Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Blood pressure increase during hospitalization for COVID-19

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To the Editor:

The first report of a rise in blood pressure (BP) associated with vaccination for coronavirus disease 2019 (COVID-19) was provided by Meylan et al. [1]. These authors published a series of subjects vaccinated with '*Comirnaty*' (by Pfizer-BioNtech) or '*Spikevax*' (by Moderna) [1]. Unexpectedly, hours or days after vaccination, BP in these subjects rose considerably up to levels of 220/115 mmHg [1]. Although subsequent studies substantially confirmed this finding, evidence remains limited [2,3]. The potential basic mechanisms of the BP rise associated with COVID-19 vaccination are elusive, although some possibilities look reasonable. For example, the down-regulation of ACE_2 receptors due to their internalization into the cells after the contact with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, either alone (i.e., produced by vaccines) [4] or combined with the entire virus (i.e., during SARS-CoV-2 infection) [5–7], would result in a loss of ACE_2 enzymatic activity at the outer cell surface. Consequently, angiotensin II would be transformed into $angiotensin_{1–7}$ to a much lesser extent, with enhancement of the typical unwanted effects of angiotensin II (vasoconstriction, inflammation, thrombosis) [5–7].

An interesting approach to investigate the potential effects of SARS-CoV-2 infection on BP could be the observation of patients hospitalized for severe COVID-19 [8]. Thus, we conducted a prospective case-control study in hospitalized patients with confirmed diagnosis of SARS-CoV-2 infection (by RNA reverse-transcriptase-polimerase-chain-reaction assays from nasopharyngeal swab specimens) and imaging features for COVID-19 pneumonia [9]. It was not a retrospective enrollment of patients, but a prospective study according to a prespecified protocol. The protocol was approved by the Ethic Committee of our Institution and patients provided their informed consent to participate. We also predefined a control group of patients who had been hospitalized for bacterial pneumonia and whose diagnostic tests for COVID-19 were negative along the entire hospitalization period.

Participants were consecutively recruited in a 2:1 allocation ratio. The primary outcome was the rate of persistent raise in BP requiring a new or intensified anti-hypertensive treatment during hospitalization. BP values $\geq$ 140 mmHg systolic or 90 mmHg diastolic for at least two consecutive days defined the persistent rise in BP. The secondary outcome was the differences between the two groups in the average BP during hospitalization. We estimated that a total of 58 cases and 29 controls would provide an 85% power to detect a clinically relevant 30% increase in the proportion of uncontrolled hypertension between patients with COVID-19 pneumonia and patients with bacterial pneumonia.

We collected demographic, laboratory, and clinical management data at admission and throughout the entire in-hospital stay. Laboratory parameters were assessed using standard techniques. We used the PaO_2/FIO_2 ratio to estimate the severity of respiratory dysfunction. We defined comorbidities according to documented medical history, as collected by investigators at study site-level, including interrogation of electronic health record data. All clinical evaluations were performed by the attending physician during the clinical interview and through interrogation of medical records. BP was measured in the morning according to current Guidelines [10]. Previous cardiac events included history of heart failure (defined by at least one prior hospitalization for acute heart failure requiring intravenous therapy) and coronary artery disease (as defined by at least one of the following criteria: (1) presence of any epicardial coronary vessels with >75% stenosis tested on coronary angiography; (2) history of acute coronary syndrome; (3) coronary revascularization, either percutaneous transluminal coronary angioplasty or coronary artery by-pass grafting). Cerebrovascular disease included previous history of stroke or transient ischemic attack.

Table 1 shows the main characteristics of patients. Mean age was 64 and 66 years for COVID-19 and bacterial pneumonia cases, respectively. Clinical features and prevalence of comorbidities were well-balanced between cases and controls. Of note, patients with COVID-19 and bacterial pneumonia had similar BP at admission (systolic: 121 vs 118 mmHg, $p = 0.426$; diastolic: 76 vs 74 mmHg, $p = 0.401$).

Conversely, mean systolic/diastolic BP recorded during

Abbreviations: BP, blood pressure; COVID-19, coronavirus disease 2019; ACE, angiotensin converting enzyme; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RNA, ribonucleic acid.

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Table 1
Main characteristics of patients according to different types of pneumonia (mean ± standard error or percentages, when appropriate).

Patients characteristics	COVID-19 Pneumonia(n = 58)	Bacterial Pneumonia(n = 29)	p
Age (years)	64±1.9	66±2.9	0.472
Females, %	38	41	0.194
Body Mass Index, Kg/m^2	27.2±0.63	24.8±1.07	0.046
Comorbidities			
Hypertension, %	55	48	0.544
Diabetes, %	17	21	0.153
Current smoker, %	28	31	0.112
Cardiac events, %	16	17	0.837
Cerebrovascular disease, %	10	7	0.600
Chronic obstructive pulmonary disease, %	5	28	0.003
Laboratory data at admission			
White blood cell count, x10^3	7.07±0.37	10.34±0.97	<0.001
Serum creatinine, mg/dl	0.83±0.03	0.97±0.10	0.078
K+, mEq/l	4.32±0.06	4.37±0.11	0.656
Haemoglobin, g/dl	12.6±0.18	12.0±0.28	0.062
PaO_2/FIO_2 ratio, mm	312±12	285±13	0.185
Blood pressure and heart rate			
Systolic BP at admission, mmHg	121±2.3	118±3.2	0.426
Diastolic BP at admission, mmHg	76±1.4	74±1.6	0.401
Heart rate at admission, bpm	79±2.0	81±2.2	0.480
Systolic BP during hospitalization, mmHg	126±1.9	118±2.2	0.016
Diastolic BP during hospitalization, mmHg	79±1.1	70±0.9	<0.0001
Short-term systolic BP variability*, mmHg	13±0.7	10±0.9	0.043
Short-term diastolic BP variability*, mmHg	8.1±0.5	6.6±0.3	0.060
Mean heart rate during hospitalization, bpm	74±1.0	76±1.7	0.400
Outcome			
Persistent raise in BP requiring drug therapy, %	45	10	0.001

Legend: BP = blood pressure; * = estimated by standard deviation of blood pressure during hospitalization.

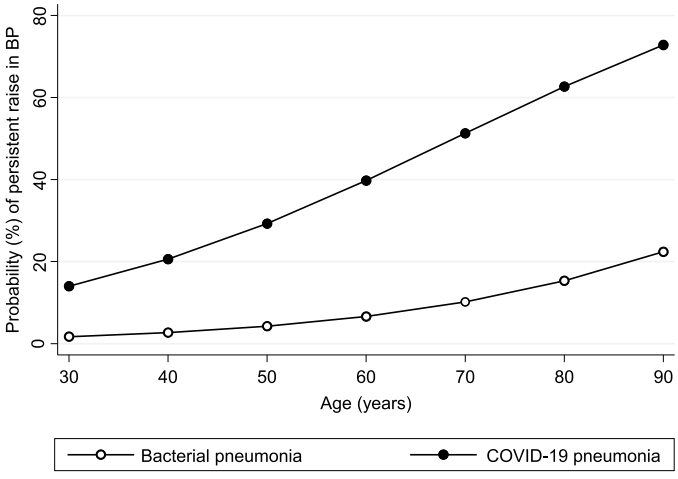

Fig. 1. Probability of persistent raise in blood pressure according to type of pneumonia and age (see text for details).

hospitalization showed a significant difference between patients with COVID-19 pneumonia and patients with bacterial pneumonia (systolic: 126 vs 118 mmHg, $p = 0.016$; diastolic: 79 vs 70 mmHg, $p < 0.0001$).

Table 2
Predictors of uncontrolled hypertension in the group with COVID-19 pneumonia (see text for details).

Variable	Comparison	OR (95% CI)	p
Age	10 years	1.91 (1.21–3.06)	0.006
Sex	Male vs Female	2.89 (0.79–10.57)	0.109
Body mass index	10 Kg/m^2	1.34 (0.43–4.17)	0.616
Comorbidities			
Hypertension	Yes vs No	7.27 (2.14–24.77)	0.002
Diabetes	Yes vs No	5.64 (1.05–30.19)	0.043
Cardiac events	Yes vs No	11.67 (1.33–20.72)	0.027
Cerebrovascular disease	Yes vs No	0.81 (0.12–5.28)	0.827
Chronic obstructive pulmonary disease	Yes vs No	2.61 (0.23–30.57)	0.445
Laboratory data at admission			
White blood cell count	10^3	1.06 (0.88–1.28)	0.554
Serum creatinine	1 mg/dl	2.39 (0.18–31.35)	0.506
K+	1 ng/mL	1.07 (0.35–3.33)	0.901
Haemoglobin	1 g/dl	0.87 (0.59–1.28)	0.475
PaO_2/FIO_2 ratio	10 mm	0.98 (0.92–1.04)	0.467
Blood pressure			
Systolic BP at admission	10 mmHg	1.22 (0.91–1.62)	0.178
Diastolic BP at admission	10 mmHg	1.15 (0.74–1.77)	0.540
Heart rate at admission	10 bpm	0.96 (0.67–1.36)	0.804

Legend: BP = blood pressure; OR=odds ratio; CI=confidence interval.

During hospitalization, 28 patients exhibited a persistent raise in BP requiring antihypertensive treatment. Specifically, 25 and 3 patients met the primary endpoint among COVID-19 and bacterial pneumonia, respectively ($p = 0.001$). Thus, COVID-19 pneumonia was associated with a 7-fold increased risk of uncontrolled hypertension when compared with bacterial pneumonia (odds ratio: 6.99, 95% confidence interval: 1.89 to 25.80, $p = 0.004$). Similar results were obtained after adjustment for age (Fig. 1, $p = 0.019$). Predictors of uncontrolled hypertension (Table 2) in the group with COVID-19 were age ($p = 0.006$), history of hypertension ($p = 0.002$), diabetes ($p = 0.043$), and previous cardiac events ($p = 0.027$). Notably, these features have been associated with ACE_2 receptor deficiency, potentially linked to a reduced generation of the potent vasodilator angiotensin$_{1–7}$, during the active phase of the disease [5,7].

To the best of our knowledge, this case-control study is the first to indicate that COVID-19 pneumonia is associated with a rise in BP in hospitalized patients. These preliminary data should be confirmed in larger case series. The potential basic mechanisms underlying this phenomenon require further research.

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