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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4   40   **Role of the Funding Source**
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7   41   Proyecto financiado por la convocatoria Next-Val 2021 de la Fundación Instituto
8
9   42   de Investigación Marqués de Valdecilla (IDIVAL) and by a grant from the Novo Nordisk
10
11   43   Foundation 0067235. The sponsors had no role in the design, collection, management,
12
13   44   analysis, or interpretation of the data, draft, review, or approval of the manuscript or its
14
15   45   content. The authors were responsible for the decision to submit the manuscript for
16
17   46   publication, and the sponsor did not participate in this decision.
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20   47
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23   48   **Declaration of interests**
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25   49   No conflict of interest is declared by any of the authors
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Dear Editor

Introduction

Pain symptoms have been found to be present as a post-COVID sequalae in up to 18% of subjects who had survived to 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.

Methods

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105   A secondary analysis of a previous observational cross-sectional cohort study was

106 conducted [4]. Briefly, patients hospitalized during the first wave of the pandemic at an

107 urban hospital in Spain due to SARS-CoV-2 infection attending to a specific post-COVID

108 unit from 1st June to 31st October 2021 were invited to participate. They were included if

109 reported pain as their primary post-COVID symptom and did not present a pre-existing

110 history of pain symptoms or any medical comorbidity explaining the presence of pain as

111 previously described [4]. The Institutional Ethic Committee of INDIVAL Cantabria (code

112 2020.416) approved the study. All participants provided their informed consent.

113   As previously described in detail [4], participants completed the following self-

114 reported questionnaires: S-LANSS for assessing the presence of neuropathic symptoms

115 [6], the Hospital Anxiety and Depression Scale for the presence of anxiety/depressive

116 levels, the 11-item Tampa Scale for Kinesiophobia for the presence of fear of movement,

117 and the Pain Catastrophizing Scale. In this secondary analysis, we used the cut-off score

118 of ≥12 points on the total score of the S-LANSS (range 0 to 24) for determining the

119 presence of neuropathic symptoms [6].

120   We obtained the following serological biomarkers collected at hospital admission

121 from hospital medical records: glucose, creatinine, aspartate transaminase (AST), alanine

122 transaminase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), albumin,

123 ferritin, leucocyte count, lymphocyte count, eosinophil count, hemoglobin, platelet count,

124 erythrocyte sedimentation rate (ESR), fibrinogen, and D-dimer.

125   Data analysis was conducted with STATA 16.1 program (StataCorp. 2019. Stata

126 Statistical Software: Release 16. TX: StataCorp LP. USA). Student t-tests were conducted

127 to compare serological biomarkers mean values between COVID-19 survivors with and

128 without neuropathic post-COVID symptoms. A $P<0.05$ was considered significant.

129   **Results**

130   Details of the recruitment process and demographics from the sample can be found

131   elsewhere [4]. From 77 individuals initially evaluated, serological biomarkers data were

132   obtained from 67 (87%), which were included in this analysis. Participants were assessed

133   a mean of 6.0±0.8 months after hospitalization. Eighteen (26.7%) exhibited neuropathic

134   post-COVID symptoms (S-LANSS score≥12/24 points). No significant differences in any

135   serological biomarker at hospital admission were observed between individuals with and

136   without neuropathic post-COVID pain symptoms (**Table**).

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138   **Discussion**

139   This secondary analysis found no association between serological biomarkers at

140   the acute phase of SARS-CoV-2 infection (hospital admission) and the development of

141   neuropathic post-COVID symptoms 6 months after infection in previously hospitalized

142   COVID-19 survivors. Our results agree with previous data also reporting that laboratory

143   biomarkers obtained at hospital admission are not related to other post-COVID symptoms

144   e.g., fatigue [7]. Similarly, the association between laboratory biomarkers at hospital

145   admission and musculoskeletal post-COVID pain one year after infection is irrelevant [8]

146   The highly expression of Angiotensin Converting Enzyme-2 (ACE2) receptors within

147   nervous system cells such as neurons and microglia of the spinal cord could explain the

148   neuro-invasive potential of the SARS-CoV-2 virus explaining the presence of neuropathic

149   symptoms in COVID-19 survivors [9]. Since several serological biomarkers analyzed,

150   e.g., higher D-dimer concentration, lower platelet count, increased blood glucose, have

151   been associated with severe COVID-19 [10], our results would suggest that severity of

152   infection is not associated with the development of neuropathic post-COVID symptoms.

153   Some limitations should be considered. First, current data can be only applicable

154   to previously hospitalized COVID-19 survivors with mild-to-moderate severity. Further,

155   the sample size could be considered small, and it is probably that the lack of association

156   in some comparisons were due to type II error. This study could be used for further sample

157   calculation in future studies. Second, we did not include individuals with pre-existing

158   pain symptoms. Third, as some specific inflammatory biomarkers, e.g., cytokines or C

159   Reactive Protein, were not analyzed, these may exhibit stronger predictive strengths for

160   development of neuropathic post-COVID pain. Finally, we determined the presence of

161   neuropathic pain features based on a patient reported outcome measure (PROM) such as

162   the S-LANSS. The inclusion of objective measures, e.g., electromyography, quantitative

163   sensory testing or skin punch biopsies, could help to confirm or refute the presence of a

164   neuropathic cause of pain symptoms in this population.

165   In conclusion, serological biomarkers at hospital admission were not associated

166   with the development of neuropathic post-COVID symptoms in previously hospitalized

167   COVID-19 survivors.

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Role of the Funding Source

229   Proyecto financiado por la convocatoria Next-Val 2021 de la Fundación Instituto

230 de Investigación Marqués de Valdecilla (IDIVAL) and by a grant from the Novo Nordisk

231 Foundation 0067235. The sponsors had no role in the design, collection, management,

232 analysis, or interpretation of the data, draft, review, or approval of the manuscript or its

233 content. The authors were responsible for the decision to submit the manuscript for

234 publication, and the sponsor did not participate in this decision.

Acknowledgements

236 The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National

237 Research Foundation (DNRF121) and Norvo Nordic Foundation (NNF21OC0067235).

Declaration of interests

239 No conflict of interest is declared by any of the authors

Author Contributions

241 All authors contributed to the study concept and design. CFdlP, and MHM conducted

242 literature review and did the statistical analysis. All authors recruited participants and

243 collected data. PPB supervised the study. All authors contributed to interpretation of data.

244 All authors contributed to drafting the paper. All authors revised the text for intellectual

245 content and have read and approved the final version of the manuscript.

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Table: Laboratory biomarkers of 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)	0.453
Creatinine (mg/dL)	0.9 (0.2)	0.9 (0.4)	0.844
Alanine transaminase (ALT, U/L)	24.8 (10.1)	25.4 (11.7)	0.864
Aspartate transaminase (AST, U/L)	22.5 (7.1)	22.7 (6.4)	0.938
Lactate dehydrogenase (LDH, U/L)	213.5 (32.7)	207.1 (45.1)	0.583
Creatine kinase (CK, mg/dL)	1.5 (2.5)	1.0 (0.4)	0.224
Albumin (g/dL)	4.5 (0.2)	4.55 (0.3)	0.424
Ferritin (ng/mL)	147.2 (187.1)	125.9 (119.8)	0.584
Leucocytes (x10^9/L)	6.9 (1.7)	7.25 (1.5)	0.419
Lymphocytes (x10^9/L)	3.4 (0.8)	3.1 (0.75)	0.202
Eosinophils (x10^9/L)	2.5 (1.9)	2.7 (2.7)	0.786
Haemoglobin (g/dL)	13.9 (1.1)	14.2 (1.5)	0.453
Platelets (x10^9/L)	238.1 (69.5)	251.0 (54.25)	0.427
Erythrocyte sedimentation rate (ESR, mm/h)	16.1 (17.65)	10.2 (9.3)	0.117
Fibrinogen (mg/dL)	432.3 (102.1)	403.85 (80.9)	0.242
D-dimer (ng/mL)	665.5 (879.7)	513.5 (404.5)	0.339

n: number; SD: Standard Deviation