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Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China

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IMPORTANCE Data are lacking whether patients with hypertension who are taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) have increased severity or risk of mortality during hospitalization for coronavirus disease 2019 (COVID-19).

OBJECTIVE To investigate the association between ACEIs/ARBs and severity of illness and mortality in patients with hypertension hospitalized for COVID-19 infection.

DESIGN, SETTING, AND PARTICIPANTS Retrospective, single-center case series of the 1178 hospitalized patients with COVID-19 infections at the Central Hospital of Wuhan, China, from January 15 to March 15, 2020.

MAIN OUTCOMES AND MEASURES COVID-19 was confirmed by real-time reverse transcription polymerase chain reaction and epidemiologic, clinical, radiologic, laboratory, and drug therapy data were analyzed in all patients. The percentage of patients with hypertension taking ACEIs/ARBs was compared between those with severe vs nonsevere illness and between survivors vs nonsurvivors.

RESULTS Of the 1178 patients with COVID-19, the median age was 55.5 years (interquartile range, 38-67 years) and 545 (46.3%) were men. The overall in-hospital mortality was 11.0%. There were 362 patients with hypertension (30.7% of the total group; median age, 66.0 years [interquartile range, 59-73 years]; 189 [52.2%] were men), of whom 115 (31.8%) were taking ACEI/ARBs. The in-hospital mortality in the patients with hypertension was 21.3%. The percentage of patients with hypertension taking ACEIs/ARBs did not differ between those with severe and nonsevere infections (32.9% vs 30.7%; $P = .645$) nor did it differ between nonsurvivors and survivors (27.3% vs 33.0%; $P = .34$). Similar findings were observed when data were analyzed for patients taking ACEIs and those taking ARBs.

CONCLUSIONS AND RELEVANCE This study provides clinical data on the association between ACEIs/ARBs and outcomes in patients with hypertension hospitalized with COVID-19 infections, suggesting that ACEIs/ARBs are not associated with the severity or mortality of COVID-19 in such patients. These data support current guidelines and societal recommendations for treating hypertension during the COVID-19 pandemic.

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Supplemental content

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The epidemiology and clinical characterization of patients with coronavirus disease 2019 (COVID-19) has been reported.[1-3] As angiotensin-converting enzyme (ACE) 2 serves as the receptor for SARS-CoV-2 to gain entry into cells,[4] ACE2-expressing cells are susceptible to COVID-19 infection.[5] The use of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) is common treatment in cardiovascular disorders, including hypertension, and data regarding the association of these drugs with ACE2 levels are conflicting.[6,7] However, to our knowledge, there are no clinical data indicating whether patients with hypertension who are taking ACEIs/ARBs have increased severity of illness or risk of mortality during COVID-19 infection and whether these patients should continue to use ACEIs/ARBs or switch to other antihypertensive drugs.

Methods

Patients with COVID-19 admitted to the Central Hospital of Wuhan (Hubei Province, China) from January 15, 2020, to March 15, 2020, were included in this retrospective analysis. The study was approved by the institutional ethics board of the Central Hospital of Wuhan and the requirement for

informed consent was waived because of the retrospective nature of the study. Epidemiologic, clinical characterization, radiologic, laboratory, treatment, and clinical outcomes data were collected and analyzed.

Definitions

The severity of COVID-19 pneumonia was classified according to the diagnosis and treatment scheme for COVID-19 of Chinese (5th edition).[1] Severe illness was defined as blood oxygen saturation levels of 93% or less, respiratory frequency of 30/min or greater, a partial pressure of arterial oxygen to fraction of inspired oxygen ratio of less than 300, lung infiltrates more than 50% within 24 to 48 hours, septic shock, respiratory failure, and/or multiple organ dysfunction or failure. Nonsevere illness was defined as the absence of the previously described characteristics. Hypertension was defined as a history of diastolic blood pressure of 90 mm Hg or greater or a systolic blood pressure of 140 mm Hg or greater or history of antihypertensive medication use.[8] A patient's ACEI/ARB use was defined as use of these drugs at the time of admission that continued through hospitalization.

Statistical Analysis

Continuous and categorical variables were represented as median (interquartile range [IQR]) and numbers (%), respectively, with comparisons using the Mann-Whitney *U* test, *t* test, χ^2 test, or Fisher exact test. A 2-sided α of less than .05 was considered statistically significant. All the analyses were done using SPSS, version 20 (IBM).

Results

As of March 15, 2020, there were 1178 patients hospitalized with COVID-19. The median age was 55.5 years and 545 (46.3%) were men. There were 130 in-hospital deaths (mortality rate, 11.0%), of whom 84 (64.6%) were men. Among the 1178 patients, there were 362 patients with hypertension (30.7%). The characteristics and clinical outcomes of the patients with hypertension compared with those without hypertension are summarized in the eTable in the Supplement. Patients with hypertension were older and had greater prevalence of chronic diseases; they also had more severe manifestations of COVID-19, including higher rates of acute respiratory distress syndrome and greater in-hospital mortality (21.3% vs 6.5%; $P < .001$).

The 362 patients with hypertension were further analyzed and form the basis of this article. There were 189 men (52.2%), 259 (71.5%) were older than 60 years, and 115 (31.8%) were taking ACEIs/ARBs. In-hospital mortality was 21.3% (n = 77). The characteristics and clinical outcomes of these patients are summarized in **Table 1** with respect to treatment with ACEIs/ARBs. Aside from a greater prevalence of coronary artery disease in those taking ACEIs/ARBs, patients with and without ACEI/ARB treatment had similar comorbidities and, with the exception of higher alkaline phosphatase in those not taking ACEIs/ARBs, had similar laboratory profile results, including blood counts, inflammatory markers, renal and liver function tests, and cardiac biomarkers. The frequency of severity of illness, acute respiratory distress syndrome, and mortality did not differ with respect to ACEI/ARB therapy.

Key Points

Question Among patients with hypertension, do those taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) have greater illness severity or increased risk of mortality during hospitalization for coronavirus disease 2019 (COVID-19) infection?

Findings In this single-center case series involving 362 patients with hypertension hospitalized with COVID-19 infection, there was no difference in severity of the disease, complications, and risk of death in those who were taking ACEIs/ARBs compared with those not treated with these medications.

Meaning In this single-center study, ACEI/ARB was not associated with severity and outcomes of COVID-19 infection in hospitalized patients with hypertension. These results support current guidelines and societal recommendations for treating hypertension.

The characteristics of patients with severe vs nonsevere infections and survivors vs nonsurvivors are presented in **Table 2** along with antihypertensive treatments. The most commonly used antihypertensive drugs were calcium-channel blockers. The percentage of patients with hypertension taking any drug or drug combination did not differ between those with severe and nonsevere infections and nonsurvivors and survivors.

With respect to ACEI/ARB use, there was no difference between those with severe vs nonsevere illness in use of ACEIs (9.2% vs 10.1%; $P = .80$), ARBs (24.9% vs 21.2%; $P = .40$), or the composite of ACEIs/ARBs (32.9% vs 30.7%; $P = .65$). Similarly, there were no differences between nonsurvivors and survivors in use of ACEIs (9.1% vs 9.8%; $P = .85$), ARBs (19.5% vs 23.9%; $P = .42$), or the composite of ACEIs/ARBs (27.3% vs 33.0%; $P = .34$).

Because comorbidities may affect treatment options for hypertension, we analyzed the use of ACEIs/ARBs among patients with hypertension and various comorbid conditions, including coronary heart disease, cerebrovascular disease, diabetes, neurological disease, and chronic renal disease, with respect to disease progression and mortality (**Table 3**). In patients with each of these chronic conditions, the frequency of severe illness and death did not differ between those treated with and without ACEIs/ARBs.

Discussion

In this study, we report data demonstrating that there was no difference in the disease progression and risk of death during hospitalization for COVID-19 with respect to various antihypertensive drugs and in the use of ACEIs/ARBs between those with severe vs nonsevere illness and between nonsurvivors and survivors. Further, there was no difference in comorbidities associated with hypertension and the length of hospital stay in patients who were taking ACEIs/ARBs or non-ACEIs/ARBs.

Table 1. Characteristics of the ACEI/ARB Group Compared With the Non–ACEI/ARB Group in Patients With Hypertension

Characteristic	Patients with hypertension			
	No. (%)			
	Total (N = 362)	ACEI/ARB (n = 115)	Non-ACEI/ARB (n = 247)	*P* value
Age, median (IQR), y	66.0 (59.0-73.0)	65.0 (57.0-73.0)	67.0 (60.0-75.0)	.22
Distribution				
<40	9 (2.5)	2 (1.7)	7 (2.8)	.56
40-60	94 (26.0)	35 (30.4)	65 (26.3)	
>60	259 (71.5)	78 (67.8)	181 (73.3)	
Sex				
Women	173 (47.8)	47 (40.9)	126 (51.0)	.07
Men	189 (52.2)	68 (59.1)	121 (49.0)	
Chronic disease				
Cerebrovascular disease	68 (18.8)	27 (23.5)	41 (16.6)	.12
Coronary heart disease	62 (17.1)	27 (23.5)	35 (14.2)	.03
Heart failure	10 (2.8)	5 (4.3)	5 (2.0)	.36
Diabetes	127 (35.1)	42 (36.5)	85 (34.4)	.70
Digestive disorder	78 (21.5)	24 (20.9)	54 (21.9)	.83
Respiratory disease	18 (5.0)	8 (7.0)	10 (4.0)	.24
Neurological disease	38 (10.5)	13 (2.6)	25 (10.1)	.73
Solid tumor	11 (3.0)	2 (1.7)	9 (3.6)	.51
Chronic kidney disease	35 (9.7)	13 (11.3)	22 (8.9)	.47
Laboratory data, median (IQR)				
Leukocytes (3.5-9.5), 10^3/L	5.7 (4.5-7.3)	6.0 (4.3-7.4)	5.6 (4.5-7.3)	.93
Neutrophils (1.8-6.3), 10^3/L	3.8 (2.9-5.5)	4.0 (2.9-5.5)	3.8 (2.9-5.5)	.81
Lymphocytes (1.1-3.2), 10^3/L	1.0 (0.7-1.4)	1.0 (0.6-1.4)	1.0 (0.7-1.5)	.17
Platelets (125-350), 10^3/L	186.5 (143.0-246.3)	182.0 (137.0-250.0)	188.0 (146.0-245.0)	.77
Hemoglobin (13.0-17.5), g/dL	12.6 (11.3-13.8)	12.6 (11.4-13.8)	12.6 (11.3-13.8)	.78
Monocytes (0.1-0.6), 10^3/L	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.4 (0.3-0.5)	.08
Activated partial thromboplastin time (20-40), s	27.7 (24.6-32.0)	27.6 (23.8-31.7)	27.7 (24.7-32.1)	.02
Fibrinogen (200-400), mg/L	300.0 (250.0-360.0)	300.0 (240.0-360.0)	300.0 (250.0-360.0)	.30
Prothrombin time (9-13), s	11.5 (10.9-12.2)	11.4 (10.7-12.1)	11.6 (10.9-12.3)	.003
International normalized ratio (0.7-1.3)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	.003
D-dimer (0-1) µg/mL	0.7 (0.4-2.2)	0.7 (0.4-1.6)	0.7 (0.3-2.5)	.39
Albumin (4.0-5.5), g/dL	3.7 (3.3-4.0)	3.7 (3.4-4.1)	3.6 (3.3-4.0)	.22
Globulin (2.0-4.0), g/dL	2.7 (2.4-3.2)	2.7 (2.5-3.1)	2.8 (2.4-3.2)	.89
Albumin-to-globulin ratio (1.2-2.4)	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.3 (1.1-1.5)	.55
Aminotransferase, U/L				
Alanine (9-50)	22.7 (14.1-37.2)	21.8 (13.3-34.4)	22.8 (14.2-38.4)	.71
Aspartate (15-40)	24.9 (18.2-36.4)	24.7 (18.0-35.0)	25.1 (18.4-36.8)	.35
Total bilirubin (0.1-1.2), mg/dL	0.5 (0.4-0.8)	0.5 (0.4-0.9)	0.5 (0.4-0.8)	.44
Serum urea (4.8-23.2), mg/dL	14.3 (10.6-18.2)	14.8 (11.2-20.4)	14.3 (10.4-17.6)	.11
Serum creatinine (0.6-1.3), mg/dL	0.8 (0.6-1.0)	0.9 (0.6-1.2)	0.8 (0.6-1.0)	.18
Alkaline phosphatase (40-150), U/L	57.0 (44.0-71.0)	45.0 (0.0-63.0)	55.5 (44.0-71.0)	<.001
Creatine kinase (38-174), U/L	79.5 (45.0-147.7)	85.0 (50.0-152.0)	76.0 (43.0-140.0)	.40
Lactate dehydrogenase (80-285), U/L	195.5 (151.8-265.5)	200.0 (160.0-267.0)	193.0 (150.0-265.0)	.36
Myoglobin (14.3-105.5), µg/L	35.7 (18.5-83.9)	37.0 (20.6-111.4)	34.1 (18.3-78.3)	.13
Troponin (<0.03), ng/mL	0.008 (0.002-0.030)	0.007 (0.000-0.030)	0.008 (0.002-0.030)	.63
Procalcitonin (<0.04), ng/mL	0.06 (0.04-0.13)	0.06 (0.04-0.13)	0.06 (0.04-0.13)	.52
Interleukin 6 (<7), pg/mL	8.4 (3.8-26.9)	7.5 (3.3-22.2)	8.8 (4.1-30.8)	.06
C-reactive protein (0-0.5), mg/dL	2.5 (0.4-5.4)	2.1 (0.3-5.2)	2.6 (0.4-6.0)	.99
Acute respiratory distress syndrome	94 (26.0)	29 (25.2)	65 (26.3)	.82
Severe	173 (47.8)	57 (49.6)	116 (47.0)	.65
Nonsurvivor	77 (21.3)	21 (18.3)	56 (22.7)	.34
Hospital stays, median (IQR), d	19.0 (12.0-27.0)	19.0 (13.0-27.0)	19.0 (11.0-27.0)	.56

Abbreviations:
ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; IQR, interquartile range.

SI conversion units: to convert alanine to nmol/L, multiply by 112.2; for alkaline phosphate, aspartate, creatine kinase, and lactate dehydrogenase to µkat/L, multiply by 0.0167; to convert albumin and hemoglobin to g/L, multiply by 10; for leukocytes, lymphocytes, monocytes, and neutrophils to $\times 10^9$L, multiply by 0.001; for platelets to $\times 10^9$L, multiply by 1; for fibrinogen to g/L, multiply by 0.01; for C-reactive protein to mg/L, multiply by 10; for creatinine to µmol/L, multiply by 88.4; for D-dimer to nmol/L, multiply by 5.476; for bilirubin to µmol/L, multiply by 17.104; for myoglobulin to nmol/L, multiply by 0.05814; for troponin to µg/L, multiply by 1; for urea to mmol/L, multiply by 0.357.

Table 2. Characteristics and Clinical Outcomes of Patients With Hypertension and COVID-19

Characteristic	Patients with hypertension						
	No. (%)				Survivor, No. (%)		
	Total (N = 362)	Severe (n = 173)	Nonsevere (n = 189)	*P* value	Yes (n = 285)	No (n = 77)	*P* value
Age, median (IQR), y	66.0 (59.0-73.0)	69.0 (62.0-76.0)	64.0 (57.0-70.5)	<.001	65.0 (57.5-71.0)	72.0 (64.5-82.0)	<.001
Distribution							
<40	9 (2.5)	3 (1.7)	6 (3.2)	.03	9 (3.2)	0 (0)	.004
40-60	94 (26.0)	35 (20.2)	59 (31.2)		82 (28.8)	12 (15.6)	
>60	259 (71.5)	135 (78.0)	124 (65.6)		194 (68.1)	65 (84.4)	
Sex							
Women	173 (47.8)	76 (43.9)	97 (51.3)	.16	146 (51.2)	27 (35.1)	.01
Men	189 (52.2)	97 (56.1)	92 (48.7)		139 (48.2)	50 (64.9)	
Chronic disease							
Cerebrovascular disease	68 (18.8)	50 (28.9)	18 (9.5)	<.001	31 (10.9)	37 (48.1)	<.001
Coronary heart disease	62 (17.1)	39 (22.5)	23 (12.2)	.01	41 (14.4)	21 (27.3)	.01
Heart failure	10 (2.8)	8 (4.6)	2 (1.1)	.08	5 (1.8)	5 (6.5)	.06
Diabetes	127 (35.1)	76 (43.9)	51 (27.0)	.001	89 (31.2)	38 (49.4)	.003
Digestive disorder	78 (21.5)	41 (23.7)	37 (19.6)	.34	66 (23.2)	12 (15.6)	.15
Respiratory disease	18 (5.0)	8 (4.6)	10 (5.3)	.77	12 (4.2)	6 (7.8)	.32
Neurological disease	38 (10.5)	25 (14.5)	13 (6.9)	.02	25 (8.8)	13 (16.9)	.04
Solid tumor	11 (3.0)	8 (4.6)	3 (1.6)	.09	6 (2.1)	5 (6.5)	.11
Chronic renal disease	35 (9.7)	30 (17.3)	5 (2.6)	<.001	15 (5.3)	20 (26.0)	<.001
Antihypertensive drugs							
Treatment scheme							
CCBs	168 (46.4)	79 (45.7)	89 (47.1)	.79	130 (45.6)	38 (49.4)	.56
CCBs+ARBs	59 (16.3)	32 (18.5)	27 (14.3)	.28	48 (16.8)	11 (14.3)	.59
CCBs+ACEIs	23 (6.4)	13 (7.5)	10 (5.3)	.39	17 (6.0)	6 (7.8)	.75
ACEIs	12 (3.3)	3 (1.7)	9 (4.8)	.11	11 (3.9)	1 (1.3)	.45
ARBs	24 (6.6)	11 (6.4)	13 (6.9)	.84	20 (7.0)	4 (5.2)	.57
β receptor blockers	14 (3.9)	8 (4.6)	6 (3.2)	.48	8 (2.8)	6 (7.8)	.09
No drug treatment	65 (18.0)	29 (16.8)	36 (19.0)	.57	53 (18.6)	12 (15.6)	.54
Classification							
ACEIs (contains ACEIs)	35 (9.7)	16 (9.2)	19 (10.1)	.80	28 (9.8)	7 (9.1)	.85
ARBs (contains ARBS)	83 (22.9)	43 (24.9)	40 (21.2)	.40	68 (23.9)	15 (19.5)	.42
ACEIs/ARBs (contains either)[a]	115 (31.8)	57 (32.9)	58 (30.7)	.65	94 (33.0)	21 (27.3)	.34
ACEIs/ARBs vs Non-ACEIs/ARBs							
ACEIs/ARBs	115 (31.8)	57 (32.9)	58 (30.7)	.65	94 (33.0)	21 (27.3)	.34
Non-ACEIs/ARBs	247 (68.2)	116 (67.1)	131 (69.3)		191 (67.0)	56 (72.7)	
Hospital stay, median (IQR), d	19.0 (12.0-27.0)	20.0 (12.0-32.0)	19.0 (11.0-24.0)	.002	19.0 (13.0-26.0)	15.0 (6.0-30.0)	.73
Nonsurvivor	77 (21.3)	77 (44.5)	0 (0)	<.001	NA	NA	NA

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; IQR, interquartile range; NA, not applicable.

[a] Three patients used ACEI + ARB at the same time, so the total number of ACEIs/ARBs was 3 less than the sum of the 2 drugs.

The prevalence of hypertension in our patient cohort (30.7%) is similar to that reported in previously studies in which 15.0% to 31.2% of patients with COVID-19 infection had hypertension.[2,9-11] Our findings also confirm data in these prior reports that patients with hypertension have more severe illness and higher mortality rates than those without hypertension. However, these previous reports did not indicate how many patients were taking ACEIs or ARBs.[2,9-11] Based on previously reported data, it was legitimate to assume that an association may exist between ACEI or ARB therapy and disease severity or risk of death in patients with hypertension infected with COVID-19. Our data provide some reassurance that ACEIs/ARBs are not associated with the progression or outcome of COVID-19 hospitalizations in patients with hypertension.

Levels of ACE2 are a double-edged sword. On one hand, the increased expression of ACE2 may facilitate infection with COVID-19 and increase the risk of developing severe and fatal

Table 3. ACEI/ARB and Non–ACEI/ARB Therapy and Comorbid Conditions in Patients With Hypertension

Characteristic	No. (%)			*P* value
	Total	ACEI/ARB	Non-ACEI/ARB	
All patients, No.	362	115	247	
Severe	173 (47.8)	57 (49.6)	116 (47.0)	.65
Nonsurvivor	77 (21.3)	21 (18.3)	56 (22.7)	.34
Coronary artery disease, No.	62	27	35	
Severe	39 (62.9)	17 (63.0)	22 (62.9)	.99
Nonsurvivor	21 (33.9)	7 (25.9)	14 (40.0)	.31
Cerebrovascular disease, No.	68	27	41	
Severe	50 (73.5)	18 (66.7)	32 (78.0)	.30
Non-survivor	37 (54.4)	13 (48.1)	24 (58.5)	.40
Diabetes, No.	127	42	85	
Severe	76 (59.8)	23 (54.8)	53 (62.4)	.41
Nonsurvivor	38 (29.9)	9 (21.4)	29 (34.1)	.14
Neurologic disease, No.	38	13	25	
Severe	25 (65.8)	9 (69.2)	16 (64.0)	.75
Nonsurvivor	13 (34.2)	4 (30.8)	9 (36.0)	.75
Chronic kidney disease, No.	35	13	22	
Severe	30 (85.7)	12 (92.3)	18 (81.8)	.39
Nonsurvivor	20 (57.1)	7 (53.8)	13 (59.1)	.76

Abbreviations:
ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

COVID-19.[12] On the other hand, decreased expression of ACE2 can induce pulmonary edema and reduce lung function, which can be reversed by recombinant ACE2[13] or losartan[14]; therefore, increased expression of ACE2 appears to be protective against acute lung injury. Currently, almost all major societies recommend that patients with hypertension do not discontinue using ACEIs, ARBs, or other renin-angiotensin-aldosterone antagonists in this setting[15] except for clinical reasons rather than COVID-19. The clinical data in the current report supports these societal recommendations.

In this study, we found that patients with hypertension had more than 3 times the mortality rate of all other patients hospitalized with COVID-19. Hypertension combined with cardiovascular and cerebrovascular diseases, diabetes, and chronic kidney disease would predispose patients to an increased risk of severity and mortality of COVID-19. Therefore, patients with these underlying conditions who develop COVID-19 require particularly intensive surveillance and care.

Limitations

This study was limited by a small number of patients with hypertension taking ACEIs/ARBs who were hospitalized with COVID-19. The current findings may not be generalizable to all patients with hypertension, and it is possible that ACEIs/ARBs could affect the chance of hospitalization. This could not be evaluated in the current data set and warrants further research. In this cohort, a nonsevere disease course of COVID-19 was still severe enough to require hospitalization. In addition, it is not certain whether the ACEI/ARB treatment at baseline was maintained throughout the hospitalization for all patients. Finally, this is an observational treatment comparison and may be biased by differences in patients taking vs not taking ACEIs/ARBs at the time of hospitalization. However, the measured baseline characteristics were similar in both groups (Table 1), suggesting that these groups are reasonably comparable.

Conclusions

The current findings did not identify an association between treatment with ACEIs/ARBs and either severity or clinical outcomes of COVID-19 hospitalizations in patients with hypertension. These data support current guidelines and societal recommendations for treating hypertension during the COVID-19 pandemic.

ARTICLE INFORMATION

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Concept and design: Li, Deng.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Li, Wang, Chen, Deng.
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