

# Serological Biomarkers at Hospital Admission Are Not Related to Long-Term Post-COVID Fatigue and Dyspnea in COVID-19 Survivors

César Fernández-de-las-Peñas<sup>a, b</sup> Pablo Ryan-Murua<sup>c</sup> Jorge Rodríguez-Jiménez<sup>a</sup>  
María Palacios-Ceña<sup>a</sup> Lars Arendt-Nielsen<sup>b, d</sup> Juan Torres-Macho<sup>c, e</sup>

<sup>a</sup>Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Madrid, Spain; <sup>b</sup>Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark; <sup>c</sup>Department of Internal Medicine, Hospital Universitario Infanta Leonor-Virgen de la Torre, Madrid, Spain; <sup>d</sup>Department of Medical Gastroenterology, Mech-Sense, Aalborg University Hospital, Aalborg, Denmark; <sup>e</sup>Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

## Keywords

COVID-19 · Post-COVID · Fatigue · Dyspnea · Biomarkers · Coagulopathy

## Abstract

**Objective:** The aim of this study was to investigate the association between serological biomarkers at the acute phase of infection at hospital admission with the development of long-term post-COVID fatigue and dyspnea. **Methods:** A cohort study including patients hospitalized due to COVID-19 in one urban hospital of Madrid (Spain) during the first wave of the outbreak (from March 20 to June 30, 2020) was conducted. Hospitalization data, clinical data, and eleven serological biomarkers were systematically collected at hospital admission. Patients were scheduled for an individual telephone interview after hospital discharge for collecting data about the presence of post-COVID fatigue and dyspnea. **Results:** A total of 412 patients (age: 62 years, standard deviation: 15 years; 47.5% women) were assessed with a mean of 6.8 and 13.2 months after discharge. The prevalence of post-COVID fatigue and dyspnea was 72.8% and 17.2% at 6 months and 45.4% and 13.6% at 12 months after hospital discharge, respectively. Patients exhibiting post-COVID fa-

tigue at 6 or 12 months exhibited a lower hemoglobin level, higher lymphocyte count, and lower neutrophil and platelets counts (all,  $p < 0.05$ ), whereas those exhibiting post-COVID dyspnea at 6 or 12 months had a lower platelet count and lower alanine transaminase, aspartate transaminase, and lactate dehydrogenase (LDH) levels (all,  $p < 0.05$ ) than those not developing post-COVID fatigue or dyspnea, respectively. The multivariate regression analyses revealed that a lower platelet count and lower LDH levels were associated but just explaining 4.5% of the variance, of suffering from post-COVID fatigue and dyspnea, respectively. **Conclusion:** Some serological biomarkers were slightly different in patients exhibiting post-COVID fatigue or dyspnea, but they could not explain the long-COVID problems in those patients.

© 2022 S. Karger AG, Basel

## Introduction

Symptoms associated to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affect different systems e.g., respiratory, gastrointestinal, neurological, cardiovascular, or musculoskeletal [1]. Hematological

(lymphocyte count, neutrophil count), immunological (interleukin IL-6), inflammatory (C-reactive protein [CRP], erythrocyte sedimentation rate, procalcitonin), and biochemical (D-dimer, troponin, creatine kinase [CK]) biomarkers have been investigated at the acute phase of infection to identify patients at a risk of developing a worse prognosis. In fact, it has been reported that patients with severe COVID-19 exhibited higher blood cell count and higher levels of CRP, procalcitonin, erythrocyte sedimentation rate, or IL-6 as compared to those with mild COVID-19 [2].

Most studies have investigated biomarker relevance during the acute phase of the infection; however, its role in the development of post-COVID (long COVID) symptoms is less unknown. Different meta-analyses had reported that the prevalence of post-COVID symptoms ranges from 35% to 60%, depending on the symptom and the follow-up [3, 4]. Fatigue and dyspnea seem to be the most prevalent post-COVID symptoms reaching up to 50% of COVID-19 survivors [5, 6]. The association between post-COVID symptoms and laboratory biomarkers is controversial. Mandal et al. [7] found that 30.1% and 9.5% of COVID-19 survivors still showed elevated D-dimer and CRP levels two months after hospital discharge, although no association with any post-COVID symptom was reported. Townsend et al. [8] and Liang et al. [9] did not either report any association between post-COVID fatigue and laboratory biomarkers, such as lymphocyte count, IL-6, and CRP, collected at two to three months after hospital discharge.

Previous studies included <200 patients, short-term follow-up periods, and collected biomarkers at follow-up assessments [7–9]. Accordingly, evidence supporting or refuting an association between laboratory biomarkers at the acute phase of the infection and the presence of long-term post-COVID fatigue or dyspnea is lacking. Monitoring laboratory biomarkers at the acute phase of SARS-CoV-2 infection could help for early identifying individuals at a risk of developing post-COVID fatigue and dyspnea and hence timely interventions. The current cohort study of previously hospitalized COVID-19 survivors investigated the development of post-COVID fatigue and dyspnea 6 and 12 months after hospital discharge. The objective was to investigate the association between serological biomarkers at the acute phase of infection at hospital admission with the development of long-term post-COVID fatigue and dyspnea in hospitalized COVID-19 survivors.

## Methods

A cohort study including patients hospitalized due to 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) was conducted. The study was conducted following the Strengthening the Reporting of Observational studies in Epidemiology guidelines (online suppl. file; for all online suppl. material, see [www.karger.com/doi/10.1159/000524042](http://www.karger.com/doi/10.1159/000524042)). 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 local Ethics Committee (HUIL/092-20) approved the study design. Participants were informed of the study, and all provided their informed consent.

Clinical and hospitalization data including age, gender, height, weight, COVID-19 onset symptoms presented at hospital admission, preexisting comorbidities, intensive care unit admission, and days at the hospital were systematically collected at hospital admission. Additionally, serological values of hemoglobin, lymphocyte count, neutrophil count, platelet count, glucose, CRP, CK, lactate dehydrogenase (LDH), D-dimer, alanine transaminase (ALT), and aspartate transaminase (AST) were also systematically collected at hospital admission.

Participants who agreed to participate in the study and provided their informed consent were scheduled for a telephone semi-structured interview conducted by trained healthcare clinicians. Participants were asked for the presence of self-reported fatigue and dyspnea appearing after hospital discharge and whether the symptom persisted at the time of the study. Fatigue was defined as generalized sensation of tiredness whereas dyspnea was defined as shortness of breath, perception of difficulty breathing, or breathlessness.

The Stata 16.1 program (StataCorp. 2019; Stata Statistical Software: Release 16; StataCorp LP; College Station, TX, USA) was used for the analysis. Data are presented as means (standard deviation) or percentages as appropriate. McNemar's  $\chi^2$  test and paired Student *t* tests were conducted to compare proportions and means between patients with and without post-COVID fatigue or dyspnea at 6- and 12-month follow-up periods. A multiple hierarchical regression analysis was conducted to determine which variables, including serological biomarkers, contributed significantly to the presence of long-term post-COVID fatigue or dyspnea. 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.

## Results

From a total of 450 hospitalized patients who were invited to participate, ten refused to participate, eight could not be contacted after three attempts, and twenty had deceased after hospital discharge. A total of 412 patients (mean age: 62 years, standard deviation: 15 years old; 47.5% women) were finally included.

**Table 1.** Demographic, clinical, and hospitalization data of COVID-19 patients according to the presence or absence of post-COVID fatigue 6 months after hospital discharge

	Post-COVID fatigue ( <i>n</i> = 300)	No post-COVID fatigue ( <i>n</i> = 112)	<i>p</i> value
Age, mean (SD),* years	63.0 (15.0)	59.5 (17.0)	0.04*
Gender, male/female,* <i>n</i> (%)	140 (46.6)/160 (53.4)	73 (65.2)/39 (34.8)	0.023*
Weight, mean (SD), kg	74.0 (16.0)	75.5 (19.0)	0.501
Height, mean (SD), cm	163.5 (11.5)	165 (9.5)	0.523
Medical comorbidities, <i>n</i>	0.9 (0.8)	0.7 (0.9)	0.097
Medical comorbidities, <i>n</i> (%)			
Hypertension	80 (26.6)	33 (29.5)	0.623
Diabetes	30 (10.0)	10 (9.0)	0.779
Cardiovascular diseases	42 (14.0)	13 (11.6)	0.569
Asthma*	27 (9)	2 (1.7)	0.008*
Obesity	15 (5)	9 (8.0)	0.270
Chronic obstructive pulmonary disease	12 (4.0)	5 (4.4)	0.814
Other (cancer, kidney disease)	48 (16)	19 (16.9)	0.816
COVID-19 symptoms at hospital admission, <i>n</i> , mean (SD)	2.15 (0.8)	2.2 (0.7)	0.811
Symptoms at hospital admission, <i>n</i> (%)			
Fever	230 (76.6)	86 (76.7)	0.983
Dyspnea*	121 (40.3)	33 (29.5)	0.03*
Cough	68 (22.7)	23 (20.5)	0.695
Myalgias	80 (26.6)	33 (29.4)	0.623
Headache	56 (18.7)	28 (25)	0.212
Diarrhea	23 (7.6)	15 (13.4)	0.101
Anosmia	25 (8.3)	10 (9.0)	0.836
Ageusia	16 (5.3)	7 (6.25)	0.712
Throat pain	8 (2.7)	5 (4.5)	0.377
Vomiting	8 (2.7)	4 (3.5)	0.625
Stay at the hospital, mean (SD), days	7.0 (4.5)	7.5 (5.5)	0.214
ICU admission			
Yes/no, <i>n</i> (%)	15 (5)/285 (95)	5 (4.4)/107 (93.6)	0.850
Stay at ICU, mean (SD), days	4.0 (2.5)	6.0 (5.5)	0.249

*n*, number; SD, standard deviation; ICU, intensive care unit. \* Statistically significant differences between groups (*p* < 0.05).

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 the study, 300 (72.8%) and 71 (17.2%) patients reported post-COVID fatigue and dyspnea 6 months after hospital discharge, whereas 187 (45.4%) and 56 (13.6%) reported post-COVID fatigue and dyspnea 12 months after hospital discharge, respectively.

Clinical and hospitalization data of patients developing and not developing post-COVID fatigue and dyspnea at 6 months are shown in Tables 1 and 2, respectively. Similar distribution at 12 months was found (online suppl. Tables). Female gender was associated with the development of post-COVID fatigue (OR 1.25, 95% CI: 1.1–1.4) and post-COVID dyspnea (OR 1.8, 95% CI: 1.15–2.95). Patients reporting dyspnea as a COVID-

19-associated onset symptom at hospital admission were more prone to develop post-COVID fatigue (OR 1.62, 95% CI: 1.01–2.58) or post-COVID or dyspnea (OR 3.88, 95% CI: 1.76–8.54) than those not presenting dyspnea as the onset symptom (see Tables 1, 2). Similarly, patients with comorbid asthma before hospitalization were also more prone to develop post-COVID fatigue (OR 5.44, 95% CI: 1.27–23.26) or dyspnea (OR 2.57, 95% CI: 1.53–4.32) than those without comorbid asthma before infection.

Patients exhibiting post-COVID fatigue exhibited higher lymphocyte count and lower neutrophil and platelets counts (all, *p* < 0.05) than those not developing post-COVID fatigue at 6 and 12 months (Table 3). In addition, hemoglobin levels were also lower in patients reporting

**Table 2.** Demographic, clinical, and hospitalization data of COVID-19 patients according to the presence or absence of post-COVID dyspnea 6 months after hospital discharge

	Post-COVID dyspnea ( <i>n</i> = 71)	No post-COVID dyspnea ( <i>n</i> = 341)	<i>p</i> value
Age, mean (SD), years	65.0 (14.5)	61.5 (16.0)	0.105
Gender, male/female,* <i>n</i> (%)	23 (32.4)/48 (67.6)	190 (55.7)/151 (44.3)	0.009*
Weight, mean (SD), kg	77.0 (17.0)	67.5 (13.0)	0.116
Height, mean (SD), cm	163.0 (9.5)	165 (11.5)	0.579
Medical comorbidities, <i>n</i>	0.8 (0.85)	0.85 (0.85)	0.754
Medical comorbidities, <i>n</i> (%)			
Hypertension	14 (19.7)	99 (29.0)	0.168
Diabetes	9 (12.7)	31 (9.1)	0.381
Cardiovascular diseases	10 (14.1)	45 (13.2)	0.826
Asthma*	12 (16.9)	17 (4.9)	0.002*
Obesity	4 (5.6)	20 (5.8)	0.987
Chronic obstructive pulmonary disease	5 (4.2)	12 (3.5)	0.213
Other (cancer, kidney disease)	13 (18.3)	54 (15.8)	0.624
COVID-19 symptoms at hospital admission, <i>n</i> , mean (SD)	2.1 (0.7)	2.2 (0.75)	0.682
Symptoms at hospital admission, <i>n</i> (%)			
Fever	61 (85.9)	255 (74.7)	0.330
Dyspnea*	40 (56.3)	114 (33.3)	0.006*
Cough	11 (15.5)	80 (23.4)	0.190
Myalgias	13 (18.3)	100 (29.3)	0.099
Headache	14 (19.7)	70 (20.5)	0.916
Diarrhea	5 (7.0)	33 (9.6)	0.533
Anosmia	8 (11.2)	27 (7.9)	0.382
Ageusia	4 (5.6)	19 (5.6)	0.940
Throat pain	3 (4.2)	10 (2.9)	0.567
Vomiting	2 (2.8)	9 (2.6)	0.881
Stay at the hospital, mean (SD), days	7.1 (4.3)	7.2 (4.5)	0.915
ICU admission			
Yes/no, <i>n</i> (%)	7 (9.8)/64 (91.2)	13 (3.8)/328 (94.2)	0.153
Stay at ICU, mean (SD), days	4.3 (2.9)	4.5 (4.0)	0.901

*n*, number; SD, standard deviation; ICU, intensive care unit. \* Statistically significant differences between groups (*p* < 0.05).

post-COVID fatigue at 6 months but not at 12 months (Table 3). The multivariate stepwise regression analysis revealed that only a lower platelet count ( $r^2$  adj: 0.045; *B*: -0.226; *p* = 0.006) was significantly associated but just explaining 4.5% of the variance, of suffering from long-term post-COVID fatigue.

Individuals exhibiting post-COVID dyspnea exhibited a lower platelet count and lower ALT, AST, and LDH levels (all, *p* < 0.05) than those not developing post-COVID dyspnea at both 6 and 12 months (Table 4). The multivariate regression analysis revealed that just lower LDH levels ( $r^2$  adj: 0.039; *B*: -0.213; *p* = 0.01) were significantly associated but just explained 4.5% of the variance, of suffering from long-term post-COVID dyspnea.

## Discussion

The current study observed a prevalence of 50% and 15% for post-COVID fatigue and dyspnea during the first year after hospital discharge. Some serological biomarkers at hospital admission were slightly different in individuals suffering from post-COVID fatigue (e.g., lower hemoglobin level, higher lymphocyte count, lower neutrophil count, and lower platelets count) or dyspnea (e.g., lower platelet count and lower ALT, AST, and LDH levels), but the multivariate analysis revealed that they could not explain long-COVID problems in those patients as only low platelet and low LDH levels were independently associated with post-COVID fatigue and dyspnea, respectively.

**Table 3.** Laboratory biomarkers of COVID-19 patients according to the presence or absence of post-COVID fatigue at 6- and 12-month follow-ups

	Post-COVID fatigue (n = 300)	No post-COVID fatigue (n = 112)	p value
<b>6-month follow-up period</b>			
Hemoglobin,* g/dL	13.8 (1.6)	14.3 (1.35)	0.01*
Lymphocyte,* ×10 <sup>9</sup> /L	1.12 (0.45)	1.00 (0.4)	0.025*
Neutrophils,* ×10 <sup>9</sup> /L	5.05 (2.6)	5.70 (2.9)	0.043*
NLR	4.5 (4.5)	5.65 (4.2)	0.185
Platelets,* ×10 <sup>9</sup> /L	225.8 (73.2)	453.7 (102.4)	0.017*
Glucose, mg/mL	118.0 (36.0)	122.0 (32.0)	0.347
CK, mg/L	103.5 (45.0)	104.0 (31.0)	0.857
ALT, U/L	47.5 (38.9)	52.0 (37.0)	0.287
AST, U/L	47.0 (32.7)	50.1 (30.5)	0.425
LDH, U/L	277.5 (95.0)	288.5 (92.5)	0.366
CRP, mg/L	79.0 (89.1)	90.4 (72.6)	0.258
D-dimer, ng/mL	971.8 (940.9)	951.0 (903.0)	0.793
	Post-COVID fatigue (n = 187)	No post-COVID fatigue (n = 225)	p value
<b>12-month follow-up period</b>			
Hemoglobin, g/dL	13.9 (1.5)	14.0 (1.4)	0.898
Lymphocyte,* ×10 <sup>9</sup> /L	1.13 (0.45)	1.03 (0.4)	0.045*
Neutrophils,* ×10 <sup>9</sup> /L	5.15 (2.6)	5.50 (2.8)	0.04*
NLR	4.5 (3.0)	5.45 (5.1)	0.195
Platelets,* ×10 <sup>9</sup> /L	274.5 (86.5)	425.5 (95.6)	0.01*
Glucose, mg/mL	112.0 (38.0)	121.0 (30.5)	0.445
CK, mg/L	102.3 (46.0)	107.5 (35.0)	0.317
ALT, U/L	46.1 (32.2)	50.2 (36.7)	0.322
AST, U/L	47.5 (30.5)	46.0 (24.5)	0.691
LDH, U/L	275.0 (99.0)	279.1 (89.0)	0.741
CRP, mg/L	79.5 (69.0)	90.3 (101.5)	0.320
D-dimer, ng/mL	1,020.0 (846.5)	1,027.3 (772.1)	0.855

n, number; SD, standard deviation. \* Statistically significant differences between groups ( $p < 0.05$ ).

Prevalence rates of post-COVID fatigue and dyspnea observed in our study agree with current meta-analyses on the topic [5, 6] suggesting that our sample is representative of long-COVID patients. Potential pathophysiologic mechanisms proposed for explaining post-COVID fatigue and dyspnea include a systemic immune response with prolonged inflammation and atypical response of the mast cells, persistent viral replication/toxicity, hypercoagulability, and the presence of residual lung injury [10–12].

A lower hemoglobin level, higher lymphocyte count (lymphocytosis), lower neutrophil count (neutropenia), and lower platelet count (thrombocytopenia) at hospital admission were associated with the development of post-COVID fatigue. The normal response of the immune sys-

tem against a systemic inflammation is characterized by lower lymphocyte (lymphopenia) and higher neutrophil (neutrophilia) counts, and it is usually reflected by the neutrophil-to-lymphocyte ratio (NLR) biomarker [13]. In fact, an increase of one unit of the NLR has been associated with higher odds of severity and all-cause mortality in COVID-19 [14]. Our results suggest that patients developing long-term post-COVID fatigue showed a better immune response against SARS-CoV-2 infection, with a higher lymphocyte count and lower neutrophil count when compared to those not developing post-COVID fatigue, biomarkers associated with lower severity of COVID-19. Further, the NLR tended (not significant) to be higher (more severe COVID-19) in those patients not developing post-COVID fatigue or dyspnea.

**Table 4.** Laboratory biomarkers of COVID-19 patients according to the presence or absence of post-COVID dyspnea at 6- and 12-month follow-ups

	Post-COVID dyspnea (n = 71)	No post-COVID dyspnea (n = 341)	p value
<b>6-month follow-up period</b>			
Hemoglobin, g/dL	14.0 (1.35)	14.0 (1.6)	0.896
Lymphocyte, ×10 <sup>9</sup> /L	1.11 (0.45)	1.09 (0.4)	0.598
Neutrophils, ×10 <sup>9</sup> /L	4.8 (2.5)	5.3 (2.75)	0.184
NLR	4.2 (4.1)	4.85 (4.5)	0.350
Platelets,* ×10 <sup>9</sup> /L	141.8 (73.2)	453.7 (102.4)	0.001*
Glucose, mg/mL	125.5 (50.5)	118.5 (30.8)	0.208
CK, mg/L	96.4 (34.0)	105.0 (43.0)	0.209
ALT,* U/L	38.5 (22.4)	51.0 (40.5)	0.017*
AST,* U/L	39.0 (20.7)	50.0 (34.0)	0.012*
LDH,* U/L	245.0 (60.5)	287.7 (98.5)	0.003*
CRP, mg/L	70.0 (67.0)	85.0 (88.5)	0.185
D-dimer, ng/mL	928.5 (849.2)	974.1 (946.4)	0.601
	Post-COVID dyspnea (n = 56)	No post-COVID dyspnea (n = 356)	p value
<b>12-month follow-up period</b>			
Hemoglobin, g/dL	13.5 (1.7)	14.0 (1.5)	0.475
Lymphocyte, ×10 <sup>9</sup> /L	1.15 (0.55)	1.08 (0.4)	0.402
Neutrophils, ×10 <sup>9</sup> /L	5.73 (3.0)	5.25 (2.6)	0.329
NLR	5.1 (3.9)	4.8 (4.5)	0.586
Platelets,* ×10 <sup>9</sup> /L	214.1 (74.25)	466.25 (92.8)	0.009*
Glucose, mg/mL	117.0 (25.7)	119.5 (36.3)	0.649
CK, mg/L	98.0 (41.1)	105.2 (42.0)	0.375
ALT,* U/L	38.9 (22.9)	48.8 (35.1)	0.025*
AST,* U/L	36.7 (16.2)	48.1 (29.2)	0.035*
LDH,* U/L	254.8 (75.8)	279.1 (96.5)	0.02*
CRP, mg/L	85.3 (90.7)	91.4 (86.0)	0.717
D-dimer, ng/mL	916.9 (758.7)	961.1 (882.9)	0.545

n, number; SD, standard deviation. \* Statistically significant differences between groups ( $p < 0.05$ ).

Elevated biomechanical biomarkers, e.g., ALT, AST, and LDH levels, have been also associated with severe COVID-19 [15]. We found lower levels of these biomechanical biomarkers in those patients developing post-COVID dyspnea, supporting the notion that patients with less severe COVID-19 could develop long-term post-COVID dyspnea.

It should be marked that the platelet count was lower in patients developing post-COVID fatigue or dyspnea symptoms, suggesting a greater probably of coagulopathy [16]; however, the association of this biomarker with severe COVID-19 is controversial [17]. Similarly, D-dimer is a biomarker also used to detect the risk of thrombosis. It is assumed that higher D-dimer levels are seen in severe COVID-19 patients [18]; although the interpretation of

D-dimer during disease is still unclear. The current study found that D-dimer concentrations were not significantly associated with post-COVID fatigue or dyspnea.

Other biomarkers included in the current study were not associated neither with post-COVID fatigue nor dyspnea. For instance, higher CK levels (i.e., hyperCKemia) have been associated with respiratory failure and a fatal outcome in patients with COVID-19 [19]. We did not find significant differences in CK levels between those developing and not developing post-COVID fatigue or dyspnea. Similarly, higher levels of CRP are associated with severe COVID-19 [20], but again, no differences were observed depending on the development or not of long-term post-COVID fatigue or dyspnea. Current results show that hematologic biomarkers were slightly different

between individuals developing post-COVID fatigue or not, whereas biochemical biomarkers were slightly different in patients reporting post-COVID dyspnea. These biomarker levels suggest a more potent immune response against the SARS-CoV-2 infection and a lower COVID-19 severity in those individuals developing post-COVID fatigue or dyspnea [21]; however, these associations were small, after adjusting all the variables during the multivariate regression analyses.

It is not possible to exclude the potential role of other risk factors associated with post-COVID symptoms such as female gender, higher number of symptoms at hospital admission, and longer hospital stay [22]. We also observed that female gender was associated with a greater prevalence of post-COVID fatigue and dyspnea. Interestingly, dyspnea as an onset symptom at hospital admission was also associated with long-term post-COVID fatigue and dyspnea. Future studies investigating other clinical risk factors associated with post-COVID fatigue and dyspnea are needed [22].

Finally, the present data should be considered according to limitations of the study design. First, data were obtained from previously hospitalized COVID-19 patients. Additionally, our cohort included Caucasian participants; hence, ethnic differences were not assessed. Second, post-COVID symptoms were collected on 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 fatigue or dyspnea [3–6]. Additionally, fatigue and dyspnea were self-reported by the participants. Future studies could use validated questionnaires, such as the Chalder Fatigue Scale [23], for assessing post-COVID fatigue. Third, although we collected data on post-COVID fatigue and dyspnea symptoms at two follow-up periods, it is difficult to exclusively attribute COVID-19 to their development. Finally, the lack of differences in some of the comparisons, e.g., the NLR, could be affected by the sample size and may be related to a potential type II error.

## Conclusions

Although some serological biomarkers were slightly different in individuals suffering from post-COVID fatigue or dyspnea, they could not explain the long-COVID problems in those patients, and only weak associations between serological biomarkers at hospital admission and the development of long-term post-COVID fatigue or dyspnea were found.

## Acknowledgments

The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121) and the Novo Nordisk Foundation (NNF21OC0067235). The LONG-COVID-EXP-CM is supported by Comunidad de Madrid y la Unión Europea, a través del Fondo Europeo de Desarrollo Regional (FEDER), and financiado como parte de la respuesta de la Unión a la pandemia de COVID-19.

## Statement of Ethics

The local Ethics Committee of the hospital (HUIL/092-20) approved the study design. Participants were informed of the study, and all provided their informed consent.

## Conflict of Interest Statement

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

## Funding Sources

The project was supported by a grant from the Novo Nordisk Foundation 0067235 (Denmark) and 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, and financiado como parte de la respuesta de la Unión a la pandemia de COVID-19 (LONG-COVID-EXP-CM). Both sponsors had no role in the design; collection, management, analysis, or interpretation of the data; and draft, review, or approval of the manuscript or its content. The authors were responsible for the decision to submit the manuscript for publication, and the sponsor did not participate in this decision.

## Author Contributions

César Fernández-de-las-Peñas, Pablo Ryan-Murua, Jorge Rodríguez-Jiménez, María Palacios-Ceña, Lars Arendt-Nielsen, and Juan Torres-Macho contributed to the study concept and design, recruited participants and collected data, contributed to interpretation of data, drafted the paper and revised the text for intellectual content, and approved the final version of the manuscript. César Fernández-de-las-Peñas, Pablo Ryan-Murua, and Jorge Rodríguez-Jiménez conducted literature review and did the statistical analysis.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

## References

- 1 Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, et al. Clinical characteristics of 3,062 COVID-19 patients: a meta-analysis. *J Med Virol.* 2020; 92:1902–14.
- 2 Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B, et al. Association of elevated inflammatory markers and severe COVID-19: a meta-analysis. *Medicine.* 2020;99:e23315.
- 3 Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep.* 2021;11(1):16144.
- 4 Fernández-de-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, et al. Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: a systematic review and meta-analysis. *Eur J Int Med.* 2021;92:55–70.
- 5 Rao S, Benzouak T, Gunpat S, Burns RJ, Tahir TA, Jolles S, et al. Fatigue symptoms associated with COVID-19 in convalescent or recovered COVID-19 patients: a systematic review and meta-analysis. *Ann Behav Med.* 2022 Mar 1;56(3):219–34.
- 6 Cares-Marambio K, Montenegro-Jiménez Y, Torres-Castro R, Vera-Urbe R, Torralba Y, Alsina-Restoy X, et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Chron Respir Dis.* 2021; 18: 14799731211002240.
- 7 Mandal S, Barnett J, Brill SE, Brown JS, Denney EK, Hare SS, et al. “Long-COVID”: a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax.* 2021;76:396–8.
- 8 Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One.* 2020;15:e0240784.
- 9 Liang L, Yang B, Jiang N, Fu W, He X, Zhou Y, et al. Three-month follow-up study of survivors of coronavirus disease 2019 after discharge. *J Korean Med Sci.* 2020 Dec 7;35:e418.
- 10 Afrin LB, Weinstock LB, Molderings GJ. COVID-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *Int J Infect Dis.* 2020 Nov;100: 327–32.
- 11 Jacobs JLL. Persistent SARS-2 infections contribute to long COVID-19. *Med Hypotheses.* 2021;149:110538.
- 12 So M, Kabata H, Fukunaga K, Takagi H, Kuno T. Radiological and functional lung sequelae of COVID-19: a systematic review and meta-analysis. *BMC Pulm Med.* 2021;21(1):97.
- 13 Russell CD, Parajuli A, Gale HJ, Bulteel NS, Schuetz P, de Jager CPC, et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. *J Infect.* 2019;78:339–48.
- 14 Ulloque-Badaracco JR, Ivan Salas-Tello W, Al-Kassab-Córdova A, Alarcón-Braga EA, Benites-Zapata VA, Maguiña JL, et al. Prognostic value of neutrophil-to-lymphocyte ratio in COVID-19 patients: a systematic review and meta-analysis. *Int J Clin Pract.* 2021; 75(11):e14596.
- 15 Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evid Based Med.* 2021;26(3):107–8.
- 16 Mitra S, Ling RR, Yang IX, Poon WH, Tan CS, Monagle P, et al. Severe COVID-19 and coagulopathy: a systematic review and meta-analysis. *Ann Acad Med Singap.* 2021;50(4): 325–35.
- 17 Kazemi E, Soldoozi Nejat R, Ashkan F, Sheibani H. The laboratory findings and different COVID-19 severities: a systematic review and meta-analysis. *Ann Clin Microbiol Antimicrob.* 2021;20(1):17.
- 18 Du WN, Zhang Y, Yu Y, Zhang RM. D-dimer levels is associated with severe COVID-19 infections: a meta-analysis. *Int J Clin Pract.* 2021;75(8):e14031.
- 19 De Rosa A, Verrengia EP, Merlo I, Rea F, Siciliano G, Corrao G, et al. Muscle manifestations and CK levels in COVID infection: results of a large cohort of patients inside a pandemic COVID-19 area. *Acta Myol.* 2021;40: 1–7.
- 20 Melo AKG, Milby KM, Caparroz ALMA, Pinto ACPN, Santos RRP, Rocha AP, et al. Biomarkers of cytokine storm as red flags for severe and fatal COVID-19 cases: a living systematic review and meta-analysis. *PLoS One.* 2021;16:e0253894.
- 21 Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci.* 2020;57:389–99.
- 22 Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: a systematic review and meta-analysis. *EClinicalMedicine.* 2021;36:100899.
- 23 Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. *J Psychosom Res.* 1993;37:147–53.