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RESEARCH ARTICLE

Sensitization symptoms are associated with psychological and cognitive variables in COVID-19 survivors exhibiting post-COVID pain

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Abstract

Objective: To investigate the association between demographic, clinical, psychological, cognitive, and health-related variables and the Central Sensitization Inventory (CSI) in previously hospitalized COVID-19 survivors exhibiting "de novo" post-COVID pain.

Methods: Seventy-seven ($n = 77$) COVID-19 survivors with "de novo" post-COVID pain completed demographic (age, height, and weight), clinical (duration and intensity of the pain), psychological (depressive/anxiety levels and sleep quality), cognitive (catastrophizing and kinesiophobia levels), and health-related quality of life variables as well as the CSI. A multivariable correlation analysis was conducted to determine the association between variables, and a stepwise multiple linear regression model was performed to identify CSI predictors.

Results: Patients were assessed a mean of 6.0 (SD 0.8) months after hospital discharge. Twenty-six (33.7%) individuals showed indications of sensitization-associated symptoms (CSI score ≥40 points). The CSI score was positively associated with pain intensity (r: 0.371), anxiety (r: 0.784), depressive (r: 0.709), catastrophizing (r: 0.620), and kinesiophobia (r: 0.359) levels (all, $p<0.001$). The stepwise regression analysis revealed that 60.2% of CSI was explained by anxiety levels and pain intensity.

Conclusion: This study found that psychological and cognitive variables were associated with the CSI score in previously hospitalized COVID-19 survivors with

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"de novo" post-COVID pain. Anxiety levels and the intensity of pain symptoms were independently associated with CSI score suggesting a significant overlap with psychological construct. The "de novo" post-COVID pain association with CSI may indicate changes in the pain processing important for managing the pain.

KEYWORDS
anxiety, COVID-19, pain, post-COVID, sensitization

INTRODUCTION

Among the multiple symptoms experienced by people affected by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), musculoskeletal pain (myalgia) is common during the acute phase of the infection.[1,2] In addition, evidence supports that up to 60% of COVID-19 survivors may develop different post-COVID symptoms (ie, long COVID) after the infection.[3] A recent meta-analysis reported a prevalence from 4.6% to 18.1% for post-COVID pain at different follow-ups during the first-year post-infection.[4]

Characterization of post-COVID pain is crucial for better understanding of potential mechanisms and for orientating personalized treatments. A recent study observed that the most common type of post-COVID pain described on social media was musculoskeletal (nociceptive) pain.[5] In fact, a large cohort study has reported a prevalence up to 45% of musculoskeletal post-COVID pain in previously hospitalized COVID-19 survivors 8 months after hospitalization.[6] Musculoskeletal chronic pain can be associated with central sensitization,[7] which is the underlying concept defining nociplastic pain. Nociplastic pain is defined as "pain that arises from altered nociception without clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing pain."[8] In fact, nociplastic pain is not just associated with exaggerated pain symptomatology but also with central nervous system-associated symptoms including fatigue, sleep problems, memory loss, and mood disturbances.[9]

Preliminary evidence suggests the presence of sensitization in people exhibiting post-COVID pain. In fact, a Delphi study tried to identify the sensitization phenotypes of individuals with post-COVID pain.[10] This study proposed that symptoms were associated with sensitization included pain, fatigue, dyspnea, orthostatic intolerance, and gastrointestinal problems.[10] Oguz-Akarsu et al.[11] found that almost 60% of COVID-19 survivors reported multiple pain sites and more than two types of pain after hospitalization. Ursini et al.[12] observed, through a web-based survey, that 30% of patients with post-COVID pain self-reported common features similar to fibromyalgia, indicating nociplastic pain. None of these studies included either objective (eg, quantitative sensory testing) or self-reported (eg, sensitization inventory) variables of sensitization.

The Central Sensitization Inventory (CSI) consists of a self-reported questionnaire used to assist within the identification of sensitization-associated symptoms.[13] Goudman et al.[14] used the CSI in people with post-COVID pain and reported that 70% of individuals showed a score of >40/100 points suggestive of altered pain processing pointing toward sensitization. However, this study did not collect other potential cofounder variables, for example, psychological or cognitive variables, which all may influence the pain processing. The exclusive use of the CSI for inferring sensitization in individuals with chronic pain is not recommended since it generally overlaps with psychological construct[15] and because just a self-reported tool cannot capture the complexity of central sensitization.[16] The current study investigated the association of sensitization-associated symptoms, as evaluated with the CSI, with psychological variables (concurrent validity) and the presence of de novo post-COVID. Our aims were as follows: (1) to analyze the associations between symptoms of central sensitization and pain-related, psychological, cognitive, and quality of life variables, and; (2) to identify the potential risk factors explaining the variance of the CSI score in a sample of previously hospitalized COVID-19 survivors exhibiting "de novo" post-COVID pain.

METHODS

Study design

An observational cross-sectional cohort study following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines[17] was conducted. This study was approved by the Local Institutional Ethics Committee of INDIVAL Cantabria (code 2020.416). Participants were informed of the study, and all provided their written informed consent prior to their inclusion in the study.

Participants

This cohort study included patients hospitalized at one urban hospital in Santander (Spain) who had recovered

from acute SARS-CoV-2 infection. Patients requiring internal care unit (ICU) admission were excluded. All were diagnosed with reverse transcription-polymerase chain reaction (PCR) assay and the presence of clinical and radiological findings at hospital admission. They were included if presented: (1) "de novo" pain symptoms starting after hospitalization compatible with a diagnosis of chronic primary musculoskeletal pain[18]; (2) symptoms experienced for at least three consecutive months, and (3) absence of any potential medical condition which could best explain pain, for example, arthritis. Participants were excluded if reported a previous history of pain symptoms and or any pre-existing medical comorbidity explaining symptoms to reduce confounding variables associated with sensitization prior to hospitalization.

Collection data procedure

Participants were recruited from those attending to a specific post-COVID unit at an urban hospital (Hospital Universitario Marqués de Valdecilla) in Santander (Spain) from June 1, 2021, to October 31, 2021. Patients reporting that their main post-COVID symptom consisted of pain were invited to participate and evaluated for the inclusion and exclusion criteria. A structured questionnaire including clinical data of their pain and self-reported questionnaires was used for data collection. Age, weight, height, and intensity (numerical pain rating scale, NPRS, 0–10) and location of pain symptoms were collected. Questionnaires included sensitization-associated symptoms, psychological variables (eg, anxiety levels, depressive levels, or sleep quality), cognitive variables (kinesiophobia and catastrophism), and health-related quality of life.

Central Sensitization Inventory

The CSI is a self-reported questionnaire assessing a total of 25 sensitization-associated symptoms, on a 5-point Likert scale rating.[19] The total score ranges from 0 to 100, where >40/100 points suggest the presence of sensitization-associated symptoms.[20] The CSI has proven psychometric strength for evaluating sensitization-associated symptom in patients with persistent chronic pain.[21]

Psychological variables

Anxiety and depressive symptoms were assessed with the anxiety (HADS-A, 7 items, 0–21 points) and depressive (HADS-D, 7 items, 0–21 points) scales of the Hospital Anxiety and Depression Scale (HADS). Higher scores suggest higher anxiety/depressive levels.[22] The following cut-off scores were considered as indicative of anxiety (HADS-A ≥12 points) and depressive (HADS-D ≥10 points) symptoms.[23]

The Pittsburgh Sleep Quality Index (PSQI, 0–21 points) evaluates sleep quality by including 19 self-rated questions assessing different aspects of sleep during the previous month.[24] Higher scores indicate worse sleep quality, and a score ≥8.0 points is indicative of poor sleeper.[24]

Cognitive variables

The Pain Catastrophizing Scale (PCS) was used to assess pain catastrophizing.[25] It includes 13 items evaluating rumination, magnification, and despair aspects in relation to the pain experience. Items are answered in a 5-point Likert scale ranging from 0 ("never") to 4 ("always"), providing a total score from 0 to 52 points.[25]

The 11-item short form of the Tampa Scale for Kinesiophobia (TSK-11, 0–44 points) was used to quantify the fear of movement perceived by the patient.[26] It consists of 11 items where the patients choose from a 4-point Likert scale (1: "complete disagreement"; 4 "complete agreement") how much they agree with each item.[26]

Health-related quality of life

The paper-based five-level version of EuroQol-5D is a generic questionnaire used for assessing health-related quality of life.[27] It includes five health dimensions (mobility, self-care, daily activities, pain, and depression/anxiety) into a 5-item Likert scale (0: no problems; 4: severe problems). Responses were converted into a single index number by applying crosswalk index values for Spain life (0: equivalent to death; 1: optimal health status).[28]

Sample size determination

An adequate sample size for prediction models was based on a range of 10–15 subjects per predictor variable, with no more than five predictors within the model as suggested by Jenkins and Quintana-Ascencio.[29] Accordingly, for five potential predictor variables, a minimum of 75 participants would be required.

Statistical analysis

Descriptive analyses (means and standard deviations -SD-) were used to describe the sample. The Kolmogorov–Smirnov test revealed that all quantitative data exhibited a normal distribution. Between-group differences depending on the CSI score (<40 or ≥40 points) were assessed with the independent Student *t*-tests. A multiple linear regression analysis was used

to determine which variables could explain the variance of CSI. First, Pearson correlation coefficients (r) were used to determine the correlation between predictors and the dependent variable (CSI). The correlation coefficients were also used to identify multicollinearity between the variables (defined when $r > 0.8$). All statistically significant variables associated with the CSI score were included in a stepwise multiple linear regression model (hierarchical regression analysis) to assess those independent variables contributing significantly to the variance of the dependent variable (CSI), except variables showing multicollinearity. The significance criterion of the critical 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 contribution of the additional variables.

RESULTS

From 150 individuals attending the post-COVID unit from June 1, 2021, to October 31, 2021, 73 (48%) were excluded because their main post-COVID symptom was respiratory (n = 45) or the presence of previous pain symptoms (n = 28). Finally, 77 patients (37.6% women, age: 60, SD: 11.5 years) satisfied all inclusion criteria, were included, and assessed a mean of 6.0 (SD 0.8) months after hospital discharge. They were hospitalized a mean of 12.4 (SD 11.1) days at a hospital ward. Table 1 details clinical, psychological, cognitive, and health-related features of the sample. All participants reported pains as their primary post-COVID symptom. In fact, 46 (59.7%) only experienced post-COVID pain. In fact, 20.8% of patients reported generalized post-COVID pain as visualized in Figure 1. The remaining 31 (40.3%) also reported other less bothersome symptomatology: anosmia (n = 10, 13%), gastrointestinal problems (n = 8, 10.4%), brain bog (n = 7, 9%), or ageusia (n = 6, 7.8%).

The mean CSI score was 30.0 (SD: 17.3), where 26 (33.7%) patients had a CSI score ≥40/100 and 51 (66.3%) a score <40/100. Individuals with sensitization-associated features (CSI ≥40 points) exhibited higher pain intensity (p = 0.01), more anxiety/depressive ($p < 0.001$), and more catastrophizing and kinesiophobia ($p < 0.001$) levels than those without sensitization-associated symptoms (CSI score <40 points).

Bivariate correlation analysis

Bivariate correlation analyses are reported in Table 2. The CSI score was positively associated with pain intensity, anxiety/depressive levels, catastrophizing, and kinesiophobia levels (all, $p < 0.001$). Significant positive associations were also found among pain-related, psychological, and cognitive variables (r from 0.321 to 0.639).

Since multicollinearity was identified between HADS-D and HADS-A (r: 0.867, $p < 0.001$), HADS-D was "a priori" excluded from the regression analysis. Its inclusion in the logistic regression did not alter the results.

Multiple regression analysis

The hierarchical regression analysis explaining the variance of the CSI score is shown in Table 3. Stepwise regression analyses revealed that anxiety (contributing 57.3%) and pain intensity (2.9%) were significant predictors of CSI, and, when combined, they explained 60.2% of the variance of the outcome (r^2 adjusted: 0.602, Figure 2).

DISCUSSION

This is the first study conducting regression analyses to study which factors may contribute to the variance of sensitization-associated symptoms in previously hospitalized COVID-19 survivors exhibiting "de novo" post-COVID pain. Sensitization-associated characteristics were correlated with psychological and cognitive variables. Anxiety levels and intensity of pain symptoms were independently associated with CSI explaining up to 65% of its variance.

Sensitization-associated symptoms and emotional-cognitive variables

Serrano-Ibañez et al.[30] found that individuals suffering from pre-existing chronic pain sensitization syndromes were at a higher risk of developing psychological distress during the worldwide COVID-19 outbreak. The current study reported an association between pain intensity, emotional distress, and sensitization-associated features. In fact, current evidence supports that stress and psychological factors had a significant impact on the pain processing and our study showed that psychological disorders, particularly anxiety levels, were associated with CSI. A possible explanation may be serotonergic and noradrenergic neurons dysfunction affecting psychological and somatic pain pathways.[31] The fact that anxiety levels were positively associated with the CSI score agrees with previous studies in people with chronic pain,[32] and the finding that high-trait anxiety-related personality predicts the extent of symptoms of sensitization in patients with chronic low back pain.[33] Anxiety was the major contributor to CSI score (up to 57%) of all the variables assessed in our study. Our results support the assumption that the CSI questionnaire can exhibit a

TABLE 1 Baseline outcomes (mean±SD) of the sample

Variable	Total sample ($n = 77$)	CSI ≥40 points ($n = 26$)	CSI <40 points ($n = 51$)
Demographic variables			
Age (years)	60.0±11.5	59.9±11.2	60.0±11.7
Height (m)	1.69±0.09	1.66±0.09	1.68±0.08
Weight (kg)	75.8±15.4	72.7±12.7	74.9±12.4
Previous medical co-morbidities			
Hypertension, *n* (%)	23 (29.9%)	8 (30.7%)	15 (29.4%)
Obesity, *n* (%)	15 (19.5%)	6 (23.1%)	9 (17.6%)
Diabetes, *n* (%)	11 (14.3%)	4 (15.4%)	7 (13.7%)
Asthma, *n* (%)	10 (13.0%)	3 (11.5%)	7 (13.7%)
Chronic obstructive pulmonary disease, *n* (%)	5 (6.5%)	2 (7.7%)	3 (5.9%)
Pain and sensitization-related variables			
Time with symptoms (months)	6.0±0.8	5.8±0.9	6.0±0.8
Pain intensity (0–10)*	5.4±1.8	6.2±1.3	4.9±2.0
CSI (0–100)*	30.0±17.3	51.3±7.5	19.9±9.8
Psychological variables			
HADS-A (0–21)*	5.8±4.4	10.7±3.5	3.5±2.6
HADS-D (0–21)*	5.7±4.7	10.5±3.9	3.4±3.1
PSQI (0–21)	8.9±4.3	9.2±4.1	8.9±4.6
Cognitive and health-related variables			
PCS (0–52)*	16.1±13.1	27.3±12.7	11.5±10.0
TSK-11 (0–44)*	24.2±9.1	29.3±8.7	22.3±7.8
EuroQol-5D (0–1)	0.75±0.25	0.8±0.2	0.7±0.25

Abbreviations: CSI, Central Sensitization Inventory; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PSQI, Pittsburgh Sleep Quality Index; TSK-11, Tampa Scale for Kinesiophobia.

*Significant differences between patients according to the CSI score (Student *t*-test, $p<0.01$).

significant overlap with psychological construct as previously suggested.[34]

Current data also identified that cognitive variables such as catastrophizing and kinesiophobia levels were linearly associated with CSI score, although these variables were not maintained in the logistic regression analysis. Hruschak et al.[35] found that chronic pain patients with worse disability and higher catastrophizing levels were at a higher risk of social isolation during the first COVID-19 outbreak. Precision pain medicine implies that patient education, management, and treatments should be adapted to pain phenotypes. For instance, implementation of telemedicine for the management of the identified factors associated with sensitization-associated symptoms such as anxiety or kinesiophobia level can be applied.[36] Supporting this assumption, preliminary evidence suggests that social technology use is associated with a decrease in depressive levels and loneliness in patients with chronic pain.[37] As sensitization is related to cognitive or emotional factors including catastrophizing, anxiety or depressive levels, kinesiophobia, stress, or maladaptive illness perception, clinicians should consider individual-tailored multimodal treatments combining pain neuroscience education with physical therapy and stress management.

Sensitization-associated symptoms and post-COVID pain

We also found the intensity of post-COVID pain to be independently positively associated with CSI after adjusting by all variables supporting that the magnitude of the nociceptive input as a relevant factor for sensitization.[38] This topic is not only relevant for COVID-19 survivors but also for people with chronic pain, but not infected. Current literature supports that individuals with chronic pain (but not infected) had exhibited an increase in their pain during the first COVID-19 lockdown.[39,40] Proper monitoring of pain symptoms and stress levels in people with chronic pain would help in the early identification of these potentially modifiable factors in people at a risk for developing changes in pain processing networks.

We found that widespread pain was the most common feature of "de novo" post-COVID pain. In line with our results, subjects who had survived to the acute severe acute respiratory syndrome (SARS) also exhibit

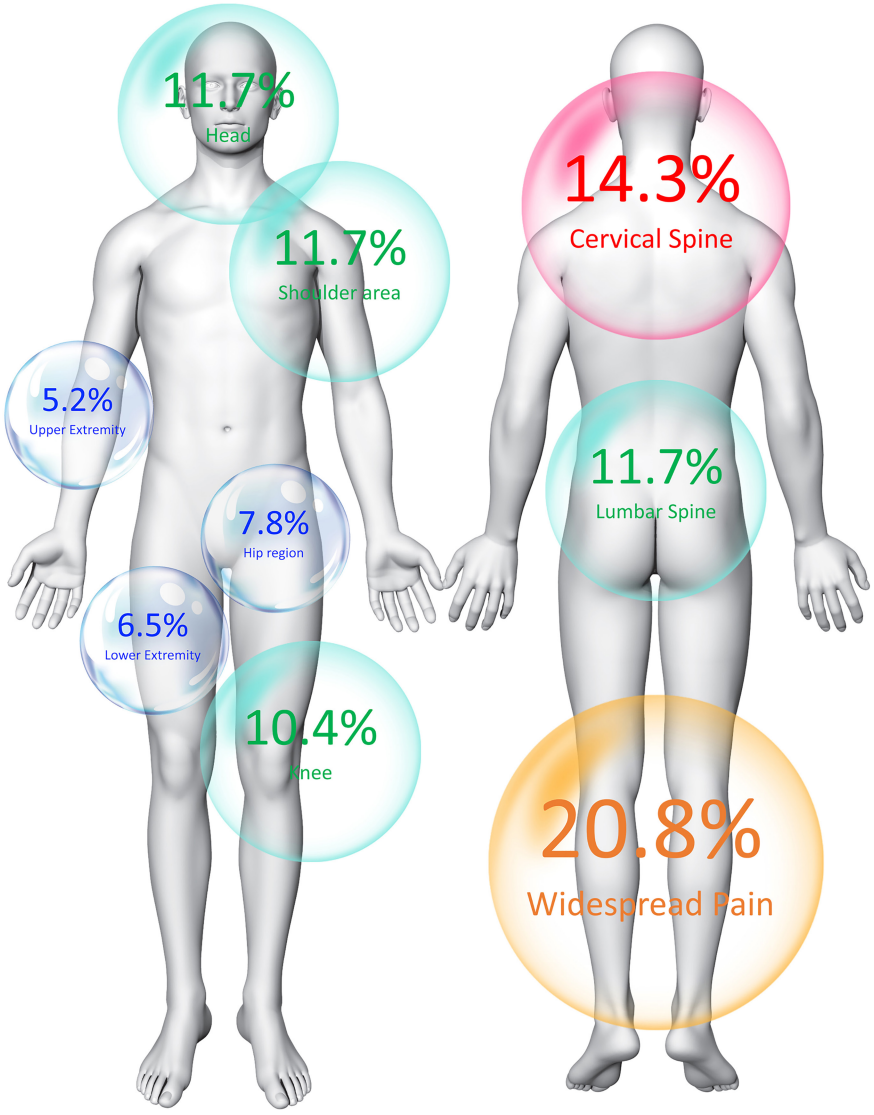

FIGURE 1 Location of pain symptomatology in previously hospitalized COVID-19 survivors exhibiting "de novo" post-COVID pain ($n = 77$)

widespread pain as a sequela 1 year after the infection.[41] Generalized pain symptomatology, combined with the presence of high CSI score, resembles the features of fibromyalgia. Our results are slightly inferior to those previously reported by Ursini et al.[12] who report that 30% of patients with post-COVID pain self-reported clinical features of fibromyalgia. In fact, spreading pain is also considered a clinical feature of sensitization[7] and is included as mandatory criteria for determining the presence of nociplastic pain.[8]

Current theories hypothesize that SARS-CoV-2 cytokine and interleukin-induced storms may lead to sensitization of pain pathways.[42,43] In such a scenario, SARS-CoV-2 infection could trigger nociplastic pain responses by altering the balance between those neuromodulation systems of nociception.[44] Additionally, widespread symptomatology has been suggested to be related to deficient immune regulatory mechanisms[45] and could indicate a prolonged immune system impact in post-COVID pain sufferers which, in fact, will promote more sensitization.

Limitations

First, current data can be only applicable to previously hospitalized COVID-19 survivors with mild-to-moderate severity, since none required ICU admission. In fact, critically ill COVID-19 survivors requiring ICU admission also develop "de novo" post-COVID pain.[46] Second, the presence of pre-existing symptoms before the infection is a risk factor for developing post-COVID pain.[6] In the current study, we included patients without previous history of pain; accordingly, we do not currently know if the presence of symptoms before the infection would lead to a facilitation

TABLE 2 Pearson-product moment correlation matrix between sociodemographic, psychological, neuro-physiological, and clinical characteristics

	1	2	3	4	5	6	7	8	9	10	11
1. Age											
2. Weight	n.s.										
3. Height	n.s.	0.521**									
4. Time with symptoms	n.s.	n.s.	n.s.								
5. Mean pain intensity	n.s.	n.s.	n.s.	n.s.							
6. HADS-A	n.s.	n.s.	n.s.	n.s.	n.s.						
7. HADS-D	n.s.	n.s.	n.s.	n.s.	0.301*	0.867**					
8. PSQI	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.				
9. PCS	n.s.	n.s.	n.s.	n.s.	0.321*	0.672**	0.619**	n.s.			
10. TKS-11	n.s.	n.s.	n.s.	n.s.	0.429**	0.409**	0.365**	n.s.	0.639**		
11. EuroQol-5D	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	
12. CSI	n.s.	n.s.	n.s.	n.s.	0.371**	0.784**	0.709**	n.s.	0.620**	0.359**	n.s.

Abbreviations: CSI, Central Sensitization Inventory; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PSQI, Pittsburgh Sleep Quality Index; TSK-11, Tampa Scale for Kinesiophobia.
*$p<0.05$; **$p<0.01$.

TABLE 3 Summary of the stepwise regression analyses to determine predictors of sensitization-associated symptoms

	Predictor outcome	*B*	SE *B*	95% CI	*B*	*t*	*p*
CSI	Step 1						
	HADS-A	2.667	0.340	1.981, 3.352	0.763	7.840	<0.001
	Step 2						
	HADS-A	2.505	0.338	1.824, 3.187	0.717	7.415	<0.001
	Mean pain intensity	1.631	0.798	0.022, 3.329	0.198	2.044	0.045

Note: $R^2_{adj.} = 0.573$ for step 1, $R^2_{adj.} = 0.602$ for step 2.
Abbreviations: CSI, Central Sensitization Inventory; HADS, Hospital Anxiety and Depression Scale.

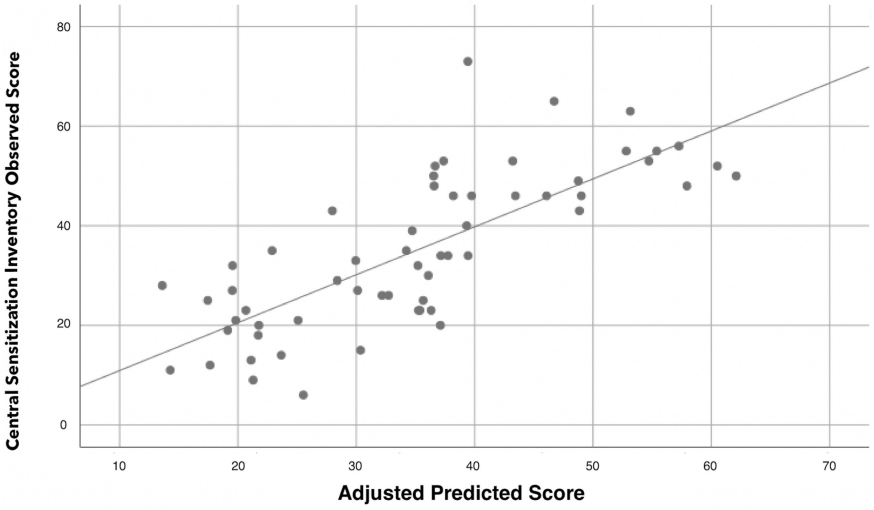

FIGURE 2 Scatter plot of the adjusted predicted score (r^2 adjusted: 0.602) explaining Central Sensitization Inventory (CSI) score in COVID-19 survivors exhibiting "de novo" post-COVID pain symptoms ($n = 77$). Note that some points can be overlapping

of sensitization. Third, we collected a patient-reported outcome measure, for example, CSI score, for assessing the presence of sensitization-associated symptoms. It has been found that scores <40/100 points in the CSI do not exclude the presence of sensitization, since CSI scores may be confounded by emotional factors with

features that tend to underreport themselves in other objective measures such as quantitative sensory tests.[33] In fact, the current study supports that CSI has a similar construct with psychological variables, particularly anxiety levels. Fourth, although our results suggest that post-COVID pain resembles a nociplastic pain condition, differentiating between nociceptive, neuropathic, or nociplastic pain conditions remains challenging.[47] In fact, it has been also seen that neuropathic pain can be also present in COVID-19 survivors.[48] Studies examining the clinimetric and psychometric properties of the proposed criteria for defining a nociplastic condition are also needed.[49] Finally, data were collected from just one hospital, questioning the external validity of the study findings.

CONCLUSIONS

Self-reported symptoms of sensitization were associated with the intensity of pain, anxiety and depressive levels and catastrophizing and kinesiophobia levels in previously hospitalized COVID-19 survivors exhibiting "de novo" post-COVID pain. The regression analysis reported that 60.2% of the variance of the CSI score was explained by anxiety levels and pain intensity. These results suggest that post-COVID pain resembles features of a nociplastic condition.

AUTHOR CONTRIBUTIONS

All authors contributed to the study concept and design. MHM and CFdlP conducted the 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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CONFLICT OF INTEREST

The authors declared that there is no conflict.

DATA AVAILABILITY STATEMENT

All data derived from this study are included in the paper.

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