neuropathic pain was noted in 1.2% of patients. Nevertheless, the parameters that determine neuropathic pain were unclear in the studies reviewed. Ozdag Acarli et al. [27] analyzed neurological symptoms and suggested that headache (52.1%) was the most common neurological symptom of COVID-19. This was followed by dizziness, altered consciousness, loss of taste and smell, acute cerebrovascular disease, encephalitis, and epilepsy, and the incidence of neuropathic pain was 1.3%. We found in our patient group that the incidence of neuropathic pain in the post-COVID-19 period was 2.9%–5.7% depending on the evaluation parameters.

Consistent with the previous literature, headache, loss of smell and taste, thromboembolism, and depression were the most frequent neurological symptoms associated with COVID-19 infection in our study. However, there was no significant difference between the presence of neurological symptoms and neuropathic pain. In a recent retrospective study conducted in Turkiye, patients with COVID-19 were evaluated with telerehabilitation in the post-COVID period of 1.5–3 months. As a result, female sex, asthenic body structure, cough, sore throat, anosmia, headache, myalgia, and high levels of ferritin at baseline were found to be determinants of neuropathic pain. This study revealed a strong association between neuropathic pain and headache. In addition, symptoms of pain in the extremities, back, and neck were found to be higher in patients with neuropathic pain [28].

In our study, NMQ-E showed that the back (20.1%), waist (15.3%), and knee (11.5%) were the most common regions where the pain was experienced. In parallel, according to PDQ, patients with neuropathic pain had significantly higher rates of disorders in the neck, back, elbow, hand/wrist, waist, knee, and foot/ankle in the past month, whereas LANSS indicated that the rate of neuropathic pain was significantly higher in the waist and knee in the past month. A recent study demonstrated that musculoskeletal pain was present in 45.1% of COVID-19 survivors at 8 months after hospital discharge, with most patients developing "de novo" post-COVID pain. The presence of myalgia and headache as COVID-19 symptoms at the acute phase and days at the hospital were reported as risk factors associated with post-COVID musculoskeletal pain [29]. Most patients had mild COVID-19 in our study and 41 (19.6%) patients experienced musculoskeletal pain (mostly in the back, lower back, and knee) at an average of 5 months after infection. In addition, back and knee pain in the post-COVID period was identified as a risk factor associated with neuropathic pain.

The absence of gold-standard diagnostic tests for neuropathic pain can increase the potential of unrecognized cases. In our study, LANSS and PDQ were employed as screening tests, and the incidence and prevalence of neuropathic pain differ in the literature. This is due to differences in definitions of neuropathic pain and pain with neuropathic characteristics, in definitions of clinical conditions/diseases associated with neuropathic pain, in the methods of case detection, and differences in case detection tools (e.g., screening tools versus electronic databases for medical cases) [30, 31]. On the other hand, the acute and chronic periods of COVID-19 are unknown, which has grabbed the attention of the world, with different symptoms and findings. The mechanisms of action of SARS-CoV-2 in the musculoskeletal and nervous systems are still a matter of debate. Our understanding of the pathophysiology of COVID-19 and the relationship between pain syndromes in COVID-19 will evolve as future studies are conducted. Defining the characteristics of pain syndromes that may be caused by different mechanisms will help to better understand different pain mechanisms and improve analgesic prescription.

Limitations

The lack of standardization in the screening tests used in this study led to differences in the incidence of neuropathic pain. The limited number of patients and the majority of outpatients (who had mild COVID-19) are the other limitations.

The strength of our study is that the incidence of neuropathic pain during the post-COVID period was evaluated using two major neuropathic pain questionnaires that are valid and reliable.

Conclusion

This study demonstrated that musculoskeletal pain was prominent mostly in the back, low back, and knee during the post-COVID-19 period. We also found that the incidence of neuropathic pain was between 2.9% and 5.7%, although it varied depending on the evaluation parameters. The most common symptoms during the post-COVID-19 period were fatigue and muscle pain; the incidence of neuropathic pain was also highly significant. Along with neurological symptoms related to COVID-19, there is a need for studies investigating the etiology and incidence of neuropathic pain during the post-COVID-19 period.

Ethics Committee Approval: The Inonu University Scientific Research Ethics Committee granted approval for this study (date: 23.02.2021, number: 2021/1682).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – EBC, RB; Design – EBC, RB; Supervision – RB, YE; Materials – EBC; Data collection and/or processing – EBC; Analysis and/or interpretation – EBC, EC; Literature review – EBC, EC, RB, SA; Writing – EBC, RB; Critical review – RB, SA, YE.

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