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Letter to the Editor

Long-term post-COVID symptoms and associated risk factors in previously hospitalized patients: A multicenter study

The word is in front of a second pandemic associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), i.e., post-COVID sequelae and "long-haulers". A preprint meta-analysis has found that 80% of COVID-19 survivors exhibit at least one post-COVID symptom after infection.[1] However, most of the studies included in this meta-analysis had follow-up periods <3 months, sample sizes < 300 participants, and were conducted at a single center.[1] In a letter to the editor in *Journal of Infection,* Garrigues et al. found that fatigue, dyspnea, and loss of memory were the most prevalent post-COVID symptoms 3 months after hospital discharge.[2] More recently, Moreno-Perez et al. observed that 59% of hospitalized and 37% of non-hospitalized patients exhibited post-COVID symptoms 3 months after the infection.[3] Here we report a multicenter study assessing post-COVID symptoms and associated risk factors seven months after hospital discharge.

This multicenter observational study included patients hospitalized with a positive diagnosis of SARS-CoV-2 by RT-PCR technique and radiological findings during the first wave of the pandemic (March 10th to May 31st, 2020) in four public hospitals in Madrid (Spain). From all hospitalized patients, a randomized sample of 300 patients from each hospital was selected. The study was approved by all the Local Ethics Committees (URJC0907202015920, HCSC20/495E, HUFA 20/126, HUF/EC1517, HUIL/092–20). Informed consent was obtained from participants before collecting data.

Patients were scheduled for a telephone interview by trained researchers. Clinical (i.e., age, gender, height, weight, pre-existing comorbidities) and hospitalization (e.g., symptoms at hospital admission, days at hospital, intensive care unit [ICU] admission) data were collected from hospital medical records. Participants were systematically asked about a list of post-COVID symptoms (dyspnea, fatigue, anosmia, ageusia, hair loss, chest pain, palpitations, diarrhea, skin rashes, brain fog, memory loss, cough) but they were free to report any symptom that they considered relevant. More than one symptom could be reported by the same participant.

Descriptive data are presented as mean (standard deviation, SD) or percentages as appropriate. Chi-square or Mann-Whitney tests were used to compare the post-COVID symptoms by gender or ICU or not admission. Multivariate Poisson regression prediction and risk models were constructed to identify those clinical and hospitalization variables associated with the number of persistent post-COVID symptoms. Adjusted incident rate ratios (IRR) with 95% confidence intervals (95%CI) were calculated.

From 1200 patients randomly selected and invited to participate, 13 refused, 10 were not contacted, and 35 had deceased after hospital discharge. A total of 1142 (48% women, mean age: 61, SD: 17 years) were included. The most prevalent symptoms at hospital admission were fever (71.1%), myalgia (33.2%), and dyspnea (33.2%).

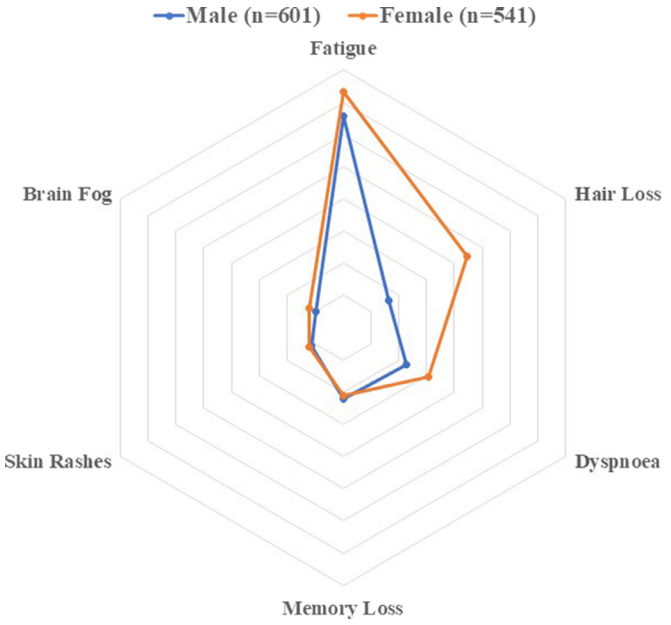

Fig. 1. Distribution of the most prevalent post-COVID symptoms (fatigue, hair loss, dyspnea, memory loss, skin rashes, and brain fog) in male and female patients.

Four hundred and eighty-two (42.2%) had no comorbidities, 406 (35.5%) had one comorbidity, 174 (15.3%) had two, and the remaining 80 (7%) had at least three comorbidities (**Table 1**).

Participants were assessed a mean of 7.0 months (SD 0.6) after hospital discharge. Only 212 (18.6%) were completely free of any post-COVID symptom, 238 (20.8%) had one symptom, 267 (23.4%) had two symptoms, and 425 (37.2%) had 3 or more. The mean number of post-COVID symptoms was 2.5 (SD 1.2). Women (mean: 2.5, SD: 1.5) had significantly (IRR1.37, 95%CI 1.26–1.49, $P < 0.002$) higher number of post-COVID symptoms than men (mean 1.8, SD: 1.4). Patients requiring ICU admission (mean: 2.5; SD; 1.5) also showed greater (IRR1.20, 95%CI 1.03–1.38, $P = 0.016$) number of post-COVID symptoms than those not requiring ICU admission (mean: 2.0, SD: 1.5). The most frequent symptoms were fatigue (60.8%), hair loss (26.3%), and dyspnea (23.5%). Women experienced fatigue (OR1.75, 95%CI 1.37–2.24; $P < 0.001$), hair loss (OR4.34, 95%CI 3.2–5.79; $P < 0.001$), and dyspnea (OR1.70, 95%CI 1.29–2.24; $P < 0.001$) more frequently than men (**Fig. 1**).

The regression model revealed that female (IRR1.37, 95%CI 1.25–1.49, $P < 0.001$), number of days at hospital (IRR1.005, 95%CI 1.002–1.009, $P = 0.002$), number of medical comorbidities (IRR1.11, 95%CI 1.05–1.16, $P < 0.001$) and number of acute COVID-19 symptoms at hospital admission (IRR1.24, 95%CI 1.17–1.31, $P < 0.001$)

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Table 1
Demographic and clinical data of the sample ($n = 1142$).

Age, mean (SD), years	61 (17)
Gender, male/female (%)	601 (52.5%) / 541 (47.5%)
Weight, mean (SD), kg.	70 (15)
Height, mean (SD), cm.	166 (10)
Body Mass Index, mean (SD), kg/cm^2	25.4 (3.0)
Smoking status, n (%)	
Active	96 (8.5%)
None or Former	1046 (91.5%)
Main Symptoms at hospital admission, n (%)	
Fever	812 (71.1%)
myalgia	380 (33.2%)
dyspnea	380 (33.2%)
Cough	315 (27.6%)
Headache	209 (18.3%)
Gastrointestinal Disorders-Diarrhoea	140 (12.2%)
Anosmia	108 (9.5%)
Ageusia	99 (8.7%)
Throat Pain	61 (5.4%)
Medical co-morbidities	
Hypertension	291 (25.5%)
Diabetes	145 (12.7%)
Chronic Heart Disease - Cardiovascular Disease	144 (12.6%)
Rheumatological Disease	61 (5.5%)
Asma	55 (4.8%)
Obesity	54 (4.7%)
Chronic Obstructive Pulmonary Disease	51 (4.4%)
Stroke	29 (2.5%)
Other (Cancer, Kidney Disease)	105 (9.1%)
Stay at the hospital, mean (SD), days	14 (12)
Intensive Care Unit (ICU) admission	
Yes/No, n (%)	80 (7%) / 1062 (93%)
Stay at ICU, mean (SD), days	15 (13)
Number of persistent post-COVID symptoms, n (%)	
None	212 (18.6%)
1 or 2	505 (44.2%)
3 or more	425 (37.2%)
Persistent post-COVID symptoms, n (%)	
Fatigue	695 (60.8%)
loss hair	305 (26.3%)
dyspnea	268 (23.5%)
Loss memory	217 (19.0%)
Skin Rashes	117 (10.2%)
Brain fog	110 (9.6%)
Attention Disorders	93 (8.1%)
Gastrointestinal Disorders-Diarrhoea	82 (7.2%)
Chest Pain	80 (7.0%)
Tachycardia-Palpitations	77 (6.7%)
Ocular/Vision Disorders	52 (4.5%)
Ageusia	38 (3.3%)
Anosmia	34 (3%)
Cough	24 (2.1%)

were significantly associated with the number of long-term post-COVID symptoms.

This multicenter study found that 80% of hospitalized COVID-19 survivors exhibited at least one post-COVID symptom seven months after hospital discharge. Fatigue, hair loss, and dyspnea were the most prevalent symptoms. Female gender, number of days at hospital, previous comorbidities, and number of symptoms at hospital admission were associated with a higher number of long-term post-COVID symptoms.

Our prevalence rates of fatigue (60.8%), hair loss (26.3%), and dyspnea (23.5%). as post-COVID sequelae agree with pooled prevalence data reported by Lopez-Leon et al.[1] Although most studies investigating post-COVID symptoms have included follow-up periods < 3 months,[1] a small number of single-center studies have included follow-ups > 6 months.[4–7] Our study increases evidence to the current literature with a large, multicenter design evaluating long-term post-COVID symptoms. Based on the available evidence, the term persistent post-COVID is supported, since symptoms are present more than six months after infection.[8]

It seems that the post-COVID-19 symptom burden will be comparable to the long-term burden of severe acute respiratory syndrome (SARS), where subjects present with symptoms one year after infection.[9] In fact, unlike other acute respiratory syndromes, COVID-19 survivors also exhibit multiple non-respiratory symptoms, e.g., tachycardia, ageusia, anosmia, brain fog, memory loss and gastrointestinal problems, several months after infection. Biological (e.g., cytokine storm) and emotional (e.g., posttraumatic stress, uncertainty on prognosis, social alarm) factors surrounding COVID-19 are suggested to be responsible of this plethora of post-COVID symptoms. This heterogeneity in post-COVID symptoms supports that they will certainly need a multidisciplinary treatment.

Identification of risk factors associated with persistent COVID-19 sequelae will facilitate diagnosis and counselling strategies for these patients. We identified that female gender, longer stay at hospital, higher number of comorbidities, and higher number of symptoms at hospital admission were risk factors associated with a higher number of post-COVID symptoms seven months after dis-

charge. These results agree with potential risk factors previously identified in other single-center studies[1].

Our study has some weaknesses. First, only hospitalized patients were included. Second, the number of patients requiring ICU admission was small. Third, we did not collect objective measures of COVID-19 disease, e.g., inflammatory biomarkers, blood oxygen saturation.

Author contributions

All authors contributed to the study concept and design. CFdlP, DMP, VGM, and VHB conducted literature review and did the statistical analysis. VGM, MVA, CG, CMEM, MLC, JAAN, LJMT, TSV, JTM, MGCD, and SPC recruited participants. JRJ, MPC, AIdlLR, SFN, LLF, ROS, MGM, SAQ and JLAB collected data. LAN supervised the study. All authors contributed to interpretation of data. CFdlP, DPC, VGM, MLC and LA 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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No conflict of interest is declared by any of the authors

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