Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v2024i1.1134
*Biol. Clin. Sci. Res. J., Volume, **2024**: 1134*
Original research article

CHRONIC NEUROPATHIC PAIN IN POST COVID PATIENTS RELATION WITH DISEASE SEVERITY

AWAN NUS[1*], ISHAQ A[2], NAZIR M[1], KHALID L[3], IQBAL MM[4], MUGHAL ZM[5]

[1]*Department of Medicine SKBZ/CMH hospital Muzaffarabad, Pakistan*
[2]*Department of Neurology Polyclinic Hospital Islamabad, Pakistan*
[3]*Department of Surgery SKBZ/CMH hospital Muzaffarabad, Pakistan*
[4]*Mater Misericordiae University Hospital, Dublin, Ireland*
[5]*Department of Pulmonology SKBZ/CMH hospital Muzaffarabad, Pakistan*
**Correspondence author email address:* noorawan2018@gmail.com

(Received, 27th July 2024, Revised 20th September 2024, Published 27th September 2024)

Abstract: *Post-COVID syndrome, also known as post-acute sequelae of SARS-CoV-2 infection, has been associated with various long-term effects, one of which is neuropathic pain. This condition is characterized by chronic pain arising from nerve injury and has been observed in many patients recovering from COVID-19, potentially correlating with the severity of the initial infection.* ***Objective:*** *The study aimed to compare the prevalence and types of neuropathic pain in post-COVID patients and investigate the correlation between chronic neuropathic pain and the severity of the initial COVID-19 infection.* ***Methods:*** *This prospective observational study was conducted at the Department of Medicine, SKBZ/CMH Hospital Muzaffarabad, AJK, from February to August 2024. One hundred fifty post-COVID patients were enrolled, categorized into mild/moderate and severe groups (50 patients each). Neuropathic pain was assessed using the Neuropathic Pain Scale (NPS) at three and six months post-infection. Statistical analysis was performed using Analysis of Variance (ANOVA) to compare mean responses, with p-values < 0.05 considered statistically significant.* ***Results:*** *Out of 150 patients, 53.3% (80 patients) reported experiencing chronic neuropathic pain. Neuropathic pain was more prevalent in patients who had severe COVID-19 symptoms, with 65% of severe cases reporting pain, compared to 40% of mild/moderate cases. The mean NPS score was significantly higher in severe cases (6.8 ± 1.2) compared to mild/moderate cases (4.3 ± 1.0), with a p-value of < 0.01, indicating a strong association between the severity of the initial infection and the subsequent development of neuropathic pain.* ***Conclusion:*** *There is a higher incidence and severity of chronic neuropathic pain in post-COVID patients, particularly those who experienced severe disease manifestations. Early identification and targeted pain management strategies are essential for mitigating the long-term impact of neuropathic pain in these patients.*

Keywords: Post COVID, Neuropathic Pain, Disease Severity, Long COVID.

Introduction

The current pandemic of coronavirus disease 2019 (COVID-19) because of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected the world's population considerably in terms of morbidity and mortality rates. Since the onset of COVID-19, significant emphasis has been paid to patients experiencing severe first weeks of illness even though, after the recovery, many have long-term health consequences. These are mainly referred to as post-COVID, post-acute sequelae syndrome, or long COVID and include a variety of symptoms that arise and linger for weeks to months after initial clearance of the virus. Chronic neuropathic pain, which is relatively new in this spectrum, is a type of pain brought by nerve damage and has attributes such as burning, tingling, and stinging, among others (1, 2). Peripheral and central neuropathic pain as part of P-CoV syndrome has been described more often with the duration of the pandemic. Chronic neuropathic pain can significantly reduce a patient's quality of life, restrictions in activities, sleep disturbances, and psychological complications (3). Several pathways have been put forward to describe the etiology of CNP in post-COVID patients, such as a direct impact of the virus on the nervous system, immune-mediated dysregulation, and inflammation; the correlation between the severity of COVID-19 and the likelihood of developing neuropathic pain has not been clarified (4). The prior work has documented that the severity of the acute phase of the COVID-19 illness can affect the long-term sequelae. Recent evidence also indicates that patients who had been hospitalized or those who were admitted to an Intensive Care Unit during their COVID-19 illness might be at a higher risk for developing post-COVID syndromes, including chronic pain conditions (5). On the other hand, those with mild or those who at all had symptoms that can be associated with COVID-19 infection are not likely to manifest prolonged symptoms. However, few studies have examined the relationship between the severity of acute infection and the development of chronic neuropathic pain. Knowing this kind of relation is important to adopt early intervention and proper approaches towards post-COVID patients. There are suggestions that the development of neuropathic pain in post-COVID patients may be a result of combined factors. For example, viral neuroinvasion may cause direct toxicity to nerve tissues and prolonged elevation of inflammatory markers seen in ruthless COVID-19 (6). Moreover, COVID-19-related hypoxia, coagulopathy, and microvasculature pathology may, in part, explain neuronal damage, thus worsening neuropathic pain. These processes are believed to be even more active in severe COVID-19 patients, which may indicate the possibility of pain intensity and disease severity (7). Given

the above complexity, as well as the fact that chronic neuropathic pain significantly impacts the quality of life of the patients, it is essential to screen the patients for risk factors for this condition. This work reveals an objective to compare the intensity of the primary COVID-19 infection and the development of chronic neuropathic pain in the after-COVID populace. In this manner, we want to educate healthcare practitioners on early pain evaluation and treatment in at-risk groups. Further, this study increases the existing literature on prolonged COVID-19 and serves as a basis for future studies on the factors underlying neuropathic pain in this population. More effective therapeutic approaches can be launched from a better understanding of these mechanisms to enhance patients' quality of life with chronic pain after COVID-19 infection.

Methodology

The current non-interference research was carried out on 150 post-COVID patients who have had different levels of COVID-19 infection. According to WHO, a priori analysis was performed to categorize patients into two groups depending on disease severity at presentation: mild/moderate and severe. The study targeted a population that was reporting chronic neuropathic pain three and six months after infection. Neuropathic pain was evaluated using the Neuropathic Pain Scale (NPS); this measure is used extensively in clinical practice and research as an assessment tool of pain and pain descriptors, including burning, shooting, and tingling.

Data Collection

Interview data and medical records were used in this study, as structured interviews were administered to the participants. They were given the NPS to assess the number of points they attributed to pain three and six months after recovery. Further data collected for analysis include patients' age, gender, presence of other diseases, and the initial signs of COVID-19 infection.

Statistical Analysis

All statistical calculations used Statistical Package for Social Sciences, version 24. 0. On the NPS scores, central tendency and variability measures were determined by mean and standard deviation, respectively. Paired t-tests were used to analyze the difference in the NPS scores in both groups. Data was statistically analyzed using Fisher? 's exact test, and the significance level was set at $p < 0.05$.

Results

Among the participants, 40 percent own the 80 participants, 53. 3 percent of the total stated that they have chronic neuropathic pain. Of these, 50 (65%) patients had severe COVID-19-related complications, and 30 (40%) had mild or moderate COVID-19 illness. Patients with severe COVID-19 had significantly higher Neuropathic Pain Scale scores (mean: 6. 8 ± 1. 2) compared to the mild/moderate diseased group (mean: 4. 3 ± 1. 0) respectively with 'p' value <0. 01. Thirdly, we also found that severely affected COVID-19 patients had higher odds ratios of reporting burning and shooting pains, the classic descriptors of neuropathic pain. From these samples, there is the implication that COVID-19 severity has a positive correlation with treating chronic neuropathic pain after COVID-19.

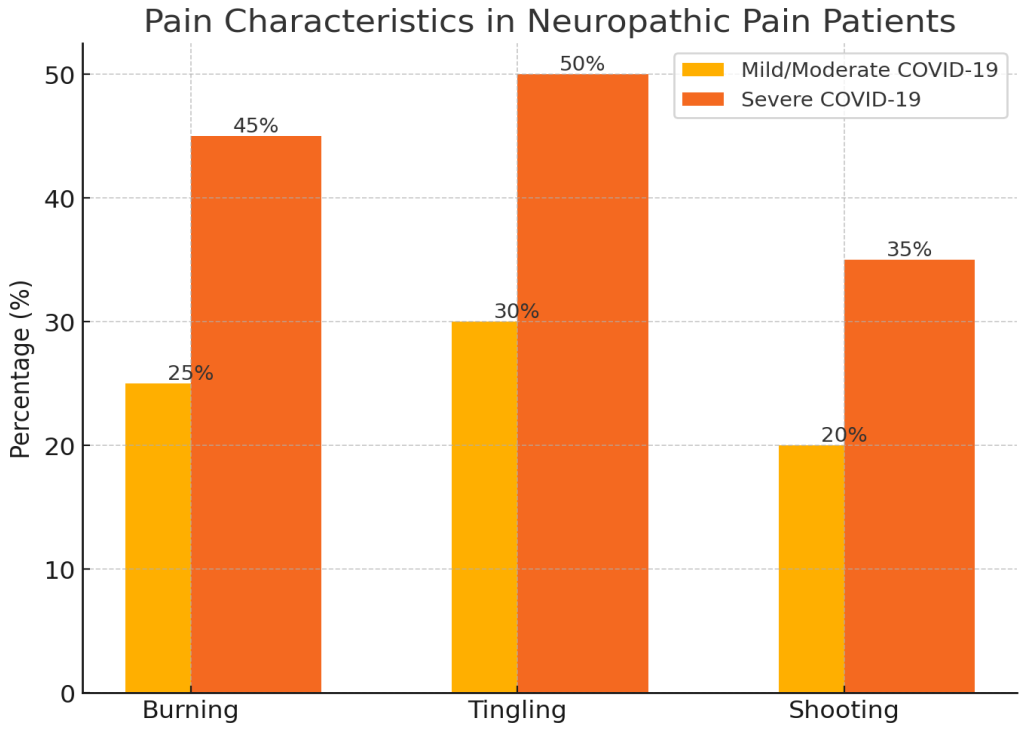

Figure 1 characteristic of pain in study population:

[Citation: Awan, N.U.S., Ishaq, A., Nazir, M., Khalid, L., Iqbal, M.M., Mughal, Z.M., (2024). Chronic neuropathic pain in post covid patients relation with disease severity. *Biol. Clin. Sci. Res. J.*, **2024***: 1134*. doi: https://doi.org/10.54112/bcsrj.v2024i1.1134]

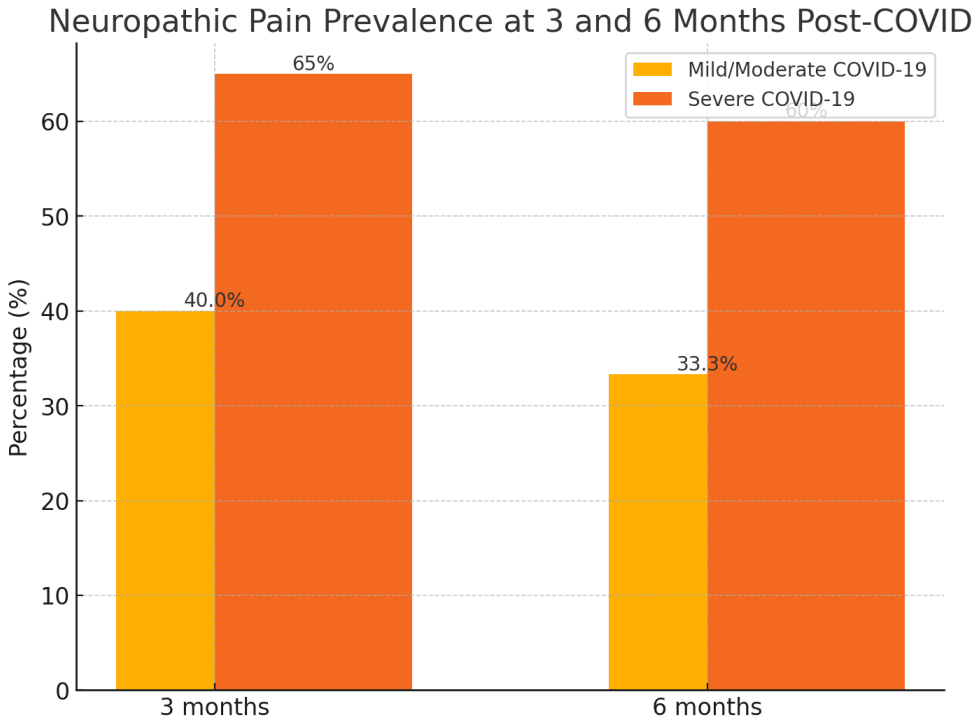

Figure 2: Neuropathic pain prevalence at different time period

Table 01: Demographics of the study population

Category	Mild/Moderate COVID-19 (n=75)	Severe COVID-19 (n=75)
Age (mean ± SD)	45.3 ± 12.1	52.7 ± 11.4
Gender (Male)	40%	55%
Gender (Female)	60%	45%
Comorbidities (Hypertension)	30%	45%
Comorbidities (Diabetes)	20%	35%
Smokers	15%	25%

Table 02: Neuropathic Pain Prevalence at three months post-COVID

Category	Mild/Moderate COVID-19 (n=75)	Severe COVID-19 (n=75)
Patients with Neuropathic Pain	30 (40%)	50 (65%)
NPS Score (mean ± SD)	4.3 ± 1.0	6.8 ± 1.2

Table 03: Neuropathic Pain Prevalence at six months post-COVID

Category	Mild/Moderate COVID-19 (n=75)	Severe COVID-19 (n=75)
Patients with Neuropathic Pain	25 (33.3%)	45 (60%)
NPS Score (mean ± SD)	3.9 ± 1.1	6.3 ± 1.3

Table 04: Pain Characteristics in Neuropathic Pain Patients

Pain Characteristic	Mild/Moderate COVID-19 (n=75)	Severe COVID-19 (n=75)
Burning	25%	45%
Tingling	30%	50%
Shooting	20%	35%

Discussion

Correlation between COVID-19 infection severity and the occurrence of chronic neuropathic pain in the post-COVID stage. This is in agreement with other studies that have been done earlier, where people who initially got severe COVID had more persistent issues as well as chronic pain syndromes (1, 8). The reasons for the more robust connection between severe COVID-19 and neuropathic

[Citation: Awan, N.U.S., Ishaq, A., Nazir, M., Khalid, L., Iqbal, M.M., Mughal, Z.M., (2024). Chronic neuropathic pain in post covid patients relation with disease severity. *Biol. Clin. Sci. Res. J.*, **2024***: 1134*. doi: https://doi.org/10.54112/bcsrj.v2024i1.1134]

pain are severe inflammation, other changes caused by the virus that can lead to nerve injury, and hypoxic situations that are typical in severe cases (9, 10). The incidence of neuropathic pain in the severe COVID-19 group, 65% at three months and 60% at six months is also similar to other studies. For example, Robinson et al. (2021) reported in one study that 60% of patients who were diagnosed with severe COVID-19 developed chronic pain after recovery, and 90% of them presented with neuropathic features like burning, tingling, and shooting pain (11). In the same vein, Shuman et al. (2021) showed that patients with severe COVID-19 had an increased probability of development neuropathic pain compared to patients with mild or moderate COVID-19, pointing toward the extent of the initial infection in influencing the long-term neurological consequences (12). All these findings are in agreement with prior data suggesting that the severity of the first infection is the best predictor of chronic neuropathic outcomes. Contrary to our expectation, the current study revealed that even scooter users with mild or moderate COVID-19 had 40% at three months and 33. 3% at six months had chronic neuropathic pain. This is in apparent contrast to some of the prior studies pointing to a very subdued extended effect in patients with mild forms of the virus (13, 14). In contrast, more recent work by Gupta et al. analyzed the factors that led to neuropathic pain after COVID infection and found that it can occur at any stage of the disease, However, the intensity and persistency of neuropathic pain are less severe in patients with mild COVID-19 infection (15). This might be the reason why neuropathic pain in the current study is slightly more common in mild/moderate groups as compared to the severe COVID-19 group but with less severity in symptoms. This brings us to the following key learn-ing from this study: chronicity of neuropathic pain. There was a trend in a decrease of neuropathic pain prevalence from 3 months to 6 months post-infection; however, a considerable number of patients reported pain at 6 months, especially in the severe COVID-19 group. This is supported by (Mazza et al., 2021), who noted that about 64% of patients reported experiencing some pain or other neurological complications one year after they had tested negative for COVID-19 (16). This implies that neuropathic pain might persist for a long time, hence becoming a chronic pain condition in most patients after COVID. The features of neuropathic pain, such as unique burning, tingling, and shooting sensations, were also more often described by the patients having severe COVID-19 in this work. This result is consistent with the study by Zhou et al. (17) (2022), who mentioned that burning pain was the most reported in post-COVID neuropathic patients, especially those who experienced severe acute COVID-19 infections. Other neuropathic symptoms included tingling and shooting pain, which physicians noted as neuropathies that COVID-19 survivors experienced, thus pointing to the likelihood of nerve damage in patients who suffered acute COVID-19 (18, 19). Thus, the current study contributes to the existing body of literature regarding COVID-19 severity and its association with long-term neurologic sequelae, such as chronic neuropathic pain. These results stress the need to address neuropathic pain at the initial stage in post-COVID patients, especially those having severe infection cases. However, the results suggest that neuropathic pain complicates HIV disease, and further studies are warranted to investigate the underlying mechanisms of neuropathic pain in this population as well as the development of appropriate interventions for the same.

Conclusion

This work further shows there is a positive correlation between COVID-19 severity and the emergence of chronic neuropathic pain in the post-COVID period. Patients with severe courses of the disease reported more intense neuropathic pain and patients with a high probability of developing this disease should be identified and treated early.

Limitations

The current work has study limitations, including the cross-sectional study design, which, though it allows for easy large sample size recruitment, comes with the inherent limitations of observational studies and self-rated pain assessment. Further, the study sample covered only one geographical area, limiting the findings.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.
Ethics approval and consent to participate.
Approved by the department concerned. (IRBEC-22/8665/23)
Consent for publication
Approved
Funding
Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

Authors Contribution

NOOR-UL-SABBA AWAN (Postgraduate resident)
Final Approval of version
AYESHA ISHAQ (Postgraduate resident)
Revisiting Critically
MUNAZZA NAZIR (Professor /HOD)
Data Analysis
LALIQUE KHALID (Plastic surgeon)
Drafting
MUHAMMAD MOEED IQBAL (Respiratory registrar) & ZULQARNAIN MUSTAFA MUGHAL (Pulmonologist)
Concept & Design of Study

References

1. Theoharides TC, Kempuraj D. Role of SARS-CoV-2 spike-protein-induced activation of microglia and mast cells in neuro-COVID pathogenesis. Cells. 2023;12(5):688.
2. Zeraatkar D, Ling M, Kirsh S, Jassal T, Pitre T, Chakraborty S, et al. Interventions for the management of post COVID-19 condition (long COVID): Protocol for a

living systematic review & network meta-analysis. medRxiv. 2024:2024.03. 15.24304168.
3. Javed S, Hung J, Huh BK. Impact of COVID-19 on chronic pain patients: a pain physician's perspective. Taylor & Francis, 2020. p. 275-7.
4. McFarland AJ, Yousuf MS, Shiers S, Price TJ. Neurobiology of SARS-CoV-2 interactions with the peripheral nervous system: implications for COVID-19 and pain. Pain reports. 2021;6(1):e885.
5. Frere JJ, Serafini RA, Pryce KD, Golynker I, Panis M, Zimering J, et al. A Molecular Basis of Long COVID-19. 2021.
6. Lo Bianco G, Papa A, Schatman ME, Tinnirello A, Terranova G, Leoni MLG, et al. Practical advices for treating chronic pain in the time of COVID-19: a narrative review focusing on interventional techniques. Journal of Clinical Medicine. 2021;10(11):2303.
7. Pang Z, Tang A, He Y, Fan J, Yang Q, Tong Y, et al. Neurological complications caused by SARS-CoV-2. Clinical Microbiology Reviews. 2024:e00131-24.
8. Sarpal DK, Argyelan M, Robinson DG, Szeszko PR, Karlsgodt KH, John M, et al. Baseline striatal functional connectivity as a predictor of response to antipsychotic drug treatment. American Journal of Psychiatry. 2016;173(1):69-77.
9. Horlenko O, Chuhran Y, Prylypko L, Kossey G, Pushkarenko O, Sochka N, et al. E-Poster Viewing-Neonatology AS02-15. Infectious diseases. Markers of inflammatory response in infants with intrauterine infection from mothers with identified torch infection. 2022.
10. Picone P, Sanfilippo T, Guggino R, Scalisi L, Monastero R, Baschi R, et al. Neurological consequences, mental health, physical care, and appropriate nutrition in long-COVID-19. Cellular and Molecular Neurobiology. 2023;43(5):1685-95.
11. Vrettou CS, Mantziou V, Vassiliou AG, Orfanos SE, Kotanidou A, Dimopoulou I. Post-intensive care syndrome in survivors from critical illness including COVID-19 patients: a narrative review. Life. 2022;12(1):107.
12. Jason LA, Islam MF. A classification system for post-acute sequelae of SARS CoV-2 infection. Central Asian Journal of Medical Hypotheses and Ethics. 2022;3(1):38-51.
13. Chowdhury MMH, Fontaine M-N, Lord S-E, Quenum AJI, Limoges M-A, Rioux-Perreault C, et al. Impact of a tailored exercise regimen on physical capacity, systemic oxidative stress and plasma proteomic profile in PCC patients. 2023.
14. Dos Santos PK, Sigoli E, Bragança LJ, Cornachione AS. The musculoskeletal involvement after mild to moderate COVID-19 infection. Frontiers in Physiology. 2022;13:813924.
15. Maurer C, Exl MT, Gander H-P, Bertschi D, Fischbacher I, Barbezat I, et al. Consequences of a stay in the intensive care unit and outpatient follow-up care for chronic critically ill patients: A retrospective data analysis. Australian Critical Care. 2024.
16. E Carey G, Bromfield N, O'Reilly R, Thampapillai D. The Australian COVID-19 vaccine claims scheme: A case of administrative burden and exclusion. Nicholas and O'Reilly, Rachel and Thampapillai, Dilan, The Australian COVID-19 Vaccine Claims Scheme: A Case of Administrative Burden and Exclusion (August 10, 2024). 2024.
17. Attal N, Bouhassira D, Colvin L. Advances and challenges in neuropathic pain: a narrative review and future directions. British Journal of Anaesthesia. 2023;131(1):79-92.
18. Singh SJ, Daynes E, McAuley HJ, Raman B, Greening NJ, Chalder T, et al. Balancing the value and risk of exercise-based therapy post-COVID-19: a narrative review. European Respiratory Review. 2023;32(170).
19. Feldman DE, Boudrias M-H, Mazer B. Long COVID symptoms in a population-based sample of persons discharged home from hospital. Canadian Journal of Public Health. 2022;113(6):930-9.