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Serological biomarkers of COVID-19 severity at hospital admission are not related to long-term post-COVID pain symptoms in hospitalized COVID-19 survivors

César Fernández-de-las-Peñas[a,b,*], Pablo Ryan-Murua[c], Ana I. de-la-Llave-Rincón[a], Víctor Gómez-Mayordomo[d], Lars Arendt-Nielsen[b,e], Juan Torres-Macho[c,f]

Abstract

This study investigated the association between serological biomarkers at hospital admission with the development of long-term post-COVID pain symptoms in previously hospitalized coronavirus disease, 2019 (COVID-19) survivors. A cohort study including patients hospitalised because of COVID-19 in 1 urban hospital of Madrid (Spain) during the first wave of the outbreak was conducted. Hospitalisation data, clinical data, and 11 serological biomarkers were collected at hospital admission. Participants were scheduled for an individual telephone interview after hospital discharge for collecting data about post-COVID pain symptoms. A total of 412 patients (mean age: 62, SD: 15 years; 46.1% women) were assessed twice, at a mean of 6.8 and 13.2 months after discharge. The prevalence of post-COVID pain symptoms was 42.7% (n = 176) and 36.2% (n = 149) at 6.8 and 13.2 months after hospital discharge. Patients reporting post-COVID pain exhibited a greater number of COVID-19–associated symptoms at hospital admission, more medical comorbidities, higher lymphocyte count, and lower glucose and creatine kinase levels (all, $P < 0.01$) than those not reporting post-COVID pain. The multivariate analysis revealed that lower creatine kinase and glucose levels were significantly associated, but just explaining 6.9% of the variance of experiencing post-COVID pain. In conclusion, the association between serological biomarkers associated with COVID-19 severity at hospital admission and the development of post-COVID pain is small. Other factors, eg, higher number of COVID-19 onset symptoms (higher symptom load) could be more relevant for the development of post-COVID pain. Because inflammatory biomarkers were not directly analyzed, they may have stronger predictive strengths for the development of post-COVID pain symptoms.

Keywords: COVID-19, Pain, Post-COVID, Biomarkers

1. Introduction

Symptoms associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affect different systems.[25] Different biomarkers had been investigated at the acute phase to identify individuals at a risk of developing a worse hospital course during the infection. Hematological (lymphocyte count and neutrophil count), inflammatory (C-reactive protein [CRP],

erythrocyte sedimentation rate, procalcitonin), immunological (interleukin IL-6), and biochemical (D-dimer, troponin, creatine kinase [CK]) markers have been investigated. A meta-analysis (56 studies, n = 8719 patients) found that patients with severe coronavirus disease, 2019 (COVID-19) exhibited higher levels of some inflammatory biomarkers such as white blood cell count, CRP, erythrocyte sedimentation rate, procalcitonin, or IL-6 than those with mild COVID-19.[13]

Most studies have investigated biomarker relevance during the acute phase of the infection; however, whether biomarkers of a worse infection prognosis were correlated with the development of post-COVID symptoms is less known. Different meta-analyses reported that 60% of COVID-19 survivors develop post-COVID symptoms 6 months after the infection.[4,15] The association between post-COVID symptoms and serological biomarkers associated with COVID-19 severity is controversial. Mandal et al.[16] reported that 30.1% and 9.5% of COVID-19 survivors showed elevated D-dimer and CRP, respectively, 2 months after hospital discharge, but no association with any post-COVID symptom was found. Townsend et al.[23] did not find an association between post-COVID fatigue and laboratory biomarkers of inflammation and cell turnover at hospital admission.

One relevant post-COVID symptom, which is not specifically reported in previous COVID-19 literature, is chronic pain.[4,15] Just 1 published meta-analysis has focused on post-COVID pain

symptoms and reported a prevalence of 10.9% and 7.7% for myalgia and arthralgia as post-COVID pain symptoms the first 6 months after the infection.[10] Of interest, studies specifically focusing on post-COVID pain symptoms have reported prevalence rates of 60% the first 3 months after infection.[2,14,22] It seems that post-COVID pain maybe underreported in general cohort post-COVID studies.[10]

Several of the proinflammatory signaling molecules elevated in patients with COVID-19 due to the cytokine storm could affect skeletal muscle. Preliminary evidence suggests an association between laboratory biomarkers and the presence of pain symptoms at hospital admission and at the post-COVID phase. Batur et al.[3] found an increase in CK levels and lymphocyte count in patients presenting myalgia as a symptom at hospital admission. Bakılan et al.[2] showed lower lymphocyte count and higher D-dimer levels in individuals developing post-COVID pain symptoms. However, both studies included small sample sizes with short-term follow-ups.[2,3] Monitoring serological biomarkers of COVID-19 severity at the acute phase could help for identifying patients at a higher risk of developing post-COVID pain and hence indicate the need for timely interventions. We present a cohort study of hospitalized COVID-19 survivors assessed at 6 and 12 months after discharge for the presence of post-COVID pain. Our aim was to investigate the association between serological biomarkers of COVID-19 severity at hospital admission with post-COVID pain symptoms in previously hospitalized COVID-19 survivors. We hypothesized that biomarkers related to COVID-19 severity could serve as antecedent biomarkers (risk of developing a condition) for post-COVID pain symptoms.

2. Methods

2.1. Participants

This cohort study included patients hospitalized because of SARS-CoV-2 infection during the first wave of the pandemic (from March 20 to June 30, 2020) from an urban hospital in Madrid (Spain). All participants have been diagnosed with real-time reverse transcription-polymerase chain reaction assay of nasopharyngeal/oral swab sample and the presence of clinical and radiological findings at hospital admission. The study was approved by the Ethics Committee of the Hospital Universitario Infanta Leonor (HUIL/092-20). Participants were informed of the study, and all provided their respective informed consent.

2.2. Hospitalization data

Clinical and hospitalization data including age, sex, height, weight, COVID-19–associated onset symptoms at hospital admission, preexisting comorbidities, and intensive care unit (ICU) admission were systematically collected at hospital admission. Furthermore, serological values of hemoglobin, lymphocyte count, neutrophil count, platelet count, glucose, CRP, CK, lactate dehydrogenase (LDH), D-dimer, alanine transaminase, and aspartate transaminase were also systematically collected. The number of days in hospital was collected from medical records.

2.3. Post-COVID pain symptoms assessment

Participants who agreed to participate in the study were scheduled for a telephone semistructured interview by trained healthcare researchers. Patients were asked to report the 3 most bothersome post-COVID symptoms. A specific questionnaire focusing on pain symptoms was developed. Participants were

asked for the presence of pain symptoms appearing after hospital discharge and whether the reported pain symptom persisted at the time of the study. We focused on the presence of post-COVID pain symptoms, eg,, neck pain, shoulder pain, and widespread pain, differentiating from headache (ie, migraine-like pain). We did not include headache because of the need for a proper diagnosis according to agreed classifications.

We defined post-COVID pain as follows: (1) pain symptoms compatible with a diagnosis of chronic primary musculoskeletal pain, as defined by the International Association for the Study of Pain[19]; (2) symptoms experienced for at least 3 consecutive months after hospital discharge, and (3) absence of any underlying medical condition that could best explain pain, eg,, arthritis. Participants were asked to differentiate the symptoms beginning after SARS-CoV-2 infection from their previous pain condition.

2.4. Statistical analysis

The STATA 16.1 program (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP) was used for the analysis. Data are presented as mean values (SD) or percentages as appropriate. The McNemar χ^2 test and paired Student t test were conducted to compare proportions and mean values between patients with and without post-COVID pain symptoms at 6-month and 12-month follow-ups. Missing values were imputed by using median imputation. A multiple lineal hierarchical regression analysis including all variables (age, sex, height, weight, COVID-19 onset symptoms at hospital admission, preexisting comorbidities, ICU admission, serological biomarkers, and days in hospital) was conducted to determine which of these variables contributed significantly to the presence of post-COVID pain symptoms. 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 association of the additional variables.

3. Results

From a total of 450 hospitalized patients invited to participate, 10 refused to participate, 8 could not be contacted after 3 attempts, and 20 had deceased after hospital discharge. Finally, 412 patients (mean age: 62, SD: 15 years; 46.1% women) were included in the study.

Participants were assessed at a mean of 6.8 (range 6-8) and 13.2 (range 12-14) months after hospital discharge. At the time of evaluation, 176 (42.7%) patients reported post-COVID pain symptoms 6 months after hospital discharge, whereas 149 (36.2%) reported post-COVID pain symptoms 12 months after.

Table 1 compares clinical and hospitalization data between individuals developing and not developing post-COVID pain at 6 months. A similar distribution at 12 months was observed (data not shown). Patients developing post-COVID pain 6 months after hospital discharge exhibited a greater number of symptoms at hospital admission, particularly a higher prevalence of myalgia and headache ($P < 0.01$) and a greater number of comorbidities than those not exhibiting post-COVID pain at 6 months (Table 1). In addition, a greater proportion ($P = 0.005$) of patients developing post-COVID pain symptoms (n = 91, 51.7%) reported previous pain symptoms. From these patients experiencing previous pain symptoms, 62 (35.2%) reported that post-COVID pain was different from previous symptomatology (new-onset post-COVID pain), whereas the remaining 29 (16.4%) experienced an increase in their previous symptoms (exacerbated post-COVID–related pain). The remaining 84 patients (48.3%) reported

Demographic, clinical, and hospitalisation data of patients with COVID-19 according to the presence or absence of post-COVID pain at 6-month follow-up.

	Post-COVID pain (n=176)	No post-COVID pain (n=236)
Age, mean (SD), y	62.5 (14.0)	62.0 (16.5)
Sex, male/female (%)	98 (55.7%)/78 (44.3%)	115 (48.7%)/121 (51.2%)
Weight, mean (SD), kg	75.1 (18.4)	75.6 (15.9)
Height, mean (SD), cm	164.0 (12.0)	165.0 (10.0)
Number of medical comorbidities*	1.0 (0.85)	0.7 (0.80)
Medical comorbidities		
Hypertension	52 (29.5%)	61 (25.8%)
Cardiovascular diseases	25 (14.2%)	30 (12.7%)
Diabetes	18 (10.3%)	22 (9.3%)
Asthma	10 (5.6%)	19 (8.0%)
Obesity	10 (5.7%)	14 (5.9%)
Chronic obstructive pulmonary disease	7 (3.9%)	10 (4.2%)
Migraine	5 (2.9%)	7 (2.9%)
Other (cancer, kidney disease)	30 (17.0%)	37 (15.7%)
Previous pain symptomatology, n (%)*	91 (51.7%)	86 (33.4%)
Number of COVID-19 symptoms at hospital admission, mean (SD)*	2.3 (0.8)	2.0 (0.7)
Symptoms at hospital admission, n (%)		
Fever	132 (75.0%)	184 (77.9%)
Dyspnoea	65 (36.9%)	89 (37.7%)
Myalgias*	59 (33.5%)	54 (23.3%)
Cough	36 (20.4%)	55 (23.3%)
Headache*	46 (26.1%)	38 (16.1%)
Diarrhoea	15 (8.5%)	23 (9.7%)
Anosmia	15 (8.5%)	20 (8.4%)
Ageusia	11 (6.3%)	12 (5.1%)
Throat pain	5 (2.8%)	8 (3.4%)
Vomiting	5 (2.8%)	7 (3.0%)
Dizziness	8 (4.5%)	11 (4.7%)
Stay at the hospital, mean (SD), d	7.5 (4.5)	7.0 (4.5)
Intensive care unit (ICU) admission		
Yes/no, n (%)	10 (5.7%)/166 (94.3%)	10 (4.2%)/226 (95.8%)
Stay at ICU, mean (SD), d	4.3 (2.7)	4.5 (4.4)

* Statistically significant differences between groups ($P < 0.01$).
n, number.

new-onset post-COVID–related pain because they did not experience previous symptoms before the infection. Accordingly, the prevalence of new-onset post-COVID pain symptoms was up to 83.6%. Furthermore, no significant differences in the prevalence of the most bothersome post-COVID symptoms, being these fatigue, dyspnea, and brain fog, was seen between those experiencing or not experiencing post-COVID pain (**Table 2**).

Patients with post-COVID pain exhibited higher lymphocyte count and lower glucose and CK levels on hospital admission (all, $P < 0.01$) than those not developing post-COVID pain symptoms at both 6 and 12 months (**Table 3**). The stepwise regression analysis revealed that lower levels of CK (step 1: r^2 adj: 0.05; B: −0.337; 95%CI −0.566 to −0.109; $P = 0.004$) and glucose (step 2: r^2 adj: 0.069; B: −0.003; 95%CI −0.005 to −0.001; $P = 0.047$) were significantly associated, but just explained 6.9% of the variance of experiencing long-term post-COVID pain.

4. Discussion

This study found that post-COVID pain symptoms were present in almost 40% of COVID-19 survivors the first year after hospital

discharge. In addition, patients reporting post-COVID pain exhibited higher lymphocyte count and lower levels of glucose and CK at hospital admission than those not reporting post-COVID pain symptoms, although this association was small.

Our prevalence data are slightly lower than those previously reported by small cohort studies, providing prevalence rates of post-COVID pain up to 60% at 1 month[2,14] and 3[22] months after the infection, but much higher than the prevalence rates (10% to 15%) reported in a recent meta-analysis including general cohort studies.[10] Data may vary significantly depending on how focused the study is on specifically pain or general post-COVID symptoms.

Potential pathophysiologic mechanisms proposed for explaining post-COVID pain symptomatology include a systemic immune response with prolonged inflammation, viral toxicity, hypercoagulability, and microvascular injury.[1] Supporting some of these hypotheses, lower lymphocyte count (lower immune response) and higher D-dimer levels (coagulopathy) have been found in individuals reporting post-COVID pain 3 months after SARS-CoV-2 infection.[2] Our results are contrary to the data reported by Bakılan et al.[2] because

Table 2

Location of post-COVID Pain Symptoms and other post-COVID symptoms according to the presence or absence of post-COVID pain at 6-month follow-up.

	Post-COVID pain (n = 176)	No post-COVID pain (n = 236)
Location of post-COVID pain		
Cervical spine	15/176 (8.5%)	
Thorax-chest	35/176 (19.9%)	
Lumbar spine	14/176 (7.9%)	
Widespread pain	40/176 (22.7%)	
Upper extremity	12/176 (6.8%)	
Shoulder area	15/176 (8.5%)	
Wrist-elbow	10/176 (5.7%)	
Lower extremity	20/176 (11.5%)	
Hip region	5/176 (2.8%)	
Knee	10/176 (5.7%)	
Other post-COVID symptoms		
Fatigue	131 (74.4%)	169 (71.6%)
Dyspnoea	29 (16.5%)	42 (17.8%)
Brain fog	26 (14.8%)	33 (14%)

higher lymphocyte count (lymphocytosis) suggesting an exaggerated immune response was observed in individuals developing long-term post-COVID pain.

In addition, because the presence of angiotensin-converting enzyme-2 and transmembrane protease serine 2 receptors is higher in the muscle tissue than in other tissues,[8] another

Table 3

Laboratory biomarkers of patients with COVID-19 according to the presence or absence of post-COVID pain at 6-month and 12-month follow-up.

6 months follow-up period

	Post-COVID pain (n = 176)	No post-COVID pain (n = 236)
Haemoglobin (g/dL)	13.9 (1.5)	14.0 (1.6)
Lymphocyte (×109/L)*	1.15 (0.5)	1.05 (0.4)
Neutrophils (×109/L)	5.15 (2.6)	5.25 (2.8)
Platelets (×109/L)	281.7 (80.9)	290 (83.8)
Glucose (mg/mL)*	112.0 (31.0)	124.0 (37.5)
Creatine (mg/L)*	97.5 (36.4)	108.0 (44.5)
Alanine transaminase (ALT, U/L)	49.0 (39.4)	48.5 (37.6)
Aspartate transaminase (AST, U/L)	47.0 (34.1)	48.6 (30.6)
Lactate dehydrogenase (LDH, U/L)	271.8 (97.7)	286.7 (91.6)
C-reactive protein (mg/L)	78.9 (80.7)	84.7 (88.3)
L-dimer (ng/mL)	935.2 (848.9)	992.1 (993)

12-month follow-up period

	Post-COVID pain (n = 149)	No post-COVID pain (n = 263)
Haemoglobin (g/dL)	13.9 (1.6)	14.0 (1.5)
Lymphocyte (×109/L)	1.2 (0.45)	1.02 (0.4)
Neutrophils (×109/L)	4.95 (2.5)	5.35 (2.8)
Platelets (×109/L)	327.0 (95.0)	265.0 (74.5)
Glucose (mg/mL)	114.0 (26.0)	122.0 (40.0)
Creatine (mg/L)	92.1 (24.4)	110.0 (47.5)
Alanine transaminase (ALT, U/L)	51.0 (49.5)	47.5 (30.0)
Aspartate transaminase (AST, U/L)	50.2 (41.3)	46.6 (25.5)
Lactate dehydrogenase (LDH, U/L)	272.4 (85.8)	285.0 (98.5)
C-reactive protein (mg/L)	75.0 (79.5)	86.2 (87.8)
L-dimer (ng/mL)	818.5 (737.7)	1056.0 (1020.1)

* Statistically significant differences between groups ($P < 0.01$).
n, number.

mechanism for developing post-COVID pain could be the presence of skeletal muscle injury. Skeletal muscle injury is associated with elevated CK levels (ie, hyperCKemia). In fact, hyperCKemia has been associated with respiratory failure and fatal outcomes in patients with COVID-19.[7] This study found lower CK levels at hospital admission in patients developing long-term post-COVID pain, suggesting that skeletal muscle injury seems to be not associated with post-COVID pain symptoms. In fact, it should be recognized that differences in CK values between pain-developing and no pain–developing individuals were extremely low (ie, a few tenths of mg/mL).

Similarly, patients reporting post-COVID pain also showed lower glucose levels. Because increased blood glucose is associated with severe COVID-19,[6] our results would suggest that individuals with less severe COVID-19 would develop post-COVID pain. Again, between-group differences in glucose levels were also low; hence, their clinical impact on the development of post-COVID pain symptoms seems to be small.

Other biomarkers included in our study were not associated with the presence of post-COVID pain. For instance, higher levels of CRP,[17] higher D-dimer concentration,[9] and lower platelet count[18] have been associated with more severe COVID-19. No differences in these biomarkers were seen depending on the development or not of long-term post-COVID pain symptoms.

The biomarker levels observed in our study suggest a greater immune response (higher lymphocyte count) against the SARS-CoV-2 infection and a lower COVID-19 severity (lower glucose and CK levels) in individuals developing long-term post-COVID pain symptoms[20]; however, associations were small, after adjusting for all the variables during the multivariate regression analyses. It is possible that the fact that our sample was relatively young (younger than 65 years) with a low number of medical comorbidities and low death rate explains the lack of association between serological biomarkers and long-term post-COVID pain symptoms.

Other potential risk factors associated with post-COVID symptoms in general such as female sex, higher number of onset symptoms at hospital admission (higher symptom load) or longer hospital stay[12] could also influence the development of post-COVID pain. In fact, a greater number of acute onset symptoms at hospital admission, ie, higher symptom load, was seen in patients developing post-COVID pain at 6 and 12 months after hospital discharge. Of interest, myalgia and headache were the symptoms at hospital admission with a greater prevalence in patients with post-COVID pain. In line with our results, previous studies reported that the presence of pain symptoms at the acute phase is a marker associated with not only good prognosis for hospitalization[21] but also post-COVID pain symptoms.[11] Based on current evidence, post-COVID pain has a multifactorial genesis where factors related to the pathogen (SARS-CoV-2–associated factors) intersect with the host response (immune and biological responses), as well as with hospitalization (treatment-associated factors) and emotional (COVID-19 outbreak surrounding elements) factors.[5]

This study did not include headache because of its specific diagnostic criteria, which could limit the generality of the results. In fact, Trigo et al. observed that patients experiencing headache as an onset symptom at hospital admission exhibited higher levels of IL-10, but not other proinflammatory biomarkers, suggesting a more intense immune response in these patients.[24] We do not currently know the biomarker profile of those individuals developing post-COVID headache.

Current data should be considered according to limitations of the study design. First, data can be applicable only to previously hospitalized patients with COVID-19. Furthermore, the number of individuals requiring ICU admission was small. Similarly, hospitalization treatments, eg,, amount of sedation, medication intake received for the acute infection, or presence of neuromuscular symptoms associated with ICU admission) were not collected. Second, post-COVID symptoms were collected by telephone, a procedure with a potential bias in population-based survey studies. Nevertheless, telephone interview is a common method used in cohort studies investigating post-COVID pain.[10] Third, although we collected data on post-COVID pain symptoms at 2 different follow-up periods, it would be difficult exclusively to attribute to SARS-CoV-2 infection to the development of post-COVID pain symptoms. Fourth, we focused on pain symptoms potentially considered of musculoskeletal origin; however, due to the use of telephone interviews, characterization of the pain symptoms was not available and we were not able to properly classify the observed post-COVID pain as musculoskeletal or neuropathic in origin. In fact, factors that could potentially influence the development of post-COVID pain, such as depression or anxiety, were not evaluated in this study. Studies characterizing and classifying the nature of post-COVID pain symptoms are clearly needed. Finally, because specific inflammatory biomarkers, eg,, cytokines, were not assessed in this study, they may exhibit strong predictive strengths for the development of post-COVID pain. Similarly, we did not collect data about the intensity or severity of post-COVID pain symptoms; therefore, we were not able to determine the proportion of patients showing disabling symptomatology.

5. Conclusions

This study found a weak association between serological biomarkers associated with COVID-19 severity at hospital admission and the development of long-term post-COVID pain symptoms in previously hospitalized patients. Other factors such as higher number of acute onset symptoms at hospital admission (higher symptom load) could be more relevant for the development of post-COVID pain symptoms.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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