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Influence of blood pressure control and application of renin-angiotensin-aldosterone system inhibitors on the outcomes in COVID-19 patients with hypertension

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Abstract

Hypertension is proved to be associated with severity and mortality in coronavirus disease 2019 (COVID-19). However, little is known about the effects of pre-admission and/or in-hospital antihypertension treatments on clinical outcomes. Thus, this study aimed to investigate the association between in-hospital blood pressure (BP) control and COVID-19–related outcomes and to compare the effects of different antihypertension treatments. This study included 2864 COVID-19 patients and 1628 were hypertensive. Patients were grouped according to their BP during hospitalization and records of medication application. Patients with higher BP showed worse cardiac and renal functions and clinical outcomes. After adjustment, subjects with pre-admission usage of renin-angiotensin-aldosterone system (RAAS) inhibitors (HR = 0.35, 95%CI 0.14-0.86, $P = .022$) had a lower risk of adverse clinical outcomes, including death, acute respiratory distress syndrome, respiratory failure, septic shock, mechanical ventilation, and intensive care unit admission. Particularly, hypertension patients receiving RAAS inhibitor treatment either before (HR = 0.35, 95%CI 0.13-0.97, $P = .043$) or after (HR = 0.18, 95%CI 0.04-0.86, $P = .031$) admission showed a significantly lower risk of adverse clinical outcomes than those receiving application of other antihypertensive medicines. Furthermore, consecutive application of RAAS inhibitors in COVID-19 patients with hypertension showed better clinical outcomes (HR = 0.10, 95%CI 0.01-0.83, $P = .033$) than non-RAAS inhibitors users. We revealed that COVID-19 patients with poor BP control during hospitalization had worse clinical outcomes. Compared with other antihypertension medicines, RAAS inhibitors were beneficial for improving clinical outcomes in COVID-19 patients with hypertension. Our findings provide direct evidence to support the administration of RAAS inhibitors to COVID-19 patients with hypertension before and after admission.

Jie Yang and Renzheng Chen equally contribute to this work

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a current pandemic infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has presented an unprecedented challenge for the healthcare community across the globe. Until now, over 13 million people are infected by SARS-CoV-2 with considerable mortality, and the number is continuously rising. This pandemic of SARS-CoV-2 is considered as a long-term public health events around the worldwide.

The clinical and epidemiological characteristics of COVID-19 have been reported in previous studies.[1,2] Hypertension has been verified to be associated with increased risk of infection and adverse clinical outcomes in patients with COVID-19.[3,4] Previous studies have stressed the importance of blood pressure control, but little information showed an association between poorly controlled blood pressure during hospitalization and outcomes in COVID-19 patients. Furthermore, some patients with hypertension were treated with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), which increase the expression of angiotensin-converting enzyme 2 (ACE2) receptor in cardiovascular and respiratory systems,[5] a known cellular receptor and a necessary binding site for SARS-CoV-2 infection.[6] Although recent studies pointed out that in-hospital application of RAAS inhibitors do not show significant difference in mortality and other adverse clinical outcomes,[7] very limited information presented that clinical outcomes are associated with pre-admission and/or in-hospital application of RAAS inhibitors compared with other antihypertensive medicines.

Therefore, this study aimed to investigate the association between in-hospital blood pressure control and COVID-19–related outcomes and to compare the effects of different antihypertension treatments. We hypothesized that pre-admission, in-hospital and consecutive application of RAAS inhibitors treatment might influence the clinical outcomes of COVID-19 patients.

2 | METHODS

2.1 | Study design and participants

This single-center retrospective cohort study was performed at Huo Shen Shan Hospital, which is dedicated solely to the treatment COVID-19 in Wuhan, China. It was urgently constructed for the diagnosis and management of COVID-19 patients. In total, 2864 adult patients (≥18 years old) were consecutively admitted from February 4, 2020, to April 11, 2020, in Wuhan without any selectivity. Patients were diagnosed with COVID-19 according to WHO interim guidance.[8] Thirty-six subjects were excluded due to missing examination data. Subsequently, we included 2828 patients and divided them into four groups according to the blood pressure grade after admission. In addition, 28 patients without clear medication records were excluded for further analysis. Hence, 2800 patients including were classified according to the use of RAAS inhibitors (ACEI and ARBs) use before and after admission. Among the 2800 patients, 386 hypertension patients had clear records of continuous antihypertensive medication applications (Supplement figure). This study was approved by the Human Ethics Committee of Huo Shen Shan Hospital (No. HSSLL023) and conformed to the ethical guidelines of the Declaration of Helsinki. Oral consent was obtained from all patients at the time of enrollment due to the rapid emergence of COVID-19.

2.2 | Data collection

All the data were collected from electronic and traditional clinical medical records, including demographic information, signs, comorbidities, nursing records, laboratory tests, chest computed tomography (CT) images, treatments, and outcomes. The time of illness onset was defined as the day when the symptom was initially reported. Diagnoses of septic shock, respiratory failure, acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission, mechanical ventilation, and death were recorded. Hospital length of stay, the time from the illness onset to normothermia, inflammatory resorption from CT images, viral shedding, and adverse clinical events occurred were calculated. All the data were carefully checked by two physicians and the third researcher, who adjudicated any differences in the interpretation between the two physicians.

2.3 | Definitions

Abnormalities in laboratory findings were based on the hospital's criteria. Hypertension was graded according to the 2018 Chinese Guidelines for Prevention and Treatment of Hypertension[9] and 2018 ESC/ESH Guidelines for the management of arterial hypertension.[10] ARDS was defined according to the Berlin Definition.[11] Septic shock was defined according to the World Health Organization interim guideline for the clinical management of severe acute respiratory infection. Acute kidney injury was identified on the basis of serum creatinine level over the upper limit of 26.5 μmol/L.[12] Cardiac injury occurred when the circulating level of cardiac biomarkers (eg, high-sensitivity assay for troponin I) were above the 99th percentile of the upper reference limit. Liver injury was diagnosed if the level of alanine aminotransferase (ALT) was above the upper limit of the reference range and coagulopathy was defined as a 3-second and 5-second extension of the prothrombin time (PT) and activated partial thromboplastin time, respectively.[13]

2.4 | Clinical outcomes

The clinical end points were death, ARDS, respiratory failure and septic shock during hospitalization, mechanical ventilation, ICU admission, as well as clinical cure and discharges. The discharge criteria included absence of fever for ≥ 3 days; obvious pulmonary inflammatory resorption in chest CT, clinical remission of

respiratory symptoms, and two negative results for SARS-CoV-2 RNA at least 24 h apart.[13] The clinical outcomes were monitored for 75 days and 64 days after the initial symptom onset among different groups.

2.5 | Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]) and categorical variables are expressed as n (%). Mann-Whitney U test, Kruskal-Wallis H test, Pearson χ^2 test, Fisher's exact test, and Mantel-Haenszel χ^2 test were employed to compare the differences as appropriate. Binary logistic regression models were used to identify the risk factors. Cox proportional hazard regression analysis was used to investigate the association between the application of RAAS inhibitors and adverse clinical events. Variables that were considered clinically relevant or showed a univariate relationship with the outcomes ($P < .10$) were included in the multivariate regression model. To ensure parsimony of the final model, variables for inclusion were carefully chosen according to the number of events available. Odds ratio (OR) or hazard ratio (HR) was employed to determine relations between risk factors and outcomes, and $P < .05$ was considered statistically significant. Statistical analyses were performed using the SPSS software version 26 (IBM Corp).

3 | RESULTS

In this retrospective study, we included 2828 COVID-19 confirmed patients hospitalized in Wuhan Huo Shen Shan Hospital from February 4 to April 11, 2020. Overall, 1442 (51.0%) patients were male, and the median age was 60.0 years (IQR 50.0-68.0). Of these patients, 152 (5.4%) were current smokers and 98 (3.5%) were alcoholics. 867 (30.7%) patients with a history of hypertension and diabetes (414 [14.6%]) were the most common comorbidities (Table 1). COVID-19 patients showed elevated peripheral blood high-sensitivity C-reactive protein (hs-CRP) at 2.3 mg/L (IQR 0.8-8.5). Almost all patients underwent chest CT scanning in the early phase of infection. 2435 (86.2%) patients exhibited ground-glass opacity. Moreover, 2517 (89.0%) patients were treated with traditional Chinese medicines and 1219 (87.6%) of hypertensive patients during hospitalization with the application of traditional Chinese medicines (Table 2, Supplement Table S1).

In this study, 2745 (97.1%) patients were successfully recovered and discharged, 20 (0.71%) were still remain in the hospital. The median hospital length of stay was 13.0 days (IQR 8.0-19.0), the median time from illness onset to normothermia was 27.0 days (IQR 10.3-28.8), the median time from illness onset to inflammatory resorption was 33.0 days (IQR 23.0-44.0), and the median time from illness onset to viral shedding was 34.0 days (IQR 25.0-44.0). However, 105 (3.7%) patients were admitted to the ICU, and the median time from illness onset to ICU admission was 20.0 days (IQR 10.3-28.8). Moreover, 63 (2.2%) patients died during hospitalization, and the median time from illness onset to death was 26.5 days (IQR 16.8-40.0) (Table 1).

The patients were classified into four groups based on the blood pressure grade after admission. 1391 patients were hypertensive according to blood pressure control during hospitalization. Thus, 1628 patients with hypertension were involved, including 867 patients with history of hypertension and 761 patients diagnosed newly after admission. Older age patients had higher blood pressure grade. Furthermore, patients with higher blood pressure grade in line with higher rate of history of hypertension and had the tendency to suffer comorbidities of diabetes, coronary heart disease, and chronic kidney diseases (Table 1).

In addition, patients with higher blood pressure grade exhibited higher leukocyte and neutrophil counts but lower lymphocyte count. Particularly, patients with increased blood pressure grade showed higher hs-CRP and procalcitonin levels, which suggested a higher inflammatory response. Levels of urea nitrogen, creatinine, and cystatin C increased with blood pressure grade elevated, indicating a worse kidney function in hypertension patients. Nearly all the biomarkers of cardiomyocyte damage were elevated in grades 2 and 3 groups, indicating that patients with higher blood pressure were more likely to suffer cardiac injury after SARS-CoV-2 infection. Patients in grade 3 group had the highest B-type natriuretic peptide and demonstrated a worse cardiac function. Besides, patients with higher blood pressure also had lower concentration of potassium (Table 2, Supplement Table S1).

Moreover, we found a significant linear relationship between the blood pressure and the incidence of mortality (P for trend $< .001$), septic shock (P for trend $< .001$), respiratory failure (P for trend $< .001$), ARDS (P for trend $< .001$), mechanical ventilation (P for trend $< .001$), and ICU admission (P for trend $< .001$) (Figure 1). Interestingly, the proportion of patients who developed adverse clinical events was higher in grade 2 and grade 3 groups than in normotensive and grade 1 group. Furthermore, the length of time from symptoms onset to normothermia, inflammatory resorption, and viral shedding increased with blood pressure grade elevated (Table 1).

In the multivariable regression analysis, age (OR 1.02, 95% confidence interval [95% CI]: 1.00-1.04, $P = .025$), cardiac injury (OR 3.09, 95% CI: 1.69-5.64, $P < .001$), acute kidney injury (OR: 3.24, 95% CI: 1.21-8.63, $P = .019$), neutrophil (OR 1.27, 95% CI: 1.18-1.37, $P < .001$), lymphocyte (OR 0.24, 95% CI: 0.15-0.40, $P < .001$), hs-CRP (OR 1.01, 95% CI: 1.00-1.01, $P = .024$), chronic obstructive pulmonary disease (OR 3.25, 95% CI: 1.48-7.13, $P = .003$), and blood pressure ≥ grade 2 (OR 3.03, 95% CI: 1.83-5.03, $P < .001$) were independently associated with the incidence of adverse clinical events (Figure 2, Supplement Table S2).

To investigate the effect of RAAS inhibitors on clinical outcomes, we analyzed the total patients (n = 2880) with clear medication records. 1601 of them were hypertension patients. These patients were classified into two groups according to pre-admission or in-hospital application of RAAS inhibitors application. As shown in Figure 3A, after adjustment, the incidence of adverse clinical

TABLE 1 Baseline characteristics and clinical outcomes of COVID-19 patients with different blood pressure grade

	Total (n = 2828)	Normotension (n = 1437)	Hypertension			P value
			Grade 1 (n = 967)	Grade 2 (n = 333)	Grade 3 (n = 91)	
Demographics						
Age, years	60.0 (50.0-68.0)	56.0 (45.0-65.0)	63.0 (53.0-70.0)	66.0 (57.0-73.0)	64.0 (54.0-72.0)	<.001
Males, n (%)	1442 (51.0%)	698 (48.6%)	502 (51.9%)	194 (58.3%)	48 (52.7%)	.013
Current smoker, n (%)	152 (5.4%)	70 (4.9%)	49 (5.1%)	31 (9.3%)	2 (2.2%)	.010
Current drinker, n (%)	98 (3.5%)	49 (3.4%)	30 (3.1%)	15 (4.5%)	4 (4.4%)	.554
History of hypertension, n (%)	867 (30.7%)	237 (16.5%)	362 (37.4%)	204 (61.3%)	64 (70.3%)	<.001
Comorbidities						
Diabetes, n (%)	414 (14.6%)	150 (10.4%)	167 (17.3%)	74 (22.2%)	23 (25.3%)	<.001
Arrhythmia, n (%)	87 (3.1%)	33 (2.3%)	35 (3.6%)	17 (5.1%)	2 (2.2%)	.034
Malignant neoplasm, n (%)	56 (2.0%)	27 (1.9%)	22 (2.3%)	4 (1.2%)	3 (3.3%)	.579
Hyperlipemia, n (%)	44 (2.0%)	16 (1.1%)	21 (2.2%)	6 (1.8%)	1 (1.1%)	.194
Coronary heart disease, n (%)	181 (6.4%)	72 (5.0%)	65 (6.7%)	37 (11.1%)	7 (7.7%)	.001
Chronic obstructive pulmonary disease, n (%)	96 (3.4%)	45 (3.1%)	33 (3.4%)	14 (4.2%)	4 (4.4%)	.602
Chronic liver disease, n (%)	72 (2.5%)	39 (2.7%)	24 (2.5%)	6 (1.8%)	3 (3.3%)	.728
Chronic kidney disease, n (%)	36 (1.3%)	13 (0.9%)	9 (0.9%)	10 (3.0%)	4 (4.4%)	.002
Outcomes						
Death, n (%)	63 (2.2%)	14 (1.0%)	17 (1.8%)	23 (6.9%)	9 (9.9%)	<.001
Septic shock, n (%)	32 (1.1%)	8 (0.6%)	8 (0.8%)	12 (3.6%)	4 (4.4%)	<.001
Respiratory failure, n (%)	88 (3.1%)	18 (1.3%)	30 (3.1%)	31 (9.3%)	9 (9.9%)	<.001
ARDS, n (%)	99 (3.5%)	22 (1.5%)	32 (3.3%)	35 (10.5%)	10 (11.0%)	<.001
Mechanical ventilation, n (%)	88 (3.1%)	18 (1.3%)	30 (3.1%)	31 (9.3%)	9 (9.9%)	<.001
ICU admission, n (%)	104 (3.7%)	22 (1.5%)	33 (3.4%)	40 (12.0%)	9 (9.9%)	<.001
Hospital length of stay, days	13.0 (8.0-19.0)	13.0 (8.0-19.0)	12.0 (8.0-19.0)	13.0 (9.0-21.0)	11.0 (7.0-17.0)	.066
Time to death, days	26.5 (16.8-40.0)	26.0 (19.5-34.3)	21.0 (12.5-35.9)	33.5 (21.8-48.5)	26.0 (16.5-49.0)	.178
Time to septic shock, days	27.5 (22.3-34.8)	26.0 (15.3-33.0)	21.5 (8.3-39.5)	33.0 (25.3-39.0)	28.0 (24.5-33.0)	.343
Time to respiratory failure, days	18.0 (10.0-29.3)	18.0 (11.0-27.0)	17.5 (12.3-36.3)	21.5 (10.0-31.5)	16.0 (9.0-25.0)	.874
Time to ARDS, days	19.0 (10.3-27.8)	18.0 (6.0-25.0)	17.0 (10.0-29.0)	22.5 (10.8-30.3)	15.5 (11.0-26.0)	.642
Time to mechanical ventilation, days	20.0 (11.0-28.0)	19.0 (11.5-27.3)	14.0 (9.0-24.8)	26.0 (15.8-31.5)	14.0 (9.0-23.5)	.039
Time to ICU admission, days	20.0 (10.3-28.8)	21.0 (14.0-26.5)	18.0 (8.0-30.0)	23.5 (13.3-32.0)	15.0 (7.8-24.5)	.354
Time to normothermia, days	27.0 (18.0-38.0)	24.0 (17.0-34.5)	30.0 (20.0-45.0)	32.0 (20.0-45.0)	32.0 (20.0-45.0)	<.001
Time to inflammatory resorption, days	33.0 (23.0-44.0)	32.0 (22.0-42.0)	35.0 (23.0-46.8)	37.0 (25.0-46.0)	36.0 (11.5-49.3)	<.001
Time to viral shedding, days	34.0 (25.0-44.0)	33.0 (24.0-43.0)	36.0 (25.0-46.0)	36.0 (27.0-45.0)	39.0 (26.5-46.8)	<.001

Note: Data were expressed as n (%) and median (IQR).

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; IQR, interquartile range; P value, Kruskal-Wallis H test; Time, time from illness onset to clinical outcomes.

TABLE 2 Laboratory examination in COVID-19 patients with different blood pressure grade

	Total (n = 2828)	Normotension (n = 1437)	Hypertension			*P* value
			Grade 1 (n = 967)	Grade 2 (n = 333)	Grade 3 (n = 91)	
Blood routine test						
Leukocyte, $\times 10^9$/L	5.7 (4.7-7.0)	5.6 (4.6-6.9)	5.8 (4.8-7)	6.0 (5.0-7.6)	6.3 (5.1-7.9)	<.001
Neutrophil, $\times 10^9$/L	3.5 (2.7-4.6)	3.4 (2.6-4.0)	3.5 (2.8-4.6)	3.8 (3.0-5.2)	3.9 (2.8-5.1)	<.001
Lymphocyte, $\times 10^9$/L	1.5 (1.1-1.9)	1.5 (1.2-1.9)	1.5 (1.1-1.9)	1.5 (1.0-1.8)	1.5 (1.1-1.8)	.009
Inflammatory biomarkers						
Hs-CRP, mg/L	2.3 (0.8-8.5)	1.8 (0.7-6.6)	2.4 (0.9-8.0)	3.9 (1.3-21.9)	3.1 (1.4-10.9)	<.001
Procalcitonin, ng/mL	0.1 (0.0-0.1)	0.0 (0.0-0.1)	0.1 (0.0-0.1)	0.1 (0.0-0.2)	0.1 (0.0-0.2)	.006
Liver function						
ALT, IU/L	23.2 (14.7-38.2)	24.0 (14.7-39.7)	22.3 (14.5-37.4)	22.7 (15.4-37.4)	20.0 (12.8-32.8)	.038
Albumin	37.7 (34.8-40.3)	37.8 (35.0-40.2)	37.8 (34.9-40.5)	36.8 (33.3-40.0)	37.9 (34.2-40.8)	.016
Liver injury, n (%)	436 (15.6%)	238 (16.8%)	145 (15.2%)	45 (13.6%)	8 (9.1%)	.144
Renal function						
Urea nitrogen, mmol/L	4.4 (3.6-5.5)	4.3 (3.6-5.2)	4.5 (3.6-5.5)	4.7 (3.7-6.0)	4.9 (4.0-6.0)	<.001
Creatinine, μmol/L	64.2 (54.8-75.4)	63.9 (55.0-74.6)	63.7 (54.5-75.2)	67.6 (56.4-82.7)	61.2 (53.8-74.5)	.001
Acute kidney injury, n (%)	51 (1.8%)	16 (1.1%)	15 (1.6%)	18 (5.4%)	2 (2.3%)	<.001
Cardiac biomarkers						
Creatine kinase-MB, IU/L	8.5 (6.8-10.9)	8.2 (6.7-10.2)	8.6 (7.0-11.1)	9.4 (7.0-12.5)	9.1 (7.1-11.8)	<.001
Hs-cTnI, ng/mL	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.0 (0.01-0.01)	0.01 (0.01-0.02)	0.01 (0.01-0.02)	<.001
Myocardial injury, n (%)	170 (6.1%)	62 (4.4%)	62 (6.6%)	39 (11.9%)	7 (7.9%)	<.001
Cardiac function						
BNP, pg/mL	0.0 (0.0-33.3)	0.0 (0.0-23.2)	0.0 (0.0-39.1)	15.0 (0.0-62.2)	23.0 (0.0-56.0)	<.001
Coagulation profiles						
PT, s	12.8 (12.3-13.6)	12.8 (12.3-13.6)	12.9 (12.2-13.6)	12.8 (12.2-13.8)	12.8 (12.2-13.9)	.956
APTT, s	28.0 (26.2-30.1)	28.1 (26.3-30.2)	28.0 (26.1-30)	27.7 (26.0-30.1)	28.0 (26.0-30.1)	.468
Coagulation disorder	44 (1.8%)	19 (1.6%)	14 (1.7%)	9 (3.0%)	2 (2.7%)	.297
Electrolyte						
Potassium, mmol/L	4.3 (4.0-4.5)	4.3 (4.0-4.6)	4.2 (3.9-4.5)	4.3 (3.9-4.6)	4.1 (3.9-4.4)	.009

Note: Data were expressed as n (%) and median (IQR).

Abbreviations: ALT, alanine aminotransferase; APTT, Activated partial thromboplastin time; BNP, brain natriuretic peptide; Hs-CRP, high-sensitivity C-reactive protein; Hs-cTnI, high-sensitivity assay for troponin I; IQR, interquartile range; *P* value, Kruskal-Wallis H test; PT, prothrombin time.

outcomes was significantly lower in patients with pre-admission application of RAAS inhibitors than those without (HR 0.35, 95% CI 0.14-0.86, $P = .022$) (Supplement Table S3). Besides, the results demonstrated that patients with persistent users of RAAS inhibitors had a lower incidence of progressing to adverse clinical outcomes than non-users (HR 0.11, 95% CI 0.02-0.88, $P = .037$) (Figure 3C, Supplement Table S3).

To compare the outcomes between RAAS inhibitors and other antihypertensive medications, including beta blockers, calcium antagonists, and diuretics (Supplement Table S7), we screened hypertension patients (n = 386) with definite records of antihypertensive medications. In these patients, the survival rate of adverse clinical outcomes was significantly higher in patients treated with RAAS inhibitors treatment either before (HR 0.35, 95% CI 0.13-0.97, $P = .043$) or after (HR 0.18, 95% CI 0.04-0.86, $P = .031$) admission than in treated with other antihypertensive medications (Figure 3D-E, Supplement Table S4). In addition, we found hypertension patients with persistent RAAS inhibitors treatment showed better clinical outcomes (HR 0.10, 95% CI 0.01-0.83, $P = .033$) (Figure 3F, Supplement Table S4).

4 | DISCUSSION

In this retrospective study, we analyzed the medical records of 2828 COVID-19 inpatients, of which 1628 were hypertensive. We demonstrated the following observations: (a) Hypertension was common among patients hospitalized with COVID-19, and subjects with

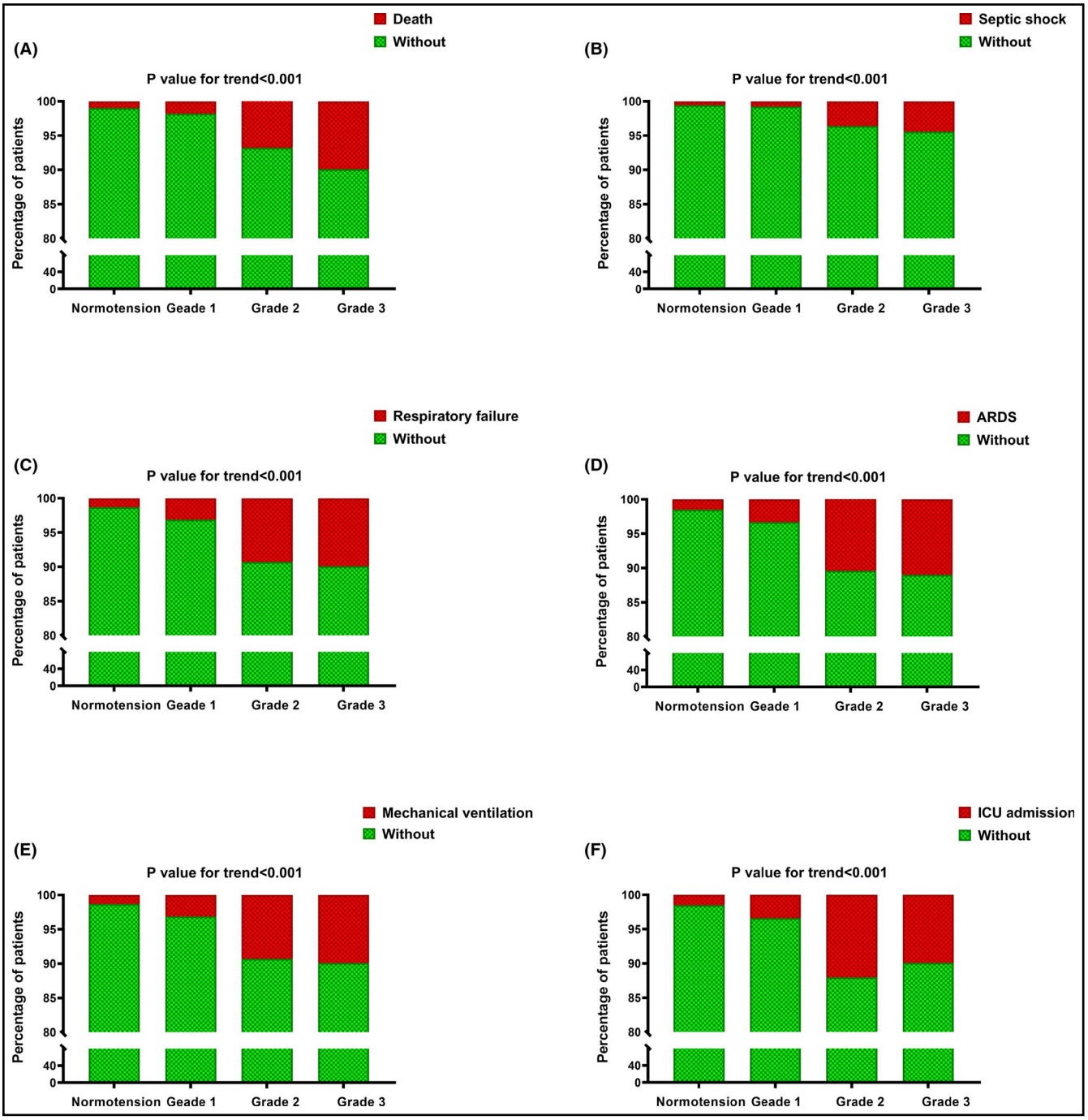

FIGURE 1 Adverse clinical outcomes in different grades of blood pressure. COVID-19 patients with higher grade of blood pressure showed worse clinical outcomes, including death (A), septic shock (B), respiratory failure (C), ARDS (D), mechanical ventilation (E), and ICU admission (F). ARDS, acute respiratory distress syndrome; ICU, intensive care unit

higher blood pressure grade showed worse cardiac, renal function, and clinical outcomes. (b) After adjustment for confounders, subjects with pre-admission application of RAAS inhibitors had a lower rate of suffering adverse clinical outcomes, including death, ARDS, respiratory failure, septic shock, mechanical ventilation, and ICU admission. (c) Of note, COVID-19 patients with hypertension receiving RAAS inhibitors treatment either before or after admission obtain better clinical outcomes than those receiving other antihypertensive medicines. 4) COVID-19 patients with hypertension with consecutive application of RAAS inhibitors showed better clinical outcomes than those with consecutive application of other antihypertension medicines. Our findings demonstrated that pre-admission application of RAAS inhibitors reduced the rate of adverse events. Particularly, COVID-19 patients with hypertension would benefit from pre-admission, in-hospital, or consecutive use of RAAS inhibitors. In this study, we provided the evidence to support that RAAS inhibitors treatment in COVID-19 patients with hypertension before admission should be continued during hospitalization.

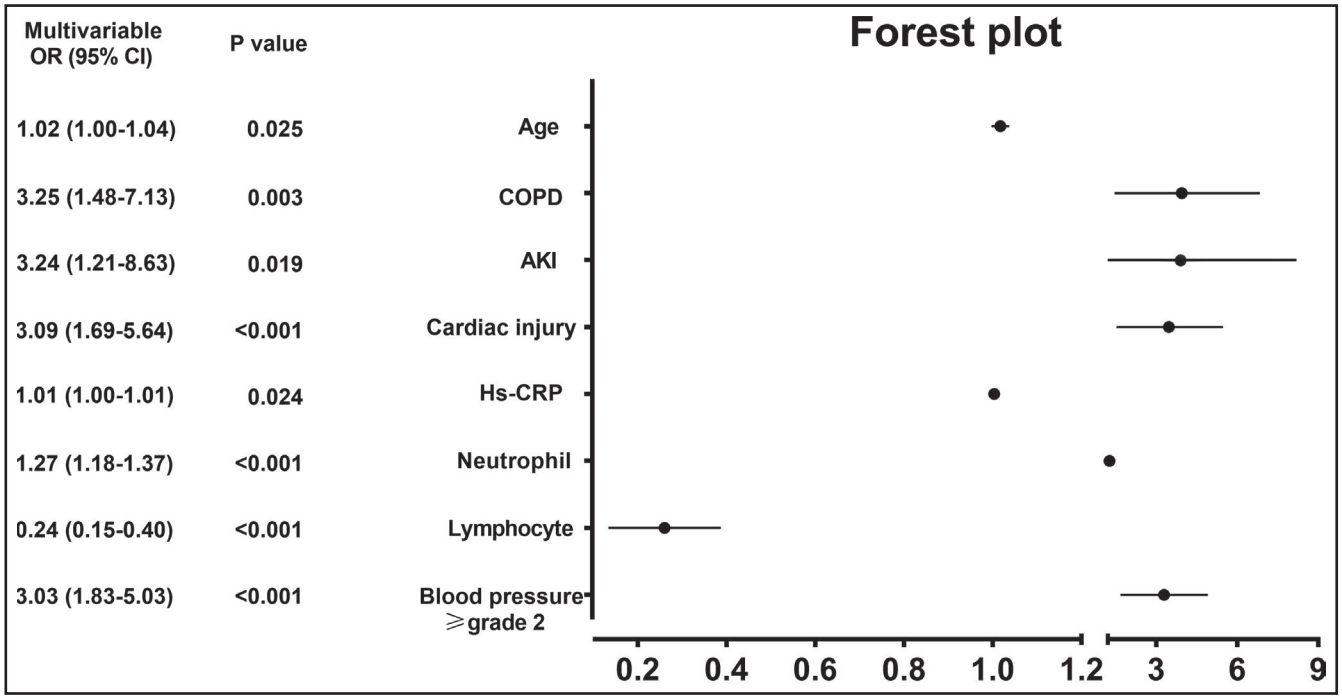

FIGURE 2 Risk factors for adverse clinical outcomes of COVID-19 patients in multivariate regression analysis. AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; Hs-CRP, hypersensitive C-reactive protein

Hypertension has been confirmed as a major comorbidity, which increased the risks of adverse outcomes in COVID-19 patients in recent clinical studies.[14] In line with these findings, we demonstrated that blood pressure up to grade 2 was an independent risk factor of adverse clinical outcomes after adjustment for confounders. Besides, we further revealed that COVID-19 patients with the higher blood pressure grade showed worse clinical outcomes (Figure 2). We considered that hypertension patients commonly co-existed with organ damage or dysfunction, such as the kidney and heart. COVID-19 infection further aggravated the primary disease and these comorbidities. In addition, patients with hypertension due to older age were more likely to be infected and progressed to severe and critical cases.[15] However, the underlying pathogenic mechanism linking hypertension and severity and prognosis of COVID-19 infection remains to be elucidated.

Until now, SARS-CoV-2 was known to invade host cells by binding to ACE2 localized on the membrane surface through spike protein of the virus.[16] The expression of ACE2 was substantially increased in patients with hypertension, who were treated with RAAS inhibitors, such as ACEI and ARB. As ACE2 facilitates the entry of coronaviruses into target cells, there have been hypotheses that preexisting use of RAAS inhibitors might increase the risk of suffering SARS-CoV-2 and application during infection might aggravate to adverse clinical outcomes.[17,18] However, three recent clinical studies from China and Italy reported that inpatient usage of ACEI/ARB was associated with lower risk of all-cause mortality than non-use of with ACEI/ARB among COVID-19 patients with hypertension.[19-21] Our results further revealed that patients who received RAAS inhibitors before admission had a lower rate of suffering adverse clinical outcomes. Hypertension patients receiving RAAS inhibitors, either before or after admission, had a decreased risk of progression to adverse clinical outcomes, including death, ARDS, respiratory failure, septic shock, mechanical ventilation, and ICU admission. However, a previous study also revealed that patients who previously used RAAS inhibitors may have a better prognosis.[22] These data above supported the recommendation of American College of Cardiology/American Heart Association (ACC/AHA) that patients should not discontinue or change their antihypertensive treatment, unless instructed by a physician.[23]

The underlying mechanism of whether patients with COVID-19 benefit from RAAS inhibitors was still unclear. A previous laboratory study found that ACE2 expression was downregulated after SARS-CoV infection, contributing to hyper-activated RAAS cascades, which facilitate neutrophil infiltration and exacerbated pulmonary inflammation.[24-26] However, soluble ACE2 has been shown to significantly block early stages of SARS-CoV-2 infections in vitro experiments.[27] In addition, transplantation of ACE2-mesenchymal stem cells improved the outcome of patients with COVID-19 patients.[28] The results above indicated that the upregulated ACE2 expression upregulated served as a protective role in SARS-CoV-2 infection, which might be attributed to organ-protective properties, but not on the vasoconstrictive, inflammatory, sodium retaining, and remodeling properties of Ang II. We considered that the physiological expression of ACE2 in the lungs or heart might have reached the saturation state for binding with spike protein on SARS-CoV-2, and the further upregulated expression of ACE2 by RAAS inhibitors would not promote the infection, but protected the lungs and heart. To further investigate the benefits of originated from the

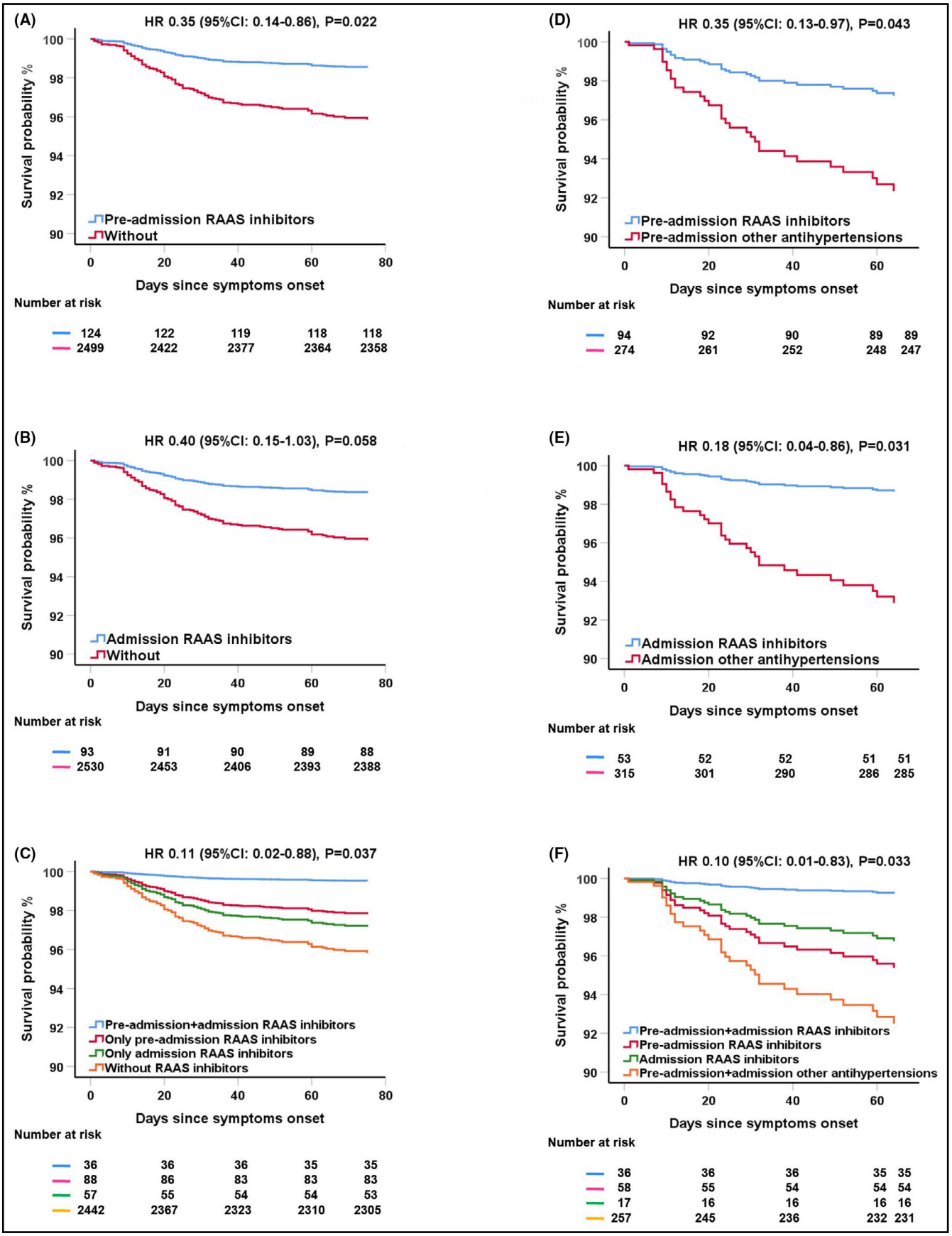
(A)
HR 0.35 (95%CI: 0.14-0.86), P=0.022
Survival probability %
Pre-admission RAAS inhibitors
Without
Days since symptoms onset
Number at risk
124 122 119 118 118
2499 2422 2377 2364 2358
(B)
HR 0.40 (95%CI: 0.15-1.03), P=0.058
Survival probability %
Admission RAAS inhibitors
Without
Days since symptoms onset
Number at risk
93 91 90 89 88
2530 2453 2406 2393 2388
(C)
HR 0.11 (95%CI: 0.02-0.88), P=0.037
Survival probability %
Pre-admission+admission RAAS inhibitors
Only pre-admission RAAS inhibitors
Only admission RAAS inhibitors
Without RAAS inhibitors
Days since symptoms onset
Number at risk
36 36 36 35 35
88 86 83 83 83
57 55 54 54 53
2442 2367 2323 2310 2305
(D)
HR 0.35 (95%CI: 0.13-0.97), P=0.043
Survival probability %
Pre-admission RAAS inhibitors
Pre-admission other antihypertensions
Days since symptoms onset
Number at risk
94 92 90 89 89
274 261 252 248 247
(E)
HR 0.18 (95%CI: 0.04-0.86), P=0.031
Survival probability %
Admission RAAS inhibitors
Admission other antihypertensions
Days since symptoms onset
Number at risk
53 52 52 51 51
315 301 290 286 285
(F)
HR 0.10 (95%CI: 0.01-0.83), P=0.033
Survival probability %
Pre-admission+admission RAAS inhibitors
Pre-admission RAAS inhibitors
Admission RAAS inhibitors
Pre-admission+admission other antihypertensions
Days since symptoms onset
Number at risk
36 36 36 35 35
58 55 54 54 54
17 16 16 16 16
257 245 236 232 231

FIGURE 3 Event-free survival of COVID 19 patients using RAAS inhibitors. A, Pre-admission use of RAAS inhibitors improve clinical outcomes in COVID-19 patients versus without pre-admission application (HR 0.35, 95% CI 0.14-0.86, $P = .022$). B, In-hospital use of RAAS inhibitors improve clinical outcomes in COVID-19 patient versus without application of RAAS inhibitors after admission (HR 0.40, 95% CI 0.15-1.03, $P = .058$). C, Persistent use of RAAS inhibitors improve clinical outcomes in COVID-19 patients versus without RAAS application (HR 0.11, 95% CI 0.02-0.88, $P = .037$). D, Pre-admission use of RAAS inhibitors improve clinical outcomes in COVID-19 patients versus pre-admission use of other antihypertensive medications (HR 0.35, 95% CI 0.13-0.97, $P = .043$). E, In-hospital use of RAAS inhibitors improve clinical outcomes in COVID-19 patients versus in-hospital use of other antihypertensive medications (HR 0.18, 95% CI 0.04-0.86, $P = .031$). F, Persistent use of RAAS inhibitors improve clinical outcomes in COVID-19 patients versus persistent use of other antihypertensive medicines medications (HR 0.10, 95% CI 0.01-0.83, $P = .033$). 95% CI, 95% confidence interval; HR, hazard ratio; RAAS, renin-angiotensin-aldosterone system

application of RAAS inhibitors, we evaluated the blood pressure among groups with different antihypertensive medication therapies. No significantly statistical difference was found in the four groups. The potential protective effect for improving clinical outcome might be more attributed to organ protection than blood pressure control (Supplement Tables S5 and S6). However, our speculation needed to be clarified in further studies.

To our knowledge, this clinical retrospective study was the first to evaluate the effect of pre-admission, in-hospital, and consecutive application of RAAS inhibitors on clinical outcomes among COVID-19 patients with hypertension. These data revealed that COVID-19 patients with higher grade of blood pressure grade had worse clinical outcomes, which could be improved by pre-admission, in-hospital, or consecutive application of RAAS inhibitors. Compared with other antihypertension medicine treatment, RAAS inhibitors users showed a lower incidence of death, ARDS, respiratory failure, septic shock, mechanical ventilation, and ICU admission. Our findings provided direct evidence to support that COVID-19 patients with hypertension should receive RAAS inhibitors, unless limited by contraindication. This study further strengthened the ACC/AHA clinical recommendation.

4.1 | Limitation

There are some limitations in this study. Firstly, the multivariable-adjusted Cox proportional hazard models were performed to estimate the true treatment effects of RAAS inhibitors. However, observational studies usually exist the deficiency of the inability to include all relevant confounders, including the classes of RAAS inhibitors and other antihypertensive drugs, and the application of traditional Chinese medicines as well as some other unmeasured parameters, such as body mass index, might causing bias that cannot be adjusted. Secondly, this is a single-center study; thus, larger prospective studies from multiple centers are needed to confirm our findings. Thirdly, considering short period of inclusion, long-term prospective studies are also needed to assess the effects of these treatments.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Prof. Lan Huang had full access to all of the data in this study and take responsibility for the integrity and accuracy of the data analysis. Drs Renzheng Chen and Jie Yang contributed equally to this work and are co-first authors. Concept and design: Lan Huang, Hu Tan and Chuan Liu. Acquisition, analysis, or interpretation of data: Hu Tan, Chuan Liu, Renzheng Chen, Jie Yang, Xubin Gao, Xiaohan Ding, Yuanqi Yang, Yang Shen, Jingbin Ke, Fangzhengyuan Yuan, Chunyan He, Hedong Xiang, Ran Cheng, Hailin Lv, Limin Zhang, Ping Li. Drafting of the manuscript: Renzheng Chen and Jie Yang. Critical revision of the manuscript for important intellectual content: Renzheng Chen, Jie Yang and Lan Huang. Statistical analysis: Renzheng Chen, Jie Yang, Xubin Gao, Xiaohan Ding, Yuanqi Yang, Yang Shen, Jingbin Ke, Fangzhengyuan Yuan, Chunyan He, Hedong Xiang, Ran Cheng, Hailin Lv. Obtained funding: Hu Tan. Administrative, technical, or material support: Hu Tan, Chuan Liu and Jie Yang. Supervision: Lan Huang.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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