LETTER

Preexisting hypertension is associated with a greater number of long-term post-COVID symptoms and poor sleep quality: a case–control study

Journal of Human Hypertension; https://doi.org/10.1038/s41371-022-00660-6

TO THE EDITOR:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disproportionately impacts individuals with preexisting medical co-morbidities, such as hypertension [1]. It seems that hypertensive patients exhibit higher mortality risk than normotensive patients during SARS-CoV-2 infection [2]. A potential hypothesis explaining this situation is the effect of the angiotensin-converting enzyme 2 (ACE2) receptor in the renin–angiotensin–aldosterone system and the pro-inflammatory response (i.e., cytokine storm) associated with SARS-CoV-2 infection [3, 4].

There has been an increasing interest in the presence of symptoms after the acute phase (post-COVID symptoms) of infection, e.g., long COVID. Long COVID is defined as those symptoms appearing during or after SARS-CoV-2 infection during far longer than it would be expected [5]. Current evidence suggests that the presence of post-COVID symptoms ranges from 35 to 60% depending on the symptom and the follow-up period [6]; however, most studies did not consider the role of previous medical co-morbidities. This study analyzed the association of hypertension and long-term post-COVID symptoms in previously hospitalized COVID-19 patients.

A case–control study including patients admitted to Hospital University Fundación Alcorcón and Severo Ochoa (Madrid, Spain) due to COVID-19 during the first wave of the pandemic (from February 20 to May 31, 2020) was conducted. All patients had a positive diagnosis of SARS-CoV-2 by RT-PCR technique (ICD-10 code). Patients with a medical diagnosis of hypertension [7] prior to hospitalization were included as cases. All patients were under regular medical control. Uncontrolled hypertensive patients were excluded. Additionally, age-and sex-matched hospitalized COVID-19 patients without preexisting hypertension were recruited as controls. The study design was approved by the local Ethics Committees (HUF/EC1517, HSO25112020). All participants provided informed consent before collecting data.

Clinical (age, gender, height, weight, and preexisting co-morbidities) and hospitalization (symptoms at hospitalization, days at hospital, intensive care unit [ICU] admission) were collected from hospital medical records. All participants were scheduled for a telephonic interview by trained healthcare professionals a mean of 7.2 months (SD 0.6) after hospital discharge. Participants were asked to report the development of any symptom appearing after hospitalization, and if the symptom persisted at the time of the study. They were systematically asked about the following list of post-COVID symptoms: dyspnea, fatigue, chest pain, headache, anosmia, ageusia, cough, palpitations, diarrhea, cognitive blunting/brain fog, or memory loss, but they were free to report any 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]. Briefly, the HADS includes an anxiety (HADS-A, 7-items, 21 points) and a depressive (HADS-D, 7-items, 21 points) symptoms subscale [9]. We considered the cut-off scores recommended for the Spanish population (HADS-A ≥ 12 points; HADS-D ≥ 10 points) for determining anxiety and depressive symptoms, respectively [10]. The PSQI evaluates the quality of sleep over the previous month throughout 19 self-rated questions assessing different sleep aspects [11]. Questions are answered on a 4-point Likert-type scale (0–3), and the sum is transformed into a global score (0–21 points) where higher scores are indicative of worse sleep quality. A total score ≥8.0 points suggests poor sleep quality [11].

The McNemar and paired Student *t* tests were applied to compare proportions and means between groups. Multivariable conditional logistic regression models, adjusted by baseline factors, was constructed to identify those variables significantly different in the hypertensive patients. Adjusted odd ratios (OR) with 95% confidence intervals (95% CI) were calculated.

Among 1850 COVID-19 patients hospitalized during the first wave of the pandemic, a total of 287 hypertensive and 287 age- and sex-matched normotensive patients were recruited. No differences in symptoms at hospital admission were observed (Table 1). A significant greater proportion of hypertensive patients had higher number of comorbid conditions than normotensive patients (X^2: 56.340, $P < 0.001$). In fact, a higher proportion of hypertensive patients reported comorbid diabetes, cardiovascular disease, and obesity when compared with normotensive patients (all, $P < 0.01$).

From the total sample, just 109 (18.9%) were completely free of any post-COVID symptom 7.2 months after hospital discharge. A greater proportion of hypertensive patients reported ≥3 post-COVID symptoms compared to normotensive patients (X^2: 13.089, $P = 0.023$). The number of post-COVID symptoms in the hypertensive group (mean: 2.1, SD: 1.4) was greater (IRR1.16, 95% CI 1.03–1.30, $P = 0.012$) than that in the normotensive group (mean: 1.8, SD: 1.4)

The most prevalent post-COVID symptoms were fatigue, dyspnea at rest and dyspnea on exertion (Table 1). No differences in the presence of fatigue (OR1.32; 95% CI 0.94–1.84; $P = 0.105$),

Received: 25 April 2021 Revised: 21 January 2022 Accepted: 4 February 2022
Published online: 16 February 2022

Table 1. Demographic, hospitalization data, and post-COVID symptoms of COVID-19 hypertensive and normotensive patients.

	Hypertensive ($n = 287$)	Normotensive ($n = 287$)	*P* value
Age, mean (SD), years	68.3 (12.6)	68.3 (12.5)	0.968
Gender, male/female (%)	114 (39.7%)/173 (61.3%)	114 (39.7%)/173 (61.3%)	N/A
Weight, mean (SD), kg.[a]	77.6 (14.7)	73.2 (13.6)	<0.001
Height, mean (SD), cm.	165.5 (10.7)	165.8 (9.3)	0.705
BMI, mean (SD), kg/cm^{2}[a]	28.4 (5.4)	26.6 (4.5)	<0.001
Smoking status, *n* (%)			
Active	25 (8.7%)	15 (5.2%)	0.139
None or former	262 (92.3%)	272 (94.8%)	
Number medical co-morbidities, *n* (%)[a]			
None	0 (0%)	133 (46.3%)	<0.001
1 or 2	224 (78.1%)	140 (48.8%)	
3 or more	63 (21.9%)	14 (4.9%)	
Medical co-morbidities			
Hypertension	287 (100%)	0 (0.0%)	0.01
Migraine	5 (1.7%)	7 (2.4%)	
Diabetes[a]	58 (20.2%)	42 (14.6%)	
Cardiovascular disease[a]	62 (22.6%)	48 (16.7%)	
Rheumatological disease	13 (4.5%)	10 (3.5%)	
Asthma	13 (4.5%)	10 (3.5%)	
Obesity[a]	21 (7.3%)	8 (2.8%)	
Chronic Obstructive Pulmonary Disease	14 (4.9%)	23 (8.0%)	
Other (Cancer, kidney disease)	65 (22.6%)	57 (19.9%)	
Symptoms at hospital admission, *n* (%)			
Fever	201 (70.0%)	199 (69.3%)	0.305
Dyspnea	98 (34.2%)	91 (31.7%)	
Myalgia	91 (31.7%)	97 (33.8%)	
Cough	83 (28.9%)	80 (27.8%)	
Diarrhea	48 (16.7%)	40 (13.9%)	
Headache	39 (13.6%)	34 (11.8%)	
Anosmia	26 (9.0%)	19 (6.6%)	
Ageusia	22 (7.7%)	26 (9.0%)	
Throat pain	19 (6.6%)	18 (6.3%)	
Stay at the hospital, mean (SD), days	15.3 (13.0)	14.6 (12.3)	0.533
Intensive Care Unit (ICU) admission			
Yes/no, *n* (%)	24 (8.3%)/263 (91.7%)	17 (5.9%)/270 (93.9%)	0.398
Stay at ICU, mean (SD), days	14.8 (14.7)	18.6 (12.9)	
Number post-COVID symptoms, *n* (%)[a]			
None	46 (16.1%)	63 (21.9%)	0.023
1 or 2	122 (42.5%)	140 (48.8%)	
3 or more	119 (41.4%)	84 (29.3%)	
Post-COVID symptoms, *n* (%)			
Fatigue	184 (64.1%)	165 (57.5%)	0.01
Dyspnea on exertion	171 (59.6%)	155 (54.0%)	
Dyspnea rest	65 (22.6%)	59 (20.6%)	
Memory loss	63 (21.9%)	59 (20.6%)	
Skin rashes	32 (11.2%)	26 (9.0%)	
Migraine-like headache[a]	31 (10.8%)	16 (5.6%)	
Concentration loss	27 (9.4%)	24 (8.3%)	
Cognitive blunting—brain fog	28 (9.7%)	21 (7.2%)	
Gastrointestinal disorders—diarrhea	18 (6.2%)	21 (7.2%)	
Tachycardia-palpitations	18 (6.2%)	12 (4.2%)	
Ocular/vision disorders	12 (4.2%)	15 (5.2%)	
Ageusia/hypogeusia	12 (4.2%)	11 (3.8%)	
Anosmia/hyposmia	10 (3.5%)	10 (3.5%)	
Cough	7 (2.4%)	5 (1.8%)	
HADS-D (0–21), mean (SD)[a]	5.8 (4.8)	4.8 (4.7)	0.013
Depressive symptoms (HADS-D ≥ 10 points) *n* (%)	66 (23.0%)	55 (19.2%)	0.352
HADS-A (0–21), mean (SD)[a]	5.6 (5.1)	4.5 (5.0)	0.010
Anxiety symptoms (HADS-A ≥ 12 points) *n* (%)	50 (17.4%)	46 (16.0%)	0.656
PSQI (0–21), mean (SD)[a]	7.1 (4.0)	5.9 (3.9)	<0.001
Poor Sleep Quality (PSQI ≥ 8 points) *n* (%)[a]	115 (40.1%)	82 (28.6%)	0.003

HADS Hospital Anxiety and Depression Scale (*A* Anxiety, *D* Depression), *PSQI* Pittsburgh Sleep Quality Index, *SD* Standard Deviation.
[a]Significant differences between hypertensive and normotensive patients ($P < 0.05$).

dyspnea at rest (OR1.13; 95% CI 0.76–1.68; $P = 0.557$) or dyspnea on exertion (OR1.25; 95% CI 0.90–2.99; $P = 0.178$) between hypertensive and normotensive patients were observed (Table 1). Migraine-like headache as a post-COVID symptom was more frequent in hypertensive than in normotensive patients (10% versus 5.6%, $P = 0.01$). A higher proportion of hypertensive patients had poor sleep quality (OR1.68, 95% CI 1.18–2.38, $P = 0.003$), but no differences were found for depressive (OR1.26, 95% CI 0.85–1.89) or anxiety symptoms (OR1.11, 95% CI 0.71–1.72) (Table 1).

Identification of the phenotype of patients at a higher risk of death during the acute infection or at a higher risk of developing post-COVID symptoms is crucial. To the best of the author's knowledge, this is the first case–control study investigating the association of hypertension with long-term post-COVID symptoms. We observed that hypertensive patients showed a greater number of post-COVID symptoms and worse sleep quality than normotensive patients. No overall differences in specific post-COVID symptoms were seen, except for a higher presence of post-COVID migraine-like headache in hypertensive patients. This finding is expected since hypertension is highly comorbid with migraine [12]. Hypertension was not associated with any particular post-COVID symptom, but they exhibited a greater number of symptoms. It is possible that hypertense individuals exhibit post-COVID symptoms in a greater extent than normotensive patients, but not any specific, symptoms. Nevertheless, hypertensive was associated with poor sleep quality. However, we cannot assume that poor sleep quality is due to COVID-19 since we do not have data before the infection and hospitalization.

As expected, hypertense patients also exhibited comorbid diabetes and diabetes. A meta-analysis has reported that the risk of obesity and diabetes is independent and non-additive between them in COVID-19 patients [13]. These data would suggest that our results are more related to the presence of hypertension rather than the presence of these other co-morbidities.

In agreement with this hypothesis, the multivariate analysis found that hypertension was independently associated with a greater number of post-COVID symptoms and poor sleep quality.

Our study has some limitations. First, patients were recruited from a single center and followed up by telephone. Second, only hospitalized patients were included. Third, we did not collect objective measures of disease severity, e.g., inflammatory biomarkers. Finally, we collected data cross-sectionally; hence, the exploratory nature of the study needs to be confirmed in longitudinal design. In fact, although we systematically asked for the presence of symptoms developed after hospitalization due to COVID-19, since we did not collect the presence of symptoms before the infection, we cannot confirm that all symptoms are just consequence of COVID-19. Additionally, we cannot firmly exclude the role of hospitalization factors, e.g., ICU admission or the treatments provided, in the development of long-term post-COVID symptoms.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study concept and design. CFdlP conducted literature review. VHB performed the statistical analysis. JTM, CG, MVA, SPC, and JAN recruited participants. CG supervised the study. All authors collected data and contributed to interpretation of data. All authors contributed to drafting the paper, revised the text for intellectual content and have read and approved the final version of the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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