LETTER

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

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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 for 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 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 covariates, 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 (X²: 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 (X²: 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),
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 N/A    | <0.001  |
| Weight, mean (SD), kg    | 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/cm²   | 28.4 (5.4)             | 26.6 (4.5)             | <0.001  |
| Smoking status, n (%)    | 25 (8.7%)              | 15 (5.2%)              | 0.139   |
| Number medical co-morbidities, n (%)a | 262 (92.3%) | 272 (94.8%) |         |
| Hypertension             | 287 (100%)             | 0 (0.0%)               | 0.01    |
| Migraine                 | 5 (1.7%)               | 7 (2.4%)               |         |
| Diabetes                 | 58 (20.2%)             | 42 (14.6%)             |         |
| Cardiovascular diseasea | 62 (22.6%)             | 48 (16.7%)             |         |
| Rheumatological disease  | 13 (4.5%)              | 10 (3.3%)              |         |
| Asthma                   | 13 (4.5%)              | 10 (3.5%)              |         |
| Obesitya                 | 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%) |         |
| Fevers at hospital admission, n (%) | 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 | 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 | 46 (16.1%) | 63 (21.9%) | 0.023   |
| Fatigue                  | 184 (64.1%)            | 165 (57.5%)            | 0.01    |
| Dyspnea on exertion      | 171 (59.6%)            | 155 (54.0%)            |         |
| Memory loss              | 65 (22.6%)             | 59 (20.6%)             |         |
| Skin rashes              | 63 (21.9%)             | 59 (20.6%)             |         |
| Migraine-like headache   | 31 (10.8%)             | 16 (5.6%)              |         |
| Concentration loss       | 27 (9.4%)              | 24 (8.3%)              |         |

Table 1. continued

|                          | Hypertensive (n = 287) | Normotensive (n = 287) | P value |
|--------------------------|------------------------|------------------------|---------|
| 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) | 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) | 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) | 115 (40.1%) | 82 (28.6%) | 0.003   |

HADS Hospital Anxiety and Depression Scale (A Anxiety, D Depression), PSQ Pittsburgh Sleep Quality Index, SD Standard Deviation.

*aSignificant 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, hypertensive 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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