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**Research Letter**

# Development of Neuropathic Post-COVID Pain Symptoms Is Not Associated with Serological Biomarkers at Hospital Admission in COVID-19 Survivors: A Secondary Analysis

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To the Editor

## Introduction

Pain symptoms have been found to be present as a post-coronavirus disease (COVID) sequalae in up to 18% of subjects who had survived the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus [1]. Although post-COVID pain of musculoskeletal origin is the most commonly reported type of pain [2], neuropathic pain is also described as potential post-COVID sequelae. Oguz-Akarsu et al reported that 25% of patients with post-COVID pain has neuropathic symptoms; however, they collected self-reported pain symptoms throughout a telephonic interview [3]. A similar prevalence of neuropathic symptoms (24.6%) has been recently found using a validated the Self-Report Leeds Assessment of Neuropathic Symptoms (S-LANSS) questionnaire by our research group [4].

Identification of potential factors associated with the development of post-COVID neuropathic pain could help for identifying individuals at a higher risk of developing post-COVID pain and, hence, timely interventions and information. Serological biomarkers at the acute phase of COVID-19 infection could be a potential risk factor contributing to the development of long COVID. There is preliminary evidence supporting that neuropathic post-COVID pain can be associated with serum levels of neurofilament light chain (NFL) as a potential biomarker [5]. We present here a secondary analysis of a previous cohort study investigating the prevalence of neuropathic symptoms in previously hospitalized COVID-19 survivors exhibiting "de novo" post-COVID pain [4]. The aim of the current secondary analysis was to investigate the association between serological biomarkers at hospital admission with the development of neuropathic post-COVID symptoms.

**Table 1.** Laboratory biomarkers of coronavirus disease 2019 (COVID-19) patients according to the presence or absence of neuropathic post-COVID pain symptoms at 6 months after hospital discharge

| | S-LANSS ≥ 12 points (n = 18) | S-LANSS < 12 points (n = 49) | *P* value |
|---|---|---|---|
| Glucose (mg/mL) | 118.7 (59.0) | 110.0 (28.0) | .453 |
| Creatinine (mg/dL) | 0.9 (0.2) | 0.9 (0.4) | .844 |
| Alanine transaminase (ALT, U/L) | 24.8 (10.1) | 25.4 (11.7) | .864 |
| Aspartate transaminase (AST, U/L) | 22.5 (7.1) | 22.7 (6.4) | .938 |
| Lactate dehydrogenase (LDH, U/L) | 213.5 (32.7) | 207.1 (45.1) | .583 |
| Creatine kinase (CK, mg/dL) | 1.5 (2.5) | 1.0 (0.4) | .224 |
| Albumin (g/dL) | 4.5 (0.2) | 4.55 (0.3) | .424 |
| Ferritin (ng/mL) | 147.2 (187.1) | 125.9 (119.8) | .584 |
| Leucocytes ($\times 10^9$/L) | 6.9 (1.7) | 7.25 (1.5) | .419 |
| Lymphocytes ($\times 10^9$/L) | 3.4 (0.8) | 3.1 (0.75) | .202 |
| Eosinophils ($\times 10^9$/L) | 2.5 (1.9) | 2.7 (2.7) | .786 |
| Hemoglobin (g/dL) | 13.9 (1.1) | 14.2 (1.5) | .453 |
| Platelets ($\times 10^9$/L) | 238.1 (69.5) | 251.0 (54.25) | .427 |
| Erythrocyte sedimentation rate (ESR, mm/h) | 16.1 (17.65) | 10.2 (9.3) | .117 |
| Fibrinogen (mg/dL) | 432.3 (102.1) | 403.85 (80.9) | .242 |
| D-dimer (ng/mL) | 665.5 (879.7) | 513.5 (404.5) | .339 |

n = number; SD = Standard Deviation.

## Methods

A secondary analysis of a previous observational cross-sectional cohort study was conducted [4]. Briefly, patients hospitalized during the first wave of the pandemic at an urban hospital in Spain due to SARS-CoV-2 infection attending to a specific post-COVID unit from 1 June to 31 October 2021 were invited to participate. They were included if reported pain as their primary post-COVID symptom and did not present a pre-existing history of pain symptoms or any medical comorbidity explaining the presence of pain as previously described [4]. The Institutional Ethic Committee of INDIVAL Cantabria (code 2020.416) approved the study. All participants provided their informed consent.

As previously described in detail [4], participants completed the following self-reported questionnaires: S-LANSS for assessing the presence of neuropathic symptoms [6], the Hospital Anxiety and Depression Scale for the presence of anxiety/depressive levels, the 11-item Tampa Scale for Kinesiophobia for the presence of fear of movement, and the Pain Catastrophizing Scale. In this secondary analysis, we used the cutoff score of ≥12 points on the total score of the S-LANSS (range 0 to 24) for determining the presence of neuropathic symptoms [6].

We obtained the following serological biomarkers collected at hospital admission from hospital medical records: glucose, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), albumin, ferritin, leucocyte count, lymphocyte count, eosinophil count, hemoglobin, platelet count, erythrocyte sedimentation rate (ESR), fibrinogen, and D-dimer.

Data analysis was conducted with STATA 16.1 program (StataCorp. 2019. Stata Statistical Software: Release 16. TX: StataCorp LP. USA). Student *t*-tests were conducted to compare serological biomarkers mean values between COVID-19 survivors with and without neuropathic post-COVID symptoms. A $P < .05$ was considered significant.

## Results

Details of the recruitment process and demographics from the sample can be found elsewhere [4]. From 77 individuals initially evaluated, serological biomarkers data were obtained from 67 (87%), which were included in this analysis. Participants were assessed a mean of 6.0 ± 0.8 months after hospitalization. Eighteen (26.7%) exhibited neuropathic post-COVID symptoms (S-LANSS score ≥ 12/24 points). No significant differences in any serological biomarker at hospital admission were observed between individuals with and without neuropathic post-COVID pain symptoms (Table 1).

## Discussion

This secondary analysis found no association between serological biomarkers at the acute phase of SARS-CoV-2 infection (hospital admission) and the development of neuropathic post-COVID symptoms 6 months after infection in previously hospitalized COVID-19 survivors. Our results agree with previous data also reporting that laboratory biomarkers obtained at hospital admission are not related to other post-COVID symptoms, for example, fatigue [7]. Similarly, the association between laboratory biomarkers at hospital admission and musculoskeletal post-COVID pain 1 year after infection is irrelevant [8].

The high expression of Angiotensin Converting Enzyme-2 (ACE2) receptors within nervous system cells such as neurons and microglia of the spinal cord could explain the neuro-invasive potential of the SARS-CoV-2

virus explaining the presence of neuropathic symptoms in COVID-19 survivors [9]. Since several serological biomarkers analyzed, for example, higher D-dimer concentration, lower platelet count, increased blood glucose, have been associated with severe COVID-19 [10], our results would suggest that severity of infection is not associated with the development of neuropathic post-COVID symptoms.

Some limitations should be considered. First, current data can be only applicable to previously hospitalized COVID-19 survivors with mild-to-moderate severity. Furthermore, the sample size could be considered small, and it is probably that the lack of association in some comparisons were due to type II error. This study could be used for further sample calculation in future studies. Second, we did not include individuals with preexisting pain symptoms. Third, as some specific inflammatory biomarkers, for example, cytokines or C-reactive protein, were not analyzed, these may exhibit stronger predictive strengths for development of neuropathic post-COVID pain. Finally, we determined the presence of neuropathic pain features based on a patient reported outcome measure (PROM) such as the S-LANSS. The inclusion of objective measures, for example, electromyography, quantitative sensory testing, or skin punch biopsies, could help to confirm or refute the presence of a neuropathic cause of pain symptoms in this population.

In conclusion, serological biomarkers at hospital admission were not associated with the development of neuropathic post-COVID symptoms in previously hospitalized COVID-19 survivors.

## Authors' Contributions

All authors contributed to the study concept and design. C.F.dlP., and M.H.M. conducted literature review and did the statistical analysis. All authors recruited participants and collected data. PPB supervised the study. All authors contributed to interpretation of data. All authors contributed to drafting the paper. All authors revised the text for intellectual content and have read and approved the final version of the manuscript.

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