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LETTERS OF BIOMEDICAL AND CLINICAL RESEARCH

The presence of rheumatological conditions is not a risk factor of long-term post-COVID symptoms after SARS-CoV-2 infection: a multicenter study

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Dear Editor,

Evidence suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disproportionately impacts people with some pre-existing medical comorbidities, e.g., diabetes or hypertension. Patients with rheumatic musculoskeletal diseases (RMDs) may be also affected by coronavirus disease 2019 (COVID-19) [1]. In fact, musculoskeletal rheumatic symptoms are present at the acute COVID-19 phase [2] but also as post-COVID sequelae [3, 4]. Additionally, SARS-CoV-2 can also trigger new-onset COVID-19-related arthritis [5]. Identification of potential factors associated with a higher risk of developing post-COVID symptoms is needed; however, current data is limited [6]. The presence of RMDs could act as a risk factor for the development post-COVID symptoms due to a potentiation of pro-inflammatory responses seen during the infection but also due to a less robust immune response [7]. In a study recently published in *Clinical Rheumatology*, Shenoy et al. found that patients with autoimmune rheumatic diseases exhibited adequate antibody responses similar to those of healthy controls, discarding this latest hypothesis [8]. Nevertheless, an invasion/injury of the musculoskeletal cells by SARS-CoV-2 by the angiotensin-converting enzyme 2 (ACE2) receptor in predisposing individuals with pre-existing RMDs could also be a risk factor for post-COVID symptoms [7]. We describe here if the presence of pre-existing RMD is a risk factor associated with a greater number of long-term post-COVID symptoms.

This multicenter study included patients with a diagnosis of SARS-CoV-2 during the first wave of the pandemic selected from five public hospitals in Madrid (Spain). All Local Ethics Committees approved the study (HCSC20/495E, HSO25112020, HUFA 20/126, HUIL/092–20, HUF/EC1517). Informed consent was obtained from all patients. Participants were scheduled for a telephone interview by healthcare professionals and were systematically asked about the presence of post-COVID symptoms and functional limitations self-perceived. The presence of pre-existing RMD was collected from hospital medical records. Univariate logistic/linear regressions (with intercept) were conducted to analyze the association between the presence of RMDs (independent) with the number of post-COVID symptoms, functional limitations, and mood disorders such as anxiety and depression (dependent variables) using Python's library statsmodels 0.11.1. The presence of other medical comorbidities, days at hospital, and sociodemographic features such as age, weight, and height were included as in the model as cofounding variables. Adjusted odds ratio (OR) and confidence intervals (95% CI) are presented.

A total of 1969 (46% women, age 61, SD 16 years) participated. Participants were assessed 8.4 months (SD 1.5) after hospital discharge. Almost 57.5% of the patients ($n = 1133$) reported at least one comorbidity. Thirty-one patients (1.5%) had pre-existing RMDs ($n = 17$ rheumatoid arthritis, $n = 8$ knee/hip osteoarthritis, $n = 6$ osteoporosis). One out of five ($n = 367$, 18.7%) patients was free of any

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post-COVID symptom, and 34.4% ($n=679$) reported ≥ 3 post-COVID symptoms. The most prevalent long-term post-COVID symptoms included fatigue (61%), musculoskeletal symptoms (45%), and dyspnea (23%). The presence of RMD was not significantly associated with the number of long-term post-COVID symptoms (OR 1.46, 95% CI 0.89–2.40, $P=0.15$), functional limitation (OR 1.058, 95% CI 0.42–2.59, $P=0.91$), anxiety (OR 2.81, 95% CI 0.43–18.24, $P=0.28$), or depression (OR 2.25, 95% CI 0.40–12.51, $P=0.35$). No association between pre-existing RMD and post-COVID musculoskeletal pain was either found (OR 1.95, 95% CI 0.94–4.05, $P=0.11$).

This multicenter study suggests that the presence of pre-existing of RMD is not a risk factor for developing more long-term post-COVID symptoms in previously COVID-19 hospitalized patients. Our results agree with the hypothesis that the presence of other medical comorbidities seen in patients with RMDs could be a more significant risk factor than RMDs themselves [9]. The inclusion of other medical co-morbidities in multivariate analysis did not reveal an association with long-term post-COVID symptoms either.

Our results should be considered with caution. First, we just recruited hospitalized patients. Second, the number of patients with RMD was small (1.5%) but this prevalence agrees with current literature [10]. Third, we did not collect objective data of COVID-19 severity. Fourth, the cross-sectional design did not permit to determine cause-and-effect associations. Finally, we did not consider the use of biological therapies. Preliminary evidence suggests that patients with RMDs treated with rituximab can present an atypical course of COVID-19 pneumonia [11]. Further research in this topic is needed.

Author contribution All authors contributed to the study conception and design. Material preparation and analysis were performed by Dr. Fernández-de-las-Peñas, Dr. Martín-Guerrero, and Dr. Pellicer-Valero. All authors participated in data collection. The first draft of the paper was written by Dr. Fernández-de-las-Peñas. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The data that support the results of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of all involved hospitals (HCSC20/495E, HSO25112020, HUFA 20/126, HUIL/092–20, HUF/EC1517).

Consent to participate Informed consent was obtained from all patients.

Disclosures None.

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