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Letter to the editor



The number of symptoms at the acute COVID-19 phase is associated with anxiety and depressive long-term post-COVID symptoms: A multicenter study

Dear Editor

Evidence supports the presence of different post-COVID symptoms in people who had surpassed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with prevalence rates ranging from 35 to 60% [1]. Deng et al. [2] reported that around 45% of COVID-19 patients experience depressive or anxiety symptoms at hospitalization. Anxiety and depressive symptoms are also present after the acute COVID-19 phase [3]; however, most of published studies included follow-up periods <3 months, sample sizes <300 participants, and were conducted at single centers [3]. A recent letter to the Editor in *Journal of Psychosomatic Research* [4] showed that anxiety levels were higher within 14 days of testing positive from COVID-19 than after following resolution of symptoms. Another recent study [5] showed that depressive and anxiety symptoms decreased during the month following hospitalization, but no long-term data is yet available. The objective of this multicenter study was to evaluate the potential risk factors associated with long-term post-COVID anxiety and depressive symptoms in patients requiring hospitalization.

A multicenter study including patients with a 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) from five public hospitals in Madrid (Spain) was conducted. From all hospitalized patients, a sample of 400 from each hospital was randomly selected. The Local Ethics Committees of all the hospitals approved the study (HCSC20/495E, HUF 20/126, HSO25112020, HUIL/092-20, HUF/EC1517). Informed consent was obtained from all individuals. Participants were scheduled for a telephone interview conducted by healthcare professionals. The Hospital Anxiety and Depression Scale (HADS) [6] was used to evaluate anxiety (HADS-A, 7 items, 0–21 points) and depressive (HADS-D, 7 items, 0–21 points) symptoms. We considered cut-off scores recommended for Spanish population (HADS-A \geq 12points; HADS-D \geq 10points) suggestive of anxiety or depressive symptoms, respectively [7]. Clinical features (age, gender, height, weight, pre-existing medical comorbidities), COVID-19 symptoms at hospital admission, and hospitalization data (days at hospital, intensive care unit [ICU] admission) were collected from medical records. Descriptive data are presented as mean, standard deviation (SD) or percentages. Missing values were imputed using median imputation. Multivariate logistic regressions were conducted to determine the influence of clinical and hospitalization data on long-term post-COVID anxiety and depressive symptoms (dependent variables) using Python's library statsmodels 0.11.1. Adjusted odds ratio (OR) with their 95%confidence intervals (95%CI) were calculated.

From 2000 patients, a total of 1969 (53.4% men, age: 61, SD: 16 years) were assessed between 6 and 10 months (mean: 8.4, SD 1.5) after hospital discharge (Table 1). At the study period, 15.7% patients showed

anxiety symptoms (\geq 12points) whereas 18.9% depressive symptoms (\geq 10points). The regression model found that female gender (OR3.11, 95%CI 1.74–5.54), the number of symptoms at hospital admission (OR3.21, 95%CI 1.87–5.51) and the days at hospital (OR1.05, 95%CI 1.025–1.071) were associated with anxiety symptoms (all, $P < 0.001$). The same factors were associated with depressive symptoms: female gender (OR2.14, 95%CI 1.25–3.65, $P = 0.005$), the number of COVID-19 symptoms at hospital admission (OR2.96, 95%CI 1.80–4.85, $P < 0.001$), and days at hospital (OR1.05, 95%CI 1.035–1.077, $P < 0.001$). Further, two specific onset COVID-19 symptoms at hospital admission were associated with anxiety/depressive symptoms: dyspnea (anxiety: OR4.22, 95%CI 2.50–7.10; depression: OR4.86, 95%CI 3.01–7.85, $P < 0.001$) and myalgia (anxiety: OR 2.85, 95%CI 1.70–4.79; depression: OR1.74, 95%CI 1.08.01–2.78, $P = 0.02$).

This multicenter study observed a prevalence of 16.2% and 19.7% of anxiety and depressive symptoms in a sample of almost 2000 hospitalization-requiring COVID-19 survivors as long-term post-COVID symptoms. Female gender, a greater number of symptoms at hospital admission and more days of hospitalization were associated with higher risk of presenting long-term post-COVID anxiety/depressive symptoms. Female gender [4] and longer hospitalization period [5] have been previously identified as risk factors for post-COVID symptoms one month after hospital discharge. Early identification of risk factors is urgently needed for close monitoring and intervention of patients at a higher risk of developing post-COVID depressive and anxiety symptoms. This study increases evidence with a large sample and a multicenter design assessing long-term post-COVID anxiety/depressive symptoms.

Finally, we acknowledge some weaknesses. First, only hospitalized patients were included. Second, we did not collect objective measures of COVID-19 disease, such as inflammatory biomarkers or blood oxygen saturation. Third, the cross-sectional design does not permit to determine a temporal relation of the development of symptoms. We do not know if anxiety/depressive symptoms were present before the infection rather than a consequence of the illness. Additionally, mood disorders such as anxiety and depressive could be also affected by external surrounding factors (e.g., relative affection by COVID-19, isolation, social pressure) which were not assessed in this study. Finally, the potential presence of post-traumatic stress disorder (PTSD) was not evaluated due to the use of telephonic interview.

In conclusion, the prevalence of anxiety and depressive symptoms eight months after hospital discharge was 16.2% and 19.7%, respectively, and both were associated with female gender, the number of symptoms at hospital admission and the number of days at the hospital.

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Table 1
Clinical/hospitalization data and post-COVID symptoms (n = 1969).

Age, mean (SD), years	61 (16)
Gender, male/female (%)	1054 (53.5%) / 915 (46.5%)
Weight, mean (SD), kg.	75 (15)
Height, mean (SD), cm.	165 (16.5)
Main Symptoms at hospital admission, n (%)	
Fever	1469 (74.6%)
Dyspnoea	620 (31.5%)
Myalgia	604 (30.7%)
Cough	549 (27.9%)
Headache	332 (16.9%)
Diarrhoea	210 (10.7%)
Anosmia	167 (8.5%)
Throat Pain	102 (5.2%)
Ageusia	66 (3.35%)
Vomiting	55 (2.8%)
Number of medical co-morbidities, n (%)	
None	836 (42.5%)
One	715 (36.3%)
Two	281 (14.2%)
3 or more	137 (7%)
Medical co-morbidities	
Hypertension	514 (26.1%)
Diabetes	236 (12.0%)
Cardiovascular Disease	234 (11.9%)
Asma	126 (6.4%)
Obesity	88 (4.5%)
Chronic Obstructive Pulmonary Disease	77 (3.9%)
Stroke	38 (2.0%)
Rheumatological Disease	31 (1.6%)
Other (Cancer, Kidney Disease)	332 (16.9%)
Stay at the hospital, mean (SD), days	11.3 (11.4)
Intensive Care Unit (ICU) admission	
Yes/No, n (%)	130 (6.6%) / 1839 (93.4%)
Anxiety/Depressive Symptom, n (%)	
Anxiety Symptoms (HADS-A \geq 12 points)	308 (15.7%)
Depressive Symptoms (HADS-D \geq 10 points)	373 (18.9%)

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