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*A Secondary Analysis of a Cohort Study*

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*Published in:*  
Journal of Clinical Medicine

*DOI (link to publication from Publisher):*  
[10.3390/jcm11123512](https://doi.org/10.3390/jcm11123512)

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*Publication date:*  
2022

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*

Fernández-de-Las-Peñas, C., Herrero-Montes, M., Ferrer-Pargada, D., Izquierdo-Cuervo, S., Arendt-Nielsen, L., Nijs, J., & Parás-Bravo, P. (2022). Sensitization-Associated Post-COVID-19 Symptoms at 6 Months Are Not Associated with Serological Biomarkers at Hospital Admission in COVID-19 Survivors: A Secondary Analysis of a Cohort Study. *Journal of Clinical Medicine*, 11(12), Article 3512. <https://doi.org/10.3390/jcm11123512>

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Brief Report

# Sensitization-Associated Post-COVID-19 Symptoms at 6 Months Are Not Associated with Serological Biomarkers at Hospital Admission in COVID-19 Survivors: A Secondary Analysis of a Cohort Study

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**Citation:** Fernández-de-las-Peñas, C.; Herrero-Montes, M.; Ferrer-Pargada, D.; Izquierdo-Cuervo, S.; Arendt-Nielsen, L.; Nijs, J.; Parás-Bravo, P. Sensitization-Associated Post-COVID-19 Symptoms at 6 Months Are Not Associated with Serological Biomarkers at Hospital Admission in COVID-19 Survivors: A Secondary Analysis of a Cohort Study. *J. Clin. Med.* **2022**, *11*, 3512. <https://doi.org/10.3390/jcm11123512>

Academic Editors: Francisco Guillen-Grima and Ersilia Lucenteforte

Received: 12 May 2022

Accepted: 15 June 2022

Published: 18 June 2022

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**Abstract:** Individuals who survived coronavirus disease, 2019 (COVID-19), often have symptoms of sensitization, but the extent to which these symptoms relate to serological biomarkers remains unclear. Therefore, this secondary analysis evaluated the association between serological biomarkers at hospital admission with sensitization-associated post-COVID-19 symptoms in a sample of previously hospitalized COVID-19 survivors. Sixty-seven individuals hospitalized due to SARS-CoV-2 infection in one urban hospital of Madrid (Spain) during the first wave of the pandemic were assessed a mean of 6.0 (SD 0.8) months after hospital discharge. The Central Sensitization Inventory (CSI) was used as rough tool to estimate the presence of sensitization-associated post-COVID-19 symptoms ( $\geq 40/100$  points). Levels of 16 serological biomarkers collected at hospital admission were obtained from medical records. Twenty-four (35.8%) patients reported sensitization-associated post-COVID-19 symptoms (CSI  $\geq 40$  points). Subjects reporting sensitization-associated symptoms had lower ferritin and hemoglobin levels than those not reporting sensitization-associated post-COVID-19 symptoms; however, these differences were small. We observed significant but small negative associations of the CSI score with ferritin ( $r: -0.251, p = 0.04$ ) and hemoglobin ( $r: -0.292, p = 0.017$ ) levels. No other significant difference was found. In conclusion, this secondary analysis did not find significant associations between the investigated serological biomarkers at hospital admission and sensitization-associated post-COVID-19 symptoms at 6 months after hospitalization in COVID-19 survivors.

**Keywords:** COVID-19; sensitization; post-COVID-19; biomarkers; hospitalization

## 1. Introduction

Recent data suggest that pain is a common post-COVID-19 symptom experienced by individuals who had survived severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. A cohort study proposed that post-COVID-19 pain primarily resembles musculoskeletal features [2]. Additionally, others have reported the presence of multiple and different pain symptoms [3], clinically mimicking the widespread pain features of fibromyalgia syndrome in up to 30% of COVID-19 survivors [4]. Musculoskeletal pain is usually associated with sensitization [5], which is an underlying characteristic of nociceptive pain [6]. Nociceptive pain, in addition to exaggerated pain responses, is also associated with central-nervous-system-derived symptoms, including fatigue, sleep problems, memory loss, and mood disturbances [7]. All these symptoms are also typically experienced by long haulers. Studies investigating the presence of sensitization in people with post-COVID-19 pain are scarce. Goudman et al. reported that 70% of post-COVID-19 patients showed sensitization-associated symptoms, based on a score of  $\geq 40$  points in the central sensitization inventory (CSI) [8]. A recent study reported that the prevalence of sensitization-associated symptoms (CSI score  $\geq 40$  points) was 33.7% [9]. Identification of those factors associated with the development of sensitization in COVID-19 survivors could help in identifying individuals at a higher risk, and, therefore, aid in implementing timely interventions. Given the close interplay between the immune system, pain, and sensitization [10,11], immune responses associated with SARS-CoV-2 may well generate immune factors (e.g., proinflammatory cytokines, elastase produced by activated leukocytes, oxidative stress) that potentially contribute in developing or sustaining sensitization, especially if they cross the blood–brain barrier. Hence, specific serological biomarkers at the acute phase of SARS-CoV-2 infection could be a potential risk factor contributing to the development of post-COVID-19 pain [12]. Here, we present a secondary analysis of a previous cohort study investigating the prevalence of sensitization-associated symptoms in previously hospitalized COVID-19 survivors exhibiting de novo post-COVID-19 pain [9]. The aim of this secondary analysis was to investigate the association between specific serological biomarkers at hospital admission with sensitization-associated post-COVID-19 pain symptoms.

## 2. Methods

A secondary analysis of a previous observational cross-sectional cohort study was conducted [9]. Briefly, patients hospitalized during the first wave of the pandemic at an urban hospital in Spain due to SARS-CoV-2 infection, attending a specific post-COVID-19 unit from 1 June to 31 October 2021, were invited to participate. They were included if they reported pain as their primary post-COVID-19 symptom and did not present a preexisting history of pain symptoms or any medical comorbidity explaining the presence of pain, as previously described [9]. The Institutional Ethics Committee of INDIVAL Cantabria (code 2020.416) approved the study. All participants provided their informed consent. As previously described in detail [9], participants completed the following self-reported questionnaires: the CSI for evaluating sensitization-associated symptoms [13,14]; the 11-item Tampa Scale for Kinesiophobia for assessing the presence of fear of movement [15]; the Pain Catastrophizing Scale [16]; the Hospital Anxiety and Depression Scale for assessing the presence of anxiety or depressive levels [17]; and the paper-based 5-level version of EuroQol-5D (EQ-5D-5L) [18]. In this secondary analysis, we used a cutoff score of  $>40$  points on the total score of the CSA (range: 0–100) for determining the presence of sensitization-associated symptoms [19]. 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 L-dimer.

Data analysis was conducted with STATA 16.1 program (StataCorp. 2019. Stata Statistical Software: Release 16. TX: StataCorp LP. USA). Differences in serological biomarker

mean values between COVID-19 survivors with and without sensitization-associated symptomatology were assessed with a one-way ANCOVA, adjusted by gender and age. The level of significance was set at a priori 0.05. In addition, a correlation analysis with Pearson (r) coefficients was used to determine the association between CSI score and serological biomarkers. All statistically significant variables associated with CSI score were included into a generalized logistic multivariate regression model to identify those biomarkers contributing significantly to the variance of CSI score. The significance criterion of the F value for entry into the regression equation was set at  $p < 0.05$ . Changes in adjusted  $R^2$  were reported after each step of the regression model to determine the association of the additional variables.

### 3. Results

Details of the recruitment process and the demographics of the sample can be found elsewhere [9]. From 77 individuals initially evaluated, serological biomarkers data were obtained from 67 (87%), which were included in this analysis. No differences in clinical data between the included patient in the original paper and those included here were observed. Participants were assessed a mean of 6 (SD 0.8) months after hospitalization. Twenty-four (35.8%) patients reported sensitization-associated post-COVID-19 symptoms (CSI  $\geq 40/100$  points). Subjects reporting sensitization-associated symptoms had lower ferritin ( $p = 0.035$ ) and hemoglobin ( $p = 0.015$ ) levels than those not reporting sensitization-associated post-COVID-19 symptoms; however, the differences were small (Table 1).

**Table 1.** Laboratory biomarkers of COVID-19 patients according to the presence or absence of sensitization-associated symptoms.

	CSI $\geq 40$ Points (n = 24)	CSI < 40 Points (n = 43)	p
Glucose (mg/mL)	105.3 (21.9)	117.1 (45.0)	0.394
Creatinine (mg/dL)	0.9 (0.45)	0.9 (0.3)	0.855
Alanine transaminase (ALT, U/L)	24.5 (12.5)	25.6 (10.5)	0.599
Aspartate transaminase (AST, U/L)	22.6 (7.5)	22.7 (6.0)	0.967
Lactate dehydrogenase (LDH, U/L)	215.2 (41.8)	205.2 (42.1)	0.346
Creatine kinase (CK, mg/dL)	0.9 (0.35)	1.3 (1.75)	0.153
Albumin (g/dL)	4.5 (0.3)	4.5 (0.2)	0.626
Ferritin (ng/mL) *	83.9 (67.6)	158.25 (161.8)	0.024 *
Leucocytes ( $\times 10^9/L$ )	7.05 (1.6)	7.25 (1.5)	0.491
Lymphocytes ( $\times 10^9/L$ )	3.2 (0.6)	3.2 (0.8)	0.899
Eosinophils ( $\times 10^9/L$ )	3.25 (3.4)	2.4 (1.95)	0.223
Hemoglobin (g/dL) *	13.55 (1.6)	14.4 (1.2)	0.047 *
Platelets ( $\times 10^9/L$ )	252.5 (66.1)	244.7 (54.4)	0.588
(ESR, mm/h)	11.6 (10.7)	11.9 (13.1)	0.908
Fibrinogen (mg/dL)	418.1 (74.5)	408.2 (94.0)	0.608
L-dimer (ng/mL)	591.25 (470.9)	535.5 (621.5)	0.734

ESR—erythrocyte sedimentation rate; n—number; SD—standard deviation. \* significant differences between subjects with and without sensitization-associated symptoms ( $p < 0.05$ ).

Significant but small negative associations of the CSI score with ferritin (r:  $-0.251$ ,  $p = 0.04$ ) and hemoglobin (r:  $-0.292$ ,  $p = 0.017$ ) levels was observed. No other significant association was found. The logistic multivariate regression model revealed that hemoglobin levels were the only laboratory biomarker associated with sensitization-associated symp-

toms by explaining the 13.7% of the variance of CSI score ( $r^2$  adj: 0.137,  $B = -0.394$ ,  $t = -2.935$ ,  $p = 0.005$ ).

#### 4. Discussion

This secondary analysis found lower ferritin and hemoglobin levels at the acute phase of infection in individuals with sensitization-associated post-COVID-19 symptoms at 6 months after hospital discharge. No other associations between the analyzed serological biomarkers at admission and sensitization-associated post-COVID-19 symptoms were seen. In general, higher levels of several of the analyzed serological biomarkers, e.g., D-dimer concentration or [20] blood glucose [21], were associated with severe COVID-19. In addition, higher ferritin levels were also found in severe–critical COVID-19 patients [22]. Accordingly, our results would suggest that severity of the infection in the acute phase is not associated with the development of sensitization-associated post-COVID-19 symptoms. It is hypothesized that SARS-CoV-2-associated cytokine and interleukin storms may lead to the sensitization of pain pathways [23,24], and trigger nociplastic pain responses by altering the balance between the neuromodulation systems of nociception [25]. Other hypotheses suggest that post-COVID-19 pain symptoms can be related to deficient immune regulatory mechanisms [26]. The current analysis did not observe different immune responses during the acute phase of the infection depending on the development of sensitization-associated symptoms; however, studies evaluating the long-term immune response in long-COVID-19 patients are needed. Indeed, it remains possible that a more pronounced and longer immune response in the subacute or chronic phase contributes to central nervous system changes and subsequent nociplastic changes. To date, few data are available on the association between the level of different cytokines and post-COVID-19 pain symptoms, because collection and preparation of blood samples for cytokine analysis is more rigorous than for standard serological biomarkers.

Additionally, it should be considered that emotional and social factors surrounding the COVID-19 outbreak could play a relevant role in the development of post-COVID-19 pain. In fact, social alarm, somatization, post-traumatic stress disorder, and fear or uncertainty about prognosis have been associated with a promotion and perpetuation of musculoskeletal post-COVID-19 symptoms [27–29]. Nevertheless, the association between laboratory biomarkers and emotional and cognitive aspects would be expected to be small.

Some limitations should be considered. Firstly, our data are only applicable to previously hospitalized COVID-19 survivors. Secondly, we did not include people with preexisting pain symptoms. Thirdly, several inflammatory biomarkers, e.g., cytokines or interleukins, were not analyzed, which may exhibit stronger associations with sensitization-associated post-COVID-19 symptoms. Finally, the exclusive use of the CSI for inferring sensitization is not recommended because it overlaps with emotional constructs, and because a self-reported tool cannot capture the complexity of central nervous system impairment [30]. In fact, our original study identified an association between anxiety levels and CSI, supporting the overlap with emotional distress [9].

#### 5. Conclusions

In conclusion, although ferritin and hemoglobin levels were lower in patients with sensitization-associated post-COVID-19 symptoms, most investigated serological biomarkers at hospital admission were not associated with sensitization-associated post-COVID-19 symptoms in previously hospitalized COVID-19 survivors.

**Author Contributions:** All authors contributed to the study concept and design. C.F.-d.-I.-P. and M.H.-M. conducted the literature review and performed the statistical analysis. All authors recruited participants and collected data. P.P.-B. 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. All authors have read and agreed to the published version of the manuscript.



**Funding:** The project was supported by a grant of Comunidad de Madrid y la Unión Europea, a través del Fondo Europeo de Desarrollo Regional (FEDER), Recursos REACT-UE del Programa Operativo de Madrid 2014–2020, financiado como parte de la respuesta de la Unión a la pandemia de COVID-19 (LONG-COVID-EXP-CM), by a grant from Next-Val 2021 de la Fundación Instituto de Investigación Marqués de Valdecilla (IDIVAL), and by a grant from the Novo Nordisk Foundation 0067235.

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of INDIVAL Cantabria (code 2020.416).

**Informed Consent Statement:** All participants provided their informed consent.

**Data Availability Statement:** All data derived from this study are reported here.

**Acknowledgments:** The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121) and Novo Nordisk Foundation (NNF21OC0067235).

**Conflicts of Interest:** The authors declare no conflict of interest.

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