ORIGINAL PAPER

Interactions between hypertension and inflammatory tone and the effect on blood pressure and outcomes in patients with COVID-19

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Abstract
Arterial hypertension represented one of the most common comorbidities in patients with COVID-19. However, the impact of hypertension on outcome in COVID-19 patients is not clear. Close connections between inflammation and blood pressure (BP) have been described, and inflammation plays a key role in the outcome for patients with COVID-19. Whether hypertension impairs the relationship between inflammation, BP, and outcomes in this context is not known. The aim of this study was to examine the effects of the interactions between inflammation and hypertension status on BP and clinical outcome in patients hospitalized with COVID-19. We designed a retrospective study in 129 patients hospitalized with COVID-19 at Toulouse University Hospital. The hospital outcome was admission to the intensive care unit or death. The inflammatory markers were blood C-reactive protein level (CRP), neutrophil to lymphocyte, and platelet to lymphocyte ratios. We identified strong correlations between CRP ($P < .01$) and the other inflammatory markers recorded on admission ($P < .001$) with mean BP within 3 days after admission in normotensive patients, whereas these correlations were absent in patients with hypertension. Also, we observed after multivariate adjustment ($P < .05$) that CRP level predicted a worse prognosis in hypertensive patients (relative risk 2.52; 95% confidence intervals [1.03-6.17]; $P = .04$), whereas CRP was not predictive of outcome in patients without hypertension. In conclusion, the study revealed that in COVID-19 patients, hypertension impairs the relationship between inflammation and BP and interacts with inflammation to affect prognosis. These findings provide insights that could explain the relationship between hypertension and outcomes in COVID-19 patients.

1 | BACKGROUND

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic disease caused by the RNA virus called severe acute respiratory syndrome coronavirus 2. Between December 31, 2019, and November 15, 2020, the number of confirmed cases of COVID-19 reached 53,507,282 including 1,305,164 deaths reported to the WHO. The mortality rate ranges from 1% to >5%. Among the determinants of the prognosis, the effect of hypertension was controversial. It has been reported to increase severity and mortality in patients with
COVID-19, especially in patients 70 years and older in some but not all studies. Thus, to date, the determinants of the prognosis for hypertensive patients with COVID-19 are not fully known. Pneumonia and acute respiratory distress syndrome are complications frequently encountered in hospitalized patients with COVID-19. They require admission to intensive care and can result in death. COVID-19-induced acute respiratory distress syndrome is caused by an overproduction of early response pro-inflammatory cytokines which in turn leads to what has been described as a cytokine storm, resulting in an increased risk of cardiovascular collapse. The impact of inflammation on blood pressure has been widely described in the literature. Observational and genetic analyses demonstrate a concordant, positive, and potentially causal relationship between inflammation and the immune system that affects systolic, diastolic, and pulse pressure. Whether hypertension impairs the relationship between inflammation and blood pressure in the context of COVID-19 is not known. The aim of this study was to investigate the effects of interactions between inflammatory markers and hypertension status on blood pressure and hospital outcome in patients hospitalized with COVID-19.

2 | METHODS

We designed a retrospective study. All patients admitted to Toulouse University Hospital with COVID-19 during the period March 2020-April 2020, except patients admitted directly to an intensive care unit, were considered eligible. Patients were included according to the following criteria: adults (over 18 years old) and laboratory confirmation of COVID-19 by real-time PCR, and/or chest computed tomography scan findings that meet the requirements for the diagnosis of COVID-19. Patients admitted directly to an intensive care unit were excluded. Demographic and biological data at inclusion were recorded. Hypertension was defined as the self-report of hypertensive patients who had a poor hospital outcome were more likely to have higher CRP level (n=18: 104.70 ± 70.69 vs n=32 66.05 ± 60.74 mg/l; p=0.02; Wilcoxon test) whereas no significant correlation was observed in patients with hypertension (Table 2). In the normotensive group, C-reactive protein was a strong predictor of systolic blood pressure, mean blood pressure, and pulse pressure within 3 days after admission, whereas PLR and NLR predicted systolic blood pressure and pulse pressure within 2 days after admission. To illustrate this finding, the scatterplot between C-reactive protein as logarithm on admission and mean blood pressure at J3 in normotensive patients is shown in Figure 1. In the multiple linear regression analysis, after adjustment for age, gender, diabetes, asthma, and body mass index, CRP predicted systolic and mean BP at day 3 and pulse pressure at day 2, NLR predicted SBP and PP at day 2, and PLR predicted PP at day 2 in normotensive patients, whereas no significant association was observed in patients with hypertension (Table 3). Also, it is interesting to note that hypertensive patients who had a poor hospital outcome were more likely to have higher CRP level (n=18: 104.70 ± 70.69 vs n=32 66.05 ± 60.74 mg/l; p=0.02; Wilcoxon test) whereas no significant difference in CRP was observed in normotensive patients according to the hospital outcome (n=21 73.66±64.13 vs n=57 64.07± 68.60 mg/l; p=0.57 Wilcoxon test). Moreover, the logistic regression analysis showed a significant link between CRP and the hospital outcome (n=21 73.66±64.13 vs n=57 64.07± 68.60 mg/l; p=0.57 Wilcoxon test).
### Table 1 Characteristics of the study population

|                        | Hypertensive N = 50 | Normotensive N = 79 | P value |
|------------------------|---------------------|---------------------|---------|
| Male gender            | 28 (56.00)          | 54 (68.35)          | .16     |
| Diabetes               | 16 (32.00)          | 6 (7.59)            | .0003   |
| CT extent of pulmonary lesions* |                     |                     |         |
| Absent or minor lesions (<10%) | 10 (20.00)       | 10 (13.16)          | .30     |
| Mild to Moderate (10%-50%) | 27 (54)               | 42 (55.26)          | .89     |
| Severe (>50%)          | 10 (20.00)          | 23 (30.26)          | .20     |
| Never smoker           | 31 (62.00)          | 64 (81.01)          | .02     |
| Current smoker         | 2 (4.00)            | 3 (3.80)            | .95     |
| Former smoker          | 17 (34.00)          | 12 (15.19)          | .01     |
| Asthma                 | 3 (6.00)            | 9 (11.39)           | .30     |
| Antihypertensive treatment |                     |                     |         |
| ACE inhibitor          | 20 (40.00)          | 0                   | <.0001  |
| Angiotensin receptor blocker | 17 (34.00)       | 0                   | <.0001  |
| Calcium channel blocker | 13 (26.00)          | 0                   | <.0001  |
| Beta blocker           | 12 (24.00)          | 2 (2.53)            | <.0001  |
| Diuretic               | 15 (30.00)          | 0                   | <.0001  |
| Age                    | 66.80 ± 9.37        | 54.84 ± 12.54       | <.0001  |
| Body mass index (kg/m2) | 28.68 ± 5.32        | 28.45 ± 5.62        | .63     |
| Oxygen saturation      | 94.54 ± 6.49        | 94.59 ± 4.86        | .61     |
| Natremia (mmol/l)      | 136.30 ± 3.79       | 136.39 ± 3.15       | .68     |
| Estimated Glomerular filtration rate (ml/min) | 73.00 ± 24.46        | 93.22 ± 14.57       | <.0001  |
| CRP (mg/l)             | 79.96 ± 66.48       | 66.65 ± 67.15       | .13     |
| Leukocytes (G/l)       | 6.58 ± 2.51         | 5.97 ± 2.51         | .14     |
| Platelets (G/l)        | 200.98 ± 59.23      | 215.00 ± 82.72      | .73     |
| Neutrophils (G/l)      | 4.91 ± 2.32         | 4.34 ± 2.27         | .18     |
| Lymphocytes (G/l)      | 1.01 ± 0.36         | 1.12 ± 0.50         | .54     |
| Platelet to lymphocyte ratio | 221.69 ± 100.96      | 223.18 ± 145.88     | .50     |
| Neutrophil to lymphocyte ratio | 5.57 ± 3.65        | 4.47 ± 3.00         | .08     |
| Blood pressure (mm Hg) |                        |                     |         |
| Systolic BP at D1      | 131.92 ± 14.48      | 126.26 ± 12.18      | .02     |
| Diastolic BP at D1     | 72.92 ± 9.02        | 76.07 ± 8.78        | .05     |
| Mean BP at admission   | 92.59 ± 9.18        | 92.80 ± 9.02        | .90     |
| Pulse pressure at admission | 59.00 ± 13.39      | 50.18 ± 9.36        | <.0001  |
| Systolic BP at D2      | 129.64 ± 15.60      | 122.38 ± 13.37      | .006    |
| Diastolic BP at D2     | 72.21 ± 8.87        | 72.92 ± 8.43        | .65     |
| Mean BP at D2          | 91.36 ± 9.79        | 89.41 ± 9.24        | .26     |
| Pulse pressure at D2   | 57.43 ± 13.01       | 49.46 ± 9.84        | .0001   |
| Systolic BP at D3      | 130.95 ± 15.24      | 122.36 ± 14.31      | .002    |
| Diastolic BP at D3     | 71.40 ± 9.17        | 72.79 ± 9.17        | .41     |
| Mean BP at D3          | 91.25 ± 9.55        | 89.31 ± 10.11       | .55     |
| Pulse pressure at D3   | 59.55 ± 14.08       | 49.57 ± 9.98        | <.0001  |
| Hospital outcome‡      | 18 (36.00)          | 21 (26.58)          | .26     |
| Death                  | 4 (8.16)            | 2 (2.56)            | .15     |
| Admission to intensive care unit | 16 (32.00)      | 21 (26.58)          | .51     |

*CT scan was not performed in 3 patients‡.
‡Hospital outcome: Death or admission to intensive care percentage in parentheses.
outcome after adjustment for age, gender, diabetes body mass index, asthma, and the severity of pneumonia in hypertensive patients, whereas no relation was observed in normotensives. In hypertensive patients, the adjusted risk of primary outcome increased as CRP increased (relative risk 2.52; 95% confidence intervals (1.03-6.17); p=0.04). To illustrate this finding, we showed the relative risk according to CRP level in hypertensive patients without severe lung lesions on CT scan and with severe lung lesions (figure 2).

### DISCUSSION

Arterial hypertension represented one of the most common comorbidities in patients with COVID-19. However, the impact of hypertension on outcome and particularly on mortality in COVID-19 patients is not clear. The current study can help clarify this issue. The main findings of this study were the interactions between inflammatory markers and hypertension status at admission, and the effect on both the blood pressure within 3 days and the hospital mortality.

### TABLE 2  Correlation (Spearman's test) between inflammatory markers and blood pressure in the population as a whole, then in normotensive patients and in hypertensive patients on its own

|          | SBP D1 | SBP D2 | SBP D3 | DBP D1 | DBP D2 | DBP D3 | PP D1 | PP D2 | PP D3 | MBP D1 | MBP D2 | MBP D3 |
|----------|--------|--------|--------|--------|--------|--------|-------|-------|-------|--------|--------|--------|
| All patients |       |        |        |        |        |        |       |       |       |        |        |        |
| PLR      | 0.054  | 0.138  | 0.098  | -0.006 | 0.029  | 0.084  | 0.104 | 0.172 | 0.087 | -0.011 | 0.071  | 0.102  |
| p        | 0.553  | 0.135  | 0.295  | 0.946  | 0.753  | 0.367  | 0.258 | 0.061 | 0.35  | 0.904  | 0.446  | 0.237  |
| n        | 121    | 119    | 117    | 121    | 119    | 117    | 121   | 119   | 117   | 121    | 119    | 117    |
| NLR      | 0.116  | 0.251  | 0.21   | 0.047  | 0.094  | 0.168  | 0.108 | 0.261 | 0.178 | 0.074  | 0.181  | 0.212  |
| p        | 0.205  | 0.006  | 0.022  | 0.608  | 0.308  | 0.669  | 0.235 | 0.004 | 0.054 | 0.418  | 0.049  | 0.022  |
| n        | 122    | 120    | 118    | 122    | 120    | 118    | 122   | 120   | 118   | 122    | 120    | 118    |
| CRP      | 0.152  | 0.199  | 0.28   | -0.038 | 0.073  | 0.106  | 0.205 | 0.238 | 0.283 | 0.032  | 0.12   | 0.2    |
| p        | 0.086  | 0.025  | 0.002  | 0.669  | 0.416  | 0.24   | 0.02  | 0.007 | 0.001 | 0.723  | 0.181  | 0.026  |
| n        | 128    | 126    | 124    | 128    | 126    | 124    | 128   | 126   | 124   | 128    | 126    | 124    |

### Note:
- r correlation coefficient (Spearman's test), p: p value; n: size of the sample analyzed. CRP: C-reactive protein; PLR: plasma to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MBP: mean blood pressure
- D1: day 1; D2 day 2; D3: day 3
- P < .01 are in bold characters
outcome. A high level of inflammation predicted blood pressure within 3 days after admission in normotensive patients, but not in patients with hypertension, whereas a high level of inflammation predicted the prognosis in hypertensive patients but not in normotensive patients. The impact of inflammation on aortic stiffness and blood pressure has been widely established. It has been shown that endothelial function via the production of nitric oxide regulates aortic stiffness, a major determinant of blood pressure.15 Furthermore, an observational population-based study has linked innate immunity and aortic stiffness.16 A randomized trial also reported that an acute immune response against a pathogen increases aortic stiffness, a major determinant of systolic blood pressure.17 In addition, similar findings to our data were reported in a population-based study indicating that blood CRP level predicts the augmentation index, which is closely related to microvascular resistance and consequently, with mean blood pressure.18 From a mechanistic point of view, it has been demonstrated that this relationship between blood pressure and CRP is not mediated by atherosclerosis.19 Several mechanisms by which inflammation and the immune system control blood pressure have been identified.20–23 Therefore, in the context of COVID-19, our observation of a strong and positive association between the level of various inflammatory markers at the time of hospital admission and blood pressure within 3 days in normotensive patients is in keeping with this body of evidence. It is important to note that these relationships were absent in patients with hypertension, in whom blood pressure appeared to be unresponsive to inflammatory tone. The mechanism of this interaction between hypertension status, inflammatory tone, and blood pressure cannot be elucidated in the context of this observational study. It is worth mentioning, however, that such an interaction has already been observed in animal models,24 and it has been shown that spontaneously hypertensive rats have an attenuated inflammatory response to bacterial lipopolysaccharide. It can be hypothesized that hypertension-induced endothelial dysfunction plays a role in the blunted effect of inflammation on blood pressure and ultimately on the prognosis of hypertensive patients with COVID-19. Interestingly, it has already been suggested that pre-existing endothelial dysfunction in patients with hypertension, diabetes, and obesity or aging, combined with vascular damage induced by SARS-CoV-2 could contribute to severe morbidity and mortality.27 Indeed, evidence shows that SARS-CoV-2 has induced endothelial dysfunction or damage. Hence, it has been shown that endothelial involvement is associated with microvascular thrombi and prothrombotic state in patients with COVID-19.28–30 Also, in a series of infected patients with SARS-COV2, evidence has been reported of direct viral infection of the endothelial cell and diffuse endothelial inflammation.31 Then, in patients who died from COVID-19-associated or influenza-associated respiratory failure, the histologic
A pattern consisting of severe endothelial injury was associated with the presence of intracellular virus and disrupted cell membrane. The current study revealed that a high level of infection-induced inflammation at the time of admission predicts a poor prognosis in patients with hypertension. Patients with chronic hypertension usually need higher mean blood pressure levels than normotensive patients to achieve and maintain adequate perfusion pressure to the vital organs. Therefore, mean blood pressure goals for these patients may need to be adapted in the context of shock. In a prospective study, it was noted that a high target for mean arterial pressure was associated with improved microcirculation in septic shock patients with previous hypertension. Moreover, the effect of such interaction between hypertension status and blood pressure on the prognosis in septic shock has been observed in humans: In a randomized, stratified, open-label trial in patients with septic shock aimed at determining the optimal BP target according to hypertension status, the authors showed that among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than those in the low-target group. Therefore, the lack of increase in BP in response to acute inflammation observed here in patients with previous hypertension may help to explain the prognosis of hypertensive patients with COVID-19.

4.1 Limitations and strengths of the study

A limitation of the study was due to limited availability of biomarkers of inflammation because of the retrospective design of the study. These biomarkers are needed to explore the interaction between inflammatory tone and hypertension status on blood pressure and outcomes. Certainly, it would be of interest to analyze the impact of inflammation on blood pressure using biomarkers such as soluble CD14, von Willebrand factor, and interleukin-6 to disentangle the biological pathway responsible for the interaction. Importantly, we analyzed all patients admitted to our hospital for infection with SARS-CoV-2 during the period March 2020-April 2020, except patients admitted directly to an intensive care unit, so there is no selection bias. Furthermore, all data required for analyzing the interaction between CRP and hypertension status on blood pressure and the prognosis were rigorously obtained in the context of patients hospitalized for SARS-CoV-2 infection. Thus, the study results were based on high-quality data.

5 CONCLUSION

This study provides evidence of interactions between inflammatory tone and hypertension status at the time of hospital admission of patients with COVID-19 that affect both blood pressure and patient outcome. These findings provide insights into the prognosis of hypertensive patients with COVID-19. Also, these results have the potential to serve physicians by providing new information about inflammation influences on blood pressure regulation according to hypertension status.

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CONFLICT OF INTEREST

None.

AUTHOR'S CONTRIBUTION

Jacques Amar conceived the study, analyzed the data, and drafted the first version of the paper. Nicolas Touron conceived the study and collected the data. Antoine Ciron collected the data and was involved in writing the manuscript. Caroline Pendaries conceived the study, collected the data, and was involved in writing the manuscript.
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