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Letter to the Editor

Similar prevalence of long-term post-COVID symptoms in patients with asthma: A case-control study

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disproportionately impacts people with some pre-existing medical comorbidities, e.g., diabetes, hypertension or cardiovascular conditions. For instance, hypertensive patients exhibit higher mortality risk than normotensive patients with SARS-CoV-2 infection.[1] Asthma is another medical comorbidity which could influence the course of COVID-19. Interestingly, asthma seems to be a "protective factor", since the risk of presenting severe COVID-19 in people with asthma is small;[2]although a recent meta-analysis concluded that pre-existing asthma was a predictor of intubation particularly just in young and obese COVID-19 patients.[3]

Current evidence supports the presence of long-COVID, that is, individuals who have recovered from COVID-19 but exhibit symptoms after the acute phase far longer than it would be expected.[4]In a letter to the editor in *Journal of Infection,* Garrigues et al.analysed the presence of post-COVID symptoms in hospitalized patients and found that the most prevalent persistent symptoms were fatigue, dyspnoea, and loss of memory.[5]Very 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.[6] In a posterior letter to the editor in *Journal of Infection*, Garcia-Pachon et al. described a series of patients with asthma showing low prevalence of symptoms 3 months after infection.[7]However, this study did not include a comparison control group including COVID-19 patients without asthma. We present the first case-control study comparing the differences in post-COVID symptoms between hospitalized patients with and without asthma.

From all patients admitted to Hospital Universitario Infanta Leonor-Virgen de la Torreand Hospital Universidad Fundación Alcorcon (Madrid, Spain) with a diagnosis of SARS-CoV-2 by RT-PCR technique during the first wave of the pandemic (March 10th to May 31st, 2020), a randomized sample of 400 patients from each hospital was selected. From those selected, patients with asthma prior to hospitalization were included as cases. Additionally, age- and sex- matched hospitalized COVID-19 patients without pre-existing asthma were recruited as controls. Asthma was classified according the 2019 Global Initiative for Asthma (GINA) guidelines (www.ginasthma.org/). The study was approved by both local Ethics Committees (HUIL/092–20, HUF/EC1517). Participants provided informed consent before collecting data.

Clinical and hospitalization data were collected from hospital records. Participants were scheduled for a telephonic interview by trained healthcare professionals around 7.5 months (SD 0.5) after hospital discharge. Patients were asked to report the presence of symptoms after hospitalization, and if these symptoms persisted at the time of the study. Participants were systematically asked about a predefined list of post-COVID symptoms including fatigue,dyspnoea at rest, dyspnoea on exertion, chest pain, headache, anosmia, ageusia, cough, palpitations,diarrhoea, cognitive blunting/brain fog, or memory loss, but they were free to report any further symptom that they considered relevant.

The Hospital Anxiety and Depression Scale (HADS) and the Pittsburgh Sleep Quality Index (PSQI) were used to assess anxiety/depression symptoms and sleep quality, respectively, as both can be adequately administered by telephone.[8]We considered cut-off scores considered on the Spanish populationfor determining the presence of anxiety (HADS-$A \geq 12/21$ points) and depressive (HADS-$D \geq 10/21$ points) symptoms and poor sleep quality (PSQI$\geq$8/21 points).[9]

The statistical analysis was conducted with STATA 16.1 (StataCorp. 2019, USA). The McNemar and paired Student t-tests were applied to compare proportions and means between groups. Multivariable conditional logistic regression models were constructed to identify variables associated to the presence of pre-existing asthma. Adjusted odd ratios (OR) or Incident Rate Ratios (IRR) with their 95% confidence intervals (95%CI) were calculated.

From 800 randomized COVID-19 patients hospitalized during the first wave of the pandemic, 61 patients with asthma and 122 age- and sex-matched patients without asthma were recruited. A greater proportion of patients with asthma experienced dyspnoea and myalgia as onset symptoms at hospital admission ($P<0.05$, Table 1). Higher number of patients with asthma also presented diabetes as comorbid condition when compared with those without asthma ($P=0.045$).

From the total sample, just 34 (18.6%) were completely free of any post-COVID symptom 7 months after hospital discharge. Individuals with pre-existing asthma showed similar (IRR1.07, 95%CI 0.87–1.33, $P=0.476$) number of post-COVID symptoms (mean: 2.4, SD: 1.4) than those without asthma (mean: 2.2, SD: 1.6). The most prevalent post-COVID symptoms weredyspnoea on exertion, fatigue, anddyspnoea at rest (Table 1). In fact, a greater proportion of patients with pre-existing asthma reporteddyspnoea on exertion (OR2.73; 95%CI 1.23–6.08; $P=0.013$) than those without asthma. No differences in the presence of fatigue (OR1.23; 95%CI 0.61–2.49; $P=0.556$),dyspnoea at rest (OR1.38; 95%CI 0.70–2.75; $P=0.347$), depressive symptoms (OR1.39, 95%CI 0.67–2.89), anxiety symptoms (OR1.32, 95%CI 0.55–3.18) or poor sleep quality (OR1.71, 95%CI 0.89–3.27, $P=0.105$) between patients with or without asthma were observed (Table 1).

Identification of the phenotype of patients at a higher risk of death during the acute infection or a higher risk of developing post-COVID symptoms is crucial. In our sample, the presence of long-term post-COVID symptoms was similar between patients with and without pre-existing asthma, suggesting that asthma seems not to be a risk factor for more severe long-term post-COVID symptoms but either was a "protective" factor for that. Our re-

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Table 1.
Demographic, hospitalisation data, and post-COVID symptoms of COVID-19 patients with and without pre-existing asthma.

	Asthmatic ($n = 61$)	Non-asthmatic ($n = 122$)
Age, mean (SD), years	55 (17)	55 (16.5)
Gender, male/female (%)	15 (24.6%) / 46 (75.4%)	30 (24.6%) / 92 (75.4%)
Weight, mean (SD), kg.*	79.5 (23)	77.0 (15.5)
Height, mean (SD), cm.	164 (11)	163 (9)
Body Mass Index, mean (SD), kg/cm^2*	29.8 (9.5)	29.0 (4.5)
Smoking status, n (%)		
Active	4 (6.6%)	9 (7.3%)
None or Former	57 (93.4%)	112 (92.7%)
Medical co-morbidities		
Asthma Treatment	61 (100%)	0 (0.0%)
Hypertension	13 (18.9%)	28 (22.9%)
Cardiovascular Disease	4 (6.5%)	10 (8.2%)
Diabetes*	1 (1.6%)	10 (8.2%)
Obesity	2 (3.3%)	7 (5.7%)
Rheumatological Disease	1 (1.6%)	4 (3.3%)
Chronic Obstructive Pulmonary Disease	3 (4.9%)	5 (4.1%)
Migraine	3 (4.9%)	3 (2.4%)
Other (Cancer, Kidney Disease)	9 (14.7%)	23 (18.8%)
Symptoms at hospital admission, n (%)		
Fever	38 (62.3%)	90 (73.7%)
Dyspnoea*	28 (45.9%)	35 (28.6%)
Myalgia*	32 (52.4%)	42 (34.4%)
Cough	21 (34.4%)	35 (28.6%)
Headache	12 (19.7%)	27 (22.1%)
Diarrhoea	11 (18.0%)	24 (19.7%)
Anosmia	6 (9.8%)	13 (10.6%)
Ageusia	4 (6.6%)	8 (6.6%)
Throat Pain	6 (9.8%)	10 (8.2%)
Stay at the hospital, mean (SD), days	14.5 (14.4)	12.8 (10.1)
Intensive Care Unit (ICU) admission		
Yes/No, n (%)	7 (11.5%) / 54 (88.5%)	5 (4.1%) / 117 (95.9%)
Stay at ICU, mean (SD), days	18.3 (21.1)	9.4 (8.4)
Number of post-COVID symptoms, n (%)		
None	8 (13.2%)	25 (20.4%)
1 or 2	23 (37.7%)	45 (36.9%)
3 or more	30 (49.1%)	52 (42.7%)
Post-COVID symptoms, n (%)		
Dyspnoea on exertion	46 (75.4%)	71 (58.2%)
Fatigue	40 (65.6%)	75 (61.5%)
Dyspnoea rest	21 (34.4%)	34 (27.8%)
Memory Loss	11 (18.0%)	20 (16.4%)
Skin Rashes	8 (13.1%)	13 (10.6%)
Concentration loss	8 (13.1%)	14 (11.4%)
Cognitive Blunting - Brain fog	6 (9.9%)	10 (8.2%)
Gastrointestinal Disorders - Diarrhoea	2 (3.3%)	5 (4.1%)
Tachycardia-Palpitations	6 (9.8%)	8 (6.5%)
Ocular/Vision Disorders	4 (6.6%)	9 (7.3%)
Ageusia/Hypogeusia	1 (1.6%)	3 (2.5%)
Anosmia/Hyposmia	4 (6.6%)	2 (1.6%)
Throat Pain	2 (3.3%)	3 (2.5%)
HADS-D (0–21), mean (SD)*	6.1 (5.6)	5.4 (4.9)
Depressive Symptoms (HADS-$D \geq 10$ points), n (%)	17 (27.9%)	27 (22.1%)
HADS-A (0–21), mean (SD)*	5.5 (5.5)	5.3 (4.8)
Anxiety Symptoms (HADS-$A \geq 12$ points), n (%)	9 (14.75%)	14 (11.5%)
PSQI (0–21), mean (SD)*	8.8 (4.6)	7.5 (4.3)
Poor Sleep Quality (PSQI $\geq$8 points), n (%)*	33 (54.1%)	51 (41.8%)

HADS: Hospital Anxiety and Depression Scale (A: Anxiety; D: Depression); PSQI: Pittsburgh Sleep Quality Index; SD: Standard Deviation.
* Significant differences between asthmatic and non-asthmatic patients ($P<0.01$).

sults are contrary to those found by Garcia-Pachon et al. in their letter to the Editor.[7] It should be considered that Garcia-Pachon et al. did not include a "control" group without asthma and also included a shorter follow-up.[7] Additionally, these authors included non-hospitalized patients, which could explain the discrepancies. Fatigue anddyspnoea where the most common post-COVID symptoms in agreement with current literature,[5,6] but the presence of dyspnoea with exertion was more frequent in patients suffering from asthma. Distinction between dyspnoea at rest and on exertion maybe crucial in these patients.

Our study has limitations. First, the prevalence of asthma in our sample was 7.6%, in agreement with a meta-analysis reporting a pooled prevalence of asthma in COVID-19 patients of 7.46% (95%CI 6.25–8.67); [10]however, this sample could be considered small. Second, we conducted the follow-up by telephone. Third, just hospitalized patients were included. Fourth, we did not collect objective measures of COVID-19 disease such as inflammatory biomarkers. Finally, we collected data cross-sectionally; therefore, future longitudinal studies are needed.

Declaration of Competing Interest

The authors declare no conflict of interest

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References

1. Zuin M, Rigatelli G, Zuliani G, Rigatelli A, Mazza A, Roncon L. Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis. *J Infect* 2020;**81**:e84–6.
2. Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, et al. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *Lancet Respir Med* 2021 Apr 1 S2213-2600(21)00095-3.
6. Hussein MH, Elshazli RM, Attia AS, Nguyen TP, Aboueisha M, Munshi R, et al. Asthma and COVID-19; different entities, same outcome: a meta-analysis of 107,983 patients. *J Asthma* 2021 Feb 22:1–8. doi:10.1080/02770903.2021.1881970.
4. Nabavi N. Long COVID: how to define it and how to manage it. *BMJ* 2020;**370**:m3489.
3. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;**81**:e4–6.
5. Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jiménez J, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: a Mediterranean cohort study. *J Infect* 2021 S0163-4453(21)0 0 0 09-8.
7. Garcia-Pachon E, Grau-Delgado J, Soler-Sempere MJ, Zamora-Molina L, Baeza–Martinez C, Ruiz-Alcaraz S, et al. Low prevalence of post-COVID-19 syndrome in patients with asthma. *J Infect* 2021 Apr 2 S0163-4453(21)00156-0.
8. Hedman E, Ljótsson B, Blom K, El Alaoui S, Kraepelien M, Rück C, et al. Telephone versus internet administration of self-report measures of social anxiety, depressive symptoms, and insomnia: psychometric evaluation of a method to reduce the impact of missing data. *J Med Internet Res* 2013;**15**:e229.
9. Grupo de Trabajo de la Guía de Práctica Clínica para el Manejo de Pacientes con Trastornos de Ansiedad en Atención Primaria. *Guías de Práctica Clínica en el SNS - UETS N° 2006/10. Madrid: Plan Nacional para el SNS del MSC*. Unidad de Evaluación de Tecnologías Sanitarias, Agencia Laín Entralgo, Comunidad de Madrid; 2008.
10. Sunjaya AP, Allida SM, Di Tanna GL, Jenkins C. Asthma and risk of infection, hospitalization, ICU admission and mortality from COVID-19: systematic review and meta-analysis. *J Asthma* 2021 Apr 1:1–14 </bib>. doi:10.1080/02770903.2021.1888116.

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