COVID-19

Impact of Arterial Stiffness on All-Cause Mortality in Patients Hospitalized With COVID-19 in Spain

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ABSTRACT: Older age and cardiovascular comorbidities are well-known risk factors for all-cause mortality in patients with coronavirus disease 2019 (COVID-19). Hypertension and age are the 2 principal determinants of arterial stiffness (AS). This study aimed to estimate AS in patients with COVID-19 requiring hospitalization and analyze its association with all-cause in-hospital mortality. This observational, retrospective, multicenter cohort study analyzed 12,170 patients admitted to 150 Spanish centers included in the SEMI-COVID-19 Network. We compared AS, defined as pulse pressure ≥60 mm Hg, and clinical characteristics between survivors and nonsurvivors. Mean age was 67.5 (±16.1) years and 42.5% were women. Overall, 2606 (21.4%) subjects died. Admission systolic blood pressure (BP) <120 and ≥140 mm Hg was a predictor of higher all-cause mortality (23.5% and 22.8%, respectively, \( P < 0.001 \)), compared with systolic BP between 120 and 140 mm Hg (18.6%). The 4379 patients with AS (36.0%) were older and had higher systolic and lower diastolic BP. Multivariate analysis showed that AS and systolic BP <120 mm Hg significantly and independently predicted all-cause in-hospital mortality (adjusted odds ratio [ORadj]: 1.27, \( P = 0.0001 \); ORadj: 1.48, \( P = 0.0001 \), respectively) after adjusting for sex (males, ORadj: 1.6, \( P = 0.0001 \)), age tertiles (second and third tertiles, ORadj: 2.0 and 4.7, \( P = 0.0001 \)), Charlson Comorbidity Index (second and third tertiles, ORadj: 4.8 and 8.6, \( P = 0.0001 \)), heart failure, and previous and in-hospital antihypertensive treatment. Our data show that AS and admission systolic BP <120 mm Hg had independent prognostic value for all-cause mortality in patients with COVID-19 requiring hospitalization. (*Hypertension. 2021;77:856–867. DOI: 10.1161/HYPERTENSIONAHA.120.16563.*)

Key Words: arterial stiffness | blood pressure | COVID-19 | heart failure | hypertension | pulse pressure

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has emerged as a worldwide pandemic of unexpected severity. Initial symptoms usually affect the respiratory system and include fever, cough, and hypoxia. However, there is growing evidence that COVID-19 is actually a classic multisystem disease with a plethora of different signs and symptoms, among which cardiovascular manifestations predominate.¹

Of the epidemiological connections between COVID-19 and the arterial system, 3 are the most notable. First, hypertension invariably ranks in first place among baseline comorbidities in patients with COVID-19.² Second, although data are scarce and controversial,³ hypertension seems to represent an independent and significant determinant of all-cause mortality in patients hospitalized with COVID-19.⁴ Third, age is indisputably the risk factor most strongly associated with worse outcomes in patients with COVID-19.⁵ Long before the COVID-19 pandemic began, arterial stiffness (AS) was a concept that unified the long-term impact of these 2 components on the cardiovascular system: hypertension and aging. It

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was originally interpreted as a marker of changes in the aortic wall and was thought to reflect underlying arteriosclerosis on multiple levels. Obesity, diabetes, smoking, and especially subclinical inflammation have been linked to pathological AS, but the 2 main determinants of AS are blood pressure (BP) and age, leading to the assertion that AS should be recognized as the best marker of vascular aging. Current guidelines for the management of hypertension include AS among the many tools for assessing hypertension-mediated organ damage because it has shown independent prognostic value beyond the commonly used risk tables.

Carotid-femoral pulse wave velocity by applanation tonometry is the gold standard for measuring large-artery stiffness. Although several techniques have been developed in recent years to estimate AS on a population scale, daily use of pulse wave velocity measurement requires training and time and is, therefore, not recommended for routine practice. A practical, simple, and proven alternative approach to estimate the burden of AS in large populations is the calculation of pulse pressure (PP; systolic BP−diastolic BP). Values above 60 mm Hg have been shown to correlate significantly with AS, especially in older people, and its use as marker of AS is widely endorsed in the literature.

We hypothesize that AS would be pathologically increased in patients with COVID-19 because they share the 2 principal risk factors: old age and hypertension. The objective of this study is to estimate AS by calculating the PP of patients with COVID-19 requiring hospital admission and analyze its association with all-cause mortality. The secondary objective is to characterize patients with AS who are included in the Spanish Society of Internal Medicine (SEMI)-COVID-19 Network database.

**MATERIAL AND METHODS**

**Study Design and Population**

Our study is based on the SEMI-COVID-19 Registry, an ongoing multicenter, nationwide, observational cohort database in which 150 hospitals in all 17 regions of Spain participate. Further information on the registry and its data collection methods can be found in the source article. The data that support the findings of this study are available from the corresponding author upon reasonable request. Inclusion criteria for the registry were age ≥18 years and first admission to a hospital in Spain with diagnosis of COVID-19 confirmed microbiologically by reverse transcription polymerase chain reaction testing of a nasopharyngeal sample, following the recommendations of the World Health Organization. The exclusion criteria were declining to participate, withdrawal of informed consent, or subsequent admissions of the same patient. Patients were admitted and treated according to the clinical judgment of the attending physicians, following local protocols and the recommendations of the Spanish Ministry of Health. Personal data management strictly complied with Spanish Law 14/2007, of July 3, on Biomedical Research and Regulation (EU) 2016/679 of the European Parliament and with the Council of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. The SEMI-COVID-19 Registry has been approved by the Provincial Research Ethics Committee of Malaga (Spain), following the recommendation of the Spanish Agency of Medicines and Medical Products (AEMPS, for its initials in Spanish). All the patients gave informed consent. From March 1 to June 24, 2020, when the last patient was included in this substudy, 13,121 consecutive patients aged between 18 and 106 years were recruited.

**Nonstandard Abbreviation and Acronyms**

| Nonstandard Abbreviation | Acronym          | Description                              |
|--------------------------|------------------|------------------------------------------|
| ACE                      | angiotensin-converting enzyme |
| ARB                      | angiotensin receptor blocker   |
| AS                       | arterial stiffness     |
| BP                       | blood pressure        |
| COVID-19                 | coronavirus disease 2019 |
| PP                       | pulse pressure        |
| SBP                      | systolic BP           |

**Novelty and Significance**

**What Is New?**

- Arterial stiffness, estimated as admission pulse pressure ≥60 mm Hg, was associated with higher risk for all-cause mortality in patients hospitalized with coronavirus disease 2019 (COVID-19).

**What Is Relevant?**

- This association was independent of other comorbidities, gender, age, and the presence of hypertension or antihypertensive treatment.

**Summary**

Elevated pulse pressure and blood pressure values <120 mm Hg at admission contribute independently to the high all-cause mortality in patients with COVID-19.
Procedures
At least one physician from the internal medicine department in each hospital is voluntarily in charge of collecting and entering patients’ data from their medical record in an online electronic data capture system developed by the Spanish Society of Internal Medicine (SEMI, for its initials in Spanish). A database manager (Dr Ramos Rincón) centrally verifies procedures and incoming data from all hospitals. An independent external agency together with the study’s scientific steering committee is responsible for database monitoring. Dissociated patient identifiable data are pseudo-anonymized to avoid direct identifiers. All information is fully encrypted through a valid Transport Layer Security certificate and hosted on a secure server.

The database includes almost 300 variables under the following headings: (1) inclusion criteria; (2) epidemiological data; (3) reverse transcription polymerase chain reaction and serology data; (4) personal medical and medication history, including antihypertensive treatment, categorized as ACEIs, ARBs, or others; (5) symptoms and physical examination findings at admission; (6) laboratory (blood gases, metabolic panel, complete blood count, coagulation) and diagnostic imaging tests; (7) additional data at seven days after admission or at admission to the intensive care unit; (8) pharmacological treatment during the hospitalization and ventilator support; (9) complications during the hospitalization; and (10) progress after discharge and 30 days from diagnosis. The age-adjusted Charlson Comorbidity Index was calculated from the data collected. A complete list of variables can be found in the source article. The primary end point was all-cause in-hospital mortality versus hospital discharge. The time of follow-up was defined as the period from admission to discharge or death. Mortality is expressed as the case fatality rate.

Statistical Analysis
Continuous variables were tested for normal distribution using Kolmogorov-Smirnov test. Results are shown as means (SD) or medians (25th–75th percentile) for continuous variables and absolute values (%) for categorical variables.

To compare baseline demographic and clinical characteristics among the different groups, we used ANOVA or the Kruskal–Wallis test for continuous variables. Differences in proportion were analyzed using the chi² test. Systolic BP (SBP) was divided into 3 categories: SBP <120 mm Hg, SBP ≥120 and simultaneously SBP <140 mm Hg, and SBP ≥140 mm Hg. The middle range group will be noted as 120 ≤SBP <140. Hypertension was categorized as absent or present, and the latter was further subcategorized into 3 groups based on treatment received: (1) no ACEIs/ARBs, (2) ACEIs, and (3) ARBs. AS was defined as present when PP (systolic minus diastolic BP) was ≥60 mm Hg. The association between AS and death was analyzed using Kaplan-Meier survival curves; the log-rank test was calculated from baseline to time of death according to the presence or absence of AS. We used a logistic regression to evaluate the relationship between significant variables found on the univariate analysis and all-cause mortality; variables with P<0.1 on the univariate analysis were included. All statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). A 2-tailed P<0.05 was considered statistically significant.

RESULTS
Demographic Characteristics of the Study Population
A total of 13,121 records were collected in the SEMI-COVID-19 Registry at June 24, 2020, of which 951 were excluded due to missing information on certain key variables. A total of 12,170 (92.8%) subjects were included in this substudy, as can be seen in the patient flowchart in Figure 1. Table 1 includes the baseline demographic and clinical features of all participants and according to the presence or absence of AS. The mean age of the total group was 67.5±16.1 years and 42.5% were women. The vast majority of patients were White (90.0%), followed by patients of Latin American origin (8.2%). The data presented only include patients who were hospitalized and either discharged or died: 72.7% were discharged home,
5.9% continued their recovery in health care institutions outside the hospitals, and 21.4% died. This proportion of deaths is consistent with official data from the Spanish Ministry of Health as of May 29, 2020 (20 534 deaths among 99 808 hospitalized patients, 20.6%). The most prevalent terminal complications of patients with COVID-19 with fatal outcome was adult respiratory distress syndrome (76.8%), followed at a considerable distance by acute renal failure (36.0%), multorgan failure (26.6%), secondary bacterial pneumonia (22.1%), sepsis (20.1%), shock (15.9%), heart failure (HF; 14.7%), and cardiac arrhythmia (9.3%). Disseminated intravascular (3.4%), myocarditis (2.5%), acute coronary disease (2.3%), pulmonary embolism (1.9%), and stroke (1.7%) were also present but far more rare.

As shown in Table 1, hypertension was the most frequent comorbidity (50.9%) in patients with COVID-19, followed by diabetes (19.1%), atrial fibrillation (11.1%), coronary heart disease (7.9%), stroke (7.7%), heart failure (HF; 7.1%), chronic obstructive pulmonary disease (COPD; 7.0%), chronic kidney disease (CKD; 6.0%), and peripheral arterial disease (4.7%). After sorting the population by presence or absence of AS, the data show that age, SBP and the Charlson Comorbidity Index score were markedly higher and diastolic BP lower in the former group compared with the latter. All the comorbidities analyzed were, without exception, far more frequent in patients with AS. We found small albeit significant differences in certain laboratory parameters.

Outcomes
Kaplan-Meier survival curves (Figure 2) according to presence or absence of AS confirm increased all-cause mortality in subjects with AS compared with those without AS (log-rank P<0.001). A noteworthy finding is that...
the difference in survival can be detected from the very beginning, and the rate shows a tendency to converge at the end of the observation period.

Given the marked differences in SBP according to the presence/absence of AS, we focused on the association between all-cause in-hospital mortality, SBP, and AS. A graphical representation of the findings can be seen in Figure 3. The lowest mortality rate was found in patients with SBP between 120 and 140 mm Hg while worse outcomes significantly increased when SBP was below 120 or exceeded 140 mm Hg (black columns), resembling a J-curve phenomenon. No significant differences were found between the group of patients with SBP <120 and SBP ≥140 mm Hg. When dividing each SBP category into 2 groups according to PP <60 mm Hg (horizontally striped bars) or PP ≥60 mm Hg (diagonally striped bars), it is observed that patients with AS constantly presented with a significantly higher all-cause mortality than those with PP <60 mm Hg across all 3 BP categories. In other words, within each BP group PP ≥60 mm Hg was always associated with higher mortality than PP <60 mm Hg.

All-Cause in-Hospital Mortality According to Selected Variables

Table 2 analyzes the baseline differences between survivors and nonsurvivors. It shows that nonsurvivors were older; predominantly male; more fragile; and with a higher proportion of previous chronic diseases, especially hypertension but also AS. Paradoxically, no significant difference was detected in SBP, but diastolic BP was decreased and PP increased in nonsurvivors. Again, significant differences in selected laboratory variables were observed, especially in glycemia, but they were small differences and likely of little clinical relevance.

Subsequently, we performed a multivariate stepwise logistic regression analysis using all covariates with a significant (P<0.1) association with all-cause mortality as dependent variables (Table 3). The 2 main factors independently predicting death were the Charlson Comorbidity Index score and age. Male sex and HF were significant determinants; atrial fibrillation and CKD had a borderline significance (P=0.057 and P=0.070, respectively); and diabetes, COPD, and peripheral arterial disease were not significant and thus were not included in the multivariate equation. In terms of BP-related variables, treatment of preexisting hypertension continued to be an independently significant risk factor and ACEIs and ARBs as in-hospital antihypertensive treatment remained variables with a beneficial predictive value. Likewise, presence of AS and BP below 120 mm Hg, as compared with BP between 120 and 140 mm Hg, represented significant deleterious risk factors. Interestingly, BP >140 mm Hg was found to be a protective factor, in contrast to what was found on the univariate analysis. We performed 2 further sensitivity analyses. First, we defined BP either as below or above 120 mm Hg. In this case, AS (odds ratio,
1.16 [CI, 1.03–1.31], \( P = 0.01 \) and BP <120 (odds ratio, 1.54 [CI, 1.36–1.75], \( P = 0.001 \)) continued to be significant independent predictors of poor outcomes. Second, removing AS from the equation, BP <120 continued to be as a risk factor (odds ratio, 1.36 [CI, 1.21–1.54], \( P = 0.001 \)) and BP >140 ceased to have any protective effect (odds ratio, 0.92 [CI, 0.81–1.03], \( P = 0.16 \)). In other words, SBP >140 was protective only when simultaneously adjusting for PP. BP values below 120 mm Hg were a consistent predictor of worse outcomes whereas BP values >140 mm Hg were only significant depending on the presence of AS.

**DISCUSSION**

To the best of our knowledge, this retrospective, multi-center cohort study represents one of the largest analysis of hospitalized, treated, and discharged patients with COVID-19 worldwide. We analyzed data on 12,170 patients with COVID-19 in 150 hospitals across Spain, obtaining a representative sample of the pandemic in our country. The most salient conclusion that can be drawn from our analysis is that pathological AS, estimated as PP ≥60 mm Hg at admission, can be interpreted as a deleterious risk factor with predictive value for all-cause in-hospital mortality in patients with COVID-19. This risk factor acts in addition to parameters that have been previously well-established as risk factors, such as age, fragility, sex, hypertension, and HF. \(^4\) It should be underscored that previous and in-hospital antihypertensive treatments were equally and simultaneously accounted for in this analysis and did not alter the conclusions; the former would seem to indicate that preexisting hypertension does act together with AS as an independent risk factor and the latter suggesting that treatment with either ACEIs/ARBs during the hospital stay improves outcomes by significantly decreasing all-cause mortality.

Data concerning admission BP in patients with COVID-19 are very scarce and are included, at best, as minor pieces of data in larger predictive scores. Two recent studies found an association between worse outcomes and low BP\(^{16,17}\) and 2 others found an association between worse outcomes and high BP\(^{18,19}\). However, none focused on the capital importance of BP per se. Furthermore, to date, this is the first study linking the severity of the COVID-19 pandemic to a marker of AS, namely PP ≥60 mm Hg. The limited availability of pulse wave velocity measurement capabilities in specialized
centers and the acuteness of COVID-19 cases during admission might explain why associations between AS and COVID-19 are lacking in the literature. Nonetheless, there is a plethora of evidence supporting the use of increased PP as a suitable surrogate marker of AS from before the COVID-19 pandemic and prospective works that include measuring pulse wave velocity in patients with COVID-19 have recently been launched.

The starting point of our analysis was the observation that the relationship between all-cause in-hospital mortality and SBP in our patients with COVID-19 resembled a J-curve phenomenon. Optimal BP targets in hypertension are a controversial matter, with some studies favoring the principle of the lower the better, while others support the existence of a J-curve in regards to BP and outcomes. In fact, the optimal range of admission BP observed in our study endorses the latest recommendations found in recent guidelines: a BP between 120 and 140 mm Hg. Our analytical approach analyzed 3 BP categories (BP <120; 120 ≤ BP <140, and BP ≥140 mm Hg) and a PP threshold of ≥60 mm Hg. SBP <120 and ≥140 mm Hg reflected worse outcomes when compared with 120 ≤ SBP <140 mm Hg. Adjusting each group according to the presence of AS revealed that higher PP was robustly associated with increased mortality across all 3 SBP groups. Due to the fact that patients with SBP ≥140 and PP <60 mm Hg, who presented the lowest mortality rate of all patients, were numerically more frequent than those with AS, SBP ≥140 was found to be a protective factor on the multivariate analysis. In other words, higher SBP values were markers of increased risk only when PP ≥60 mm Hg. This observation is not surprising and physiologically understandable, given the fact that PP

| Variable                         | Total study population (N=12 170) | Nonsurvivors (N=2606) | Survivors (N=9564) | P value |
|----------------------------------|----------------------------------|-----------------------|--------------------|---------|
| Anthropomorphic measures         |                                  |                       |                    |         |
| Age, y                           | 67.5±16.1                        | 79.7±10.5             | 64.1±15.7          | 0.0001  |
| Women, %                         | 42.5                             | 37.8                  | 44.8               | 0.0001  |
| Height, cm                       | 165.3±9.5                        | 163.5±9.7             | 165.6±9.5          | 0.0061  |
| Weight, kg                       | 78.5±16.5                        | 78.3±17.4             | 78.6±16.2          | NS      |
| Obesity (BMI >30 kg/m²), %       | 21.3                             | 22.9                  | 20.9               | 0.0443  |
| Blood pressure and selected laboratory values |                                  |                       |                    |         |
| Systolic BP, mm Hg               | 129±21.0                         | 128±23.4              | 129±20.3           | NS      |
| Diastolic BP, mm Hg              | 74±12.8                          | 70±13.6               | 75±12.4            | 0.0001  |
| Heart rate, bpm                  | 88±17.3                          | 89±18.9               | 88±16.9            | NS      |
| Pulse pressure, mm Hg            | 55±19.8                          | 59±19.7               | 54±17.2            | 0.0001  |
| Glycemia, mg/dL*                 | 112 (98–136)                     | 128 (108–165)         | 109 (97–129)       | 0.0001  |
| Creatinine, mg/dL*               | 0.8 (0.68–1.05)                  | 1.1 (0.80–1.80)       | 0.80 (0.67–0.97)   | 0.0001  |
| Sodium, mg/dL                    | 137±54.8                         | 138±56.6              | 137±4.1            | 0.0062  |
| Potassium, mg/dL                 | 4.1±0.8                          | 4.3±0.69              | 4.1±0.52           | 0.0015  |
| Triglycerides, mg/dL*            | 121 (94–158)                     | 121 (93–163)          | 121 (94–157)       | NS      |
| Comorbidities                    |                                  |                       |                    |         |
| Hypertension, %                  | 50.9                             | 70.7                  | 45.5               | 0.0001  |
| Diabetes, %                      | 19.1                             | 28.2                  | 16.6               | 0.0001  |
| COPD, %                          | 7.0                              | 12.6                  | 5.5                | 0.0001  |
| CKD, %                           | 6.0                              | 12.5                  | 4.2                | 0.0001  |
| Coronary heart disease, %        | 7.9                              | 14.0                  | 6.3                | 0.0001  |
| Heart failure, %                 | 7.1                              | 15.4                  | 4.9                | 0.0001  |
| Stroke, %                        | 7.7                              | 14.1                  | 6.0                | 0.0001  |
| Atrial fibrillation, %           | 11.1                             | 21.6                  | 8.3                | 0.0001  |
| Peripheral vascular disease, %   | 4.7                              | 9.0                   | 3.5                | 0.0001  |
| Arterial stiffness, %            | 36.0                             | 43.7                  | 33.9               | 0.0001  |
| Charlson Comorbidity Index       | 3.6±2.7                          | 5.7±2.4               | 3.1±2.5            | 0.0001  |

Values are average (SD). BMI indicates body mass index; BP, blood pressure; CKD, chronic kidney disease; and COPD, chronic obstructive pulmonary disease.

*Values are median (interquartile range).
includes SBP as part of its definition. The extent that the predictive value of PP exceeds that of BP alone is a long-standing unresolved controversy.26–28

Several mechanisms may account for the role of AS in the COVID-19 pandemic. Older age has been invariably shown as the principal risk factor in the COVID-19. Aging is a process characterized by quantitative and qualitative alterations of the immune system, with an increase in proinflammatory and a decrease in anti-inflammatory cytokines resulting in a state of chronic, low-grade inflammation often referred to as immunosenescence.29 Furthermore, the COVID-19-related cytokine storm has been hypothesized to be the consequence of aging, leading to the coining of the term inflame-aging.30

On the contrary, although there is no unanimous consensus on the causal association between systemic inflammation and cardiovascular events,31 several studies have fueled interest in vasculature properties and inflammatory molecules as surrogate markers of cardiovascular risk, with contradictory results.32–35 Hypertension is the strongest modifiable risk factor for cardiovascular disease worldwide, and low-grade inflammatory components have repeatedly been identified in the pathophysiology of hypertension.36,37 The characteristic features of hypertension include premature changes in vascular function and structure that can be demonstrated earlier and are more severe than those predicted as part of the normal aging process, leading to the so-called early

| Table 3. Association of Selected Variables With All-Cause In-Hospital Mortality as Dependent Variable |
| Variable | Univariate analysis | Multivariate analysis |
|----------|-------------------|---------------------|
|          | OR (95% CI) | P value | ORadj (95% CI) | P value |
| Age, tertiles |          |          |          |          |
| <60.9 | 1 | 1 | |
| ≥60.9 and <76.3 | 5.3 (4.38–6.30) | 0.0001 | 2.0 (1.56–2.44) | 0.0001 |
| ≥76.3 | 20.5 (17.18–24.38) | 0.0001 | 4.7 (3.77–5.97) | 0.0001 |
| Blood pressure treatment |          |          |          |          |
| Normotensive subjects | 1 | 1 | |
| Other than ACEIs/ARBs | 3.5 (3.11–3.97) | 0.0001 | 1.30 (1.13–1.50) | 0.0001 |
| ACEIs | 3.0 (2.63–3.36) | 0.0001 | 1.62 (1.38–1.90) | 0.0001 |
| ARBs | 2.3 (2.07–2.64) | 0.0001 | 1.21 (1.03–1.41) | 0.0182 |
| Charlson Comorbidity Index, tertiles |          |          |          |          |
| <2 | 1 | 1 | |
| ≥2 and <5 | 11.4 (9.51–13.70) | 0.0001 | 4.8 (3.82–6.02) | 0.0001 |
| ≥5 | 28.6 (23.75–34.50) | 0.0001 | 8.6 (6.72–10.90) | 0.0001 |
| Sex |          |          |          |          |
| Female | 1 | 1 | |
| Male | 1.3 (1.16–1.38) | 0.0001 | 1.6 (1.43–1.75) | 0.0001 |
| Arterial stiffness |          |          |          |          |
| No | 1 | 1 | |
| Yes | 1.5 (1.39–1.65) | 0.0001 | 1.27 (1.11–1.45) | 0.0001 |
| Use of ACE inhibitors |          |          |          |          |
| No | 1 | 1 | |
| Yes | 1.1 (0.94–1.25) | 0.30 | 0.56 (0.47–0.68) | 0.0001 |
| Use of ARBs |          |          |          |          |
| No | 1 | 1 | |
| Yes | 0.86 (0.75–1.00) | 0.050 | 0.56 (0.47–0.67) | 0.0001 |
| HF |          |          |          |          |
| No | 1 | 1 | |
| Yes | 3.6 (3.09–4.10) | 0.0001 | 1.24 (1.06–1.46) | 0.0091 |
| SBP at admission |          |          |          |          |
| ≥120 and <140 | 1 | 1 | |
| <120 | 1.34 (1.21–1.49) | 0.0001 | 1.48 (1.30–1.68) | 0.0001 |
| ≥140 | 1.29 (1.16–1.44) | 0.0001 | 0.82 (0.72–0.94) | 0.0041 |

Univariate analysis and adjusted multivariate logistic regression model. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HF, heart failure; OR, odds ratio; ORadj, adjusted OR; and SBP, systolic blood pressure.
vascular aging. What is more, AS has been claimed to precede incident hypertension and hypertension, A variety of mechanisms may be responsible for the association between age, inflammation, hypertension, and AS, but there is a growing body of evidence that adverse remodeling through proinflammatory signaling secondary to the angiotensin II signaling cascade with aging is of paramount importance.

The strengths of our study are the large number of participants, the use of a hard end point for analysis, and previous experience in handling databases by a scientific society. Nevertheless, its retrospective design, the high proportion of White participants, the unknown true spread of COVID-19 among outpatients, the strict inclusion of patients with COVID-19 requiring hospitalization, and the indirect estimation of AS mean that our results cannot be easily extrapolated to the general population.

**APPENDIX**

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