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RESEARCH ARTICLE

Renin–angiotensin system inhibitor is associated with the reduced risk of all-cause mortality in COVID-19 among patients with/without hypertension

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Abstract **Consecutively hospitalized patients with confirmed coronavirus disease 2019 (COVID-19) in Wuhan, China were retrospectively enrolled from January 2020 to March 2020 to investigate the association between the use of renin–angiotensin system inhibitor (RAS-I) and the outcome of this disease. Associations between the use of RAS-I (angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)), ACEI, and ARB and in-hospital mortality were analyzed using multivariate Cox proportional hazards regression models in overall and subgroup of hypertension status. A total of 2771 patients with COVID-19 were included, with moderate and severe cases accounting for 45.0% and 36.5%, respectively. A total of 195 (7.0%) patients died. RAS-I (hazard ratio (HR)= 0.499, 95% confidence interval (CI) 0.325–0.767) and ARB (HR = 0.410, 95% CI 0.240–0.700) use was associated with a reduced risk of all-cause mortality among patients with COVID-19. For patients with hypertension, RAS-I and ARB applications were also associated with a reduced risk of mortality with HR of 0.352 (95% CI 0.162–0.764) and 0.279 (95% CI 0.115–0.677), respectively. RAS-I exhibited protective effects on the survival outcome of COVID-19. ARB use was associated with a reduced risk of all-cause mortality among patients with COVID-19.**

Keywords COVID-19; RAS inhibitor; hypertension; all-cause mortality

Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Angiotensin-converting enzyme 2 (ACE2) serves as the target receptor of SARS-CoV-2 by facilitating virus entry and replication in host cells, such as alveolar epithelial cells [3,4]. ACE2 is an essential component of the renin–angiotensin system (RAS), a major hormonal system regulating physiological homeostasis through multiple pathways including hemodynamics, electrolyte balance, vasomotion, inflammation, and tissue fibrosis [3,5,6]. Studies on SARS-CoV (pathogen of SARS, sharing 76.3% homology of amino acid sequence with SARS-CoV-2) found that injecting the binding domain of SARS-CoV (similar to that of SARS-CoV-2) into mice exacerbates lung injury, which could be attenuated by blocking RAS and is strongly associated with ACE2 expression [3,7]. Despite the evidence on its

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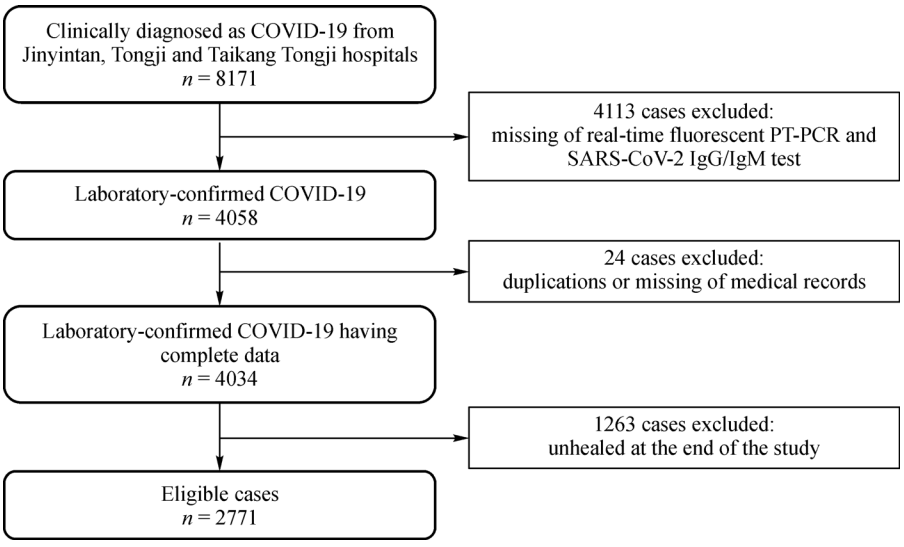

Fig. 1 Flowchart of enrollment process.

role as a virus–target co-receptor, its physiologically protective effects on RAS, and experimental indication in SARS, RAS inhibitor (RAS-I) administration among patients with COVID-19 remains controversial [8].

RAS-Is, including angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB), are routinely administered to patients with hypertension, diabetes, kidney diseases, and several types of cardiovascular diseases. Evidence on the association between RAS-I and COVID-19 outcome is clinically relevant for the treatment of patients with COVID-19. Several studies investigated the association between RAS-I use and COVID-19 outcome, but the results were inconsistent [9–13]. Li *et al.* found no substantial difference in the severity and outcomes of 1178 patients with COVID-19 and hypertension who received RAS-I [9]. Mehta *et al.* enrolled 18 472 participants receiving COVID-19 tests and showed that RAS-I use was not associated with COVID-19 risk; however, the correlation of this treatment with the risk of hospital admission and intensive care unit (ICU) admission was observed among 1735 patients with COVID-19. A high mortality was reported among RAS-I users compared with that among non-RAS-I users (3.8% vs. 2.1%) [13]. Xu *et al.* investigated the effects of RAS-I administration among 702 patients with COVID-19 and reported no remarkable association between RAS-I use and disease outcomes [14]. The inconsistency of these results might be caused by the heterogeneous population, various sample size, different documentation techniques for RAS-I use, and involvement of potential confounders. Further studies using large sample size are needed.

This study investigated the association between RAS-I use and COVID-19 outcome in a large sample of patients with COVID-19 from Wuhan, China.

Materials and methods

Study population

The National Health Commission of China collected COVID-19-related medical records from the designated hospitals in China to provide scientific evidence on medical treatment for patients with COVID-19. The standardized in-patient discharge summaries and the electronic full medical records of confirmed COVID-19 cases were submitted to the COVID-19 reporting system of National Health Commission of China. This retrospective analysis was based on the national database of the COVID-19 reporting system. The beginning and the cutoff dates for data gathering were January 1, 2020 and March 23, 2020, respectively. Participant enrollment process is shown in Fig. 1.

All data, including demographic characteristics, comorbidities, laboratory tests, treatments, morbidities, and survival status, were extracted from the data sets. Two researchers independently reviewed the collected data and extraction forms for quality control purposes.

COVID-19 was diagnosed according to the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) issued by the National Health Commission of China on March 3, 2020 [15]. Patients with positive result of real-time fluorescence PT-PCR or SARS-CoV-2 IgG/IgM test were regarded as confirmed cases with COVID-19.

Disease severity was evaluated according to the above protocol [15]. Mild cases were identified as having mild clinical symptoms without any sign of pneumonia on CT scanning. Moderate cases were radiologically defined as having pneumonia, fever, and respiratory symptoms. Severe cases were defined as meeting any of the following

Table 1 Demographic characteristics

Factors	Overall (n = 2771)	RAS-I administration		P value
		Yes (n = 280)	No (n = 2491)	
Age, n (%)				<0.001
<18 years	16 (0.6%)	0 (0.0%)	16 (0.6%)	
18–44 years	477 (17.2%)	12 (4.3%)	465 (18.7%)	
45–64 years	1262 (45.5%)	113 (40.4%)	1149 (46.1%)	
⩾ 65 years	1016 (36.7%)	155 (55.4%)	861 (34.6%)	
Male, n (%)	1328 (47.9%)	147 (52.5%)	1181 (47.4%)	0.110
Comorbidity, n (%)				
Hypertension	590 (21.5%)	141 (50.4%)	449 (18.2%)	<0.001
Diabetes	299 (10.9%)	56 (20.0%)	243 (9.8%)	<0.001
Cardiovascular disease	133 (4.8%)	31 (11.1%)	102 (4.1%)	<0.001
Chronic kidney disease	26 (0.9%)	4 (1.4%)	22 (0.9%)	0.330
Chronic obstructive pulmonary disease	56 (2.0%)	5 (1.8%)	51 (2.1%)	0.750
Cancer	30 (1.1%)	6 (2.1%)	24 (1.0%)	0.120
None of above	1947 (70.3%)	128 (45.7%)	1819 (73.0%)	<0.001
Laboratory test				
WBC ($\times 10^9$ cells/L)	6.8 (5.4, 8.9)	7.9 (5.6, 13.2)	6.8 (5.4, 8.8)	0.007
LYM ($\times 10^9$ cells/L)	1.2 (0.7, 1.6)	0.9 (0.4, 1.3)	1.2 (0.7, 1.6)	<0.001
hs-CRP (mg/L)	19.9 (2.4, 78.4)	65.7 (5.0, 161.6)	19.3 (2.3, 75.6)	<0.001
PCT (ng/L)	0.07 (0.04, 0.21)	0.14 (0.05, 0.61)	0.07 (0.04, 0.21)	0.003
IL-6 (pg/mL)	6.3 (2.1, 14.4)	12.7 (4.0, 72.6)	6.3 (2.1, 14.2)	<0.001
hs-cTn (ng/mL)	4.5 (1.9, 11.7)	11.5 (4.7, 29.6)	4.4 (1.9, 11.4)	<0.001
SCr (μmol/L)	70.0 (58.0, 86.0)	88.4 (71.0, 133.0)	70.0 (58.0, 85.6)	<0.001
SBP (mmHg)	124.4 (116.7, 132.5)	119.5 (71.9, 135.6)	124.4 (116.8, 132.5)	0.087
DBP (mmHg)	75.4 (71.1, 80.7)	86.2 (74.7, 117.3)	75.2 (71.0, 80.5)	<0.001
Complication, n (%)				
Acute respiratory distress syndrome	416 (15.0%)	68 (24.3%)	348 (14.0%)	<0.001
Heart failure	296 (10.7%)	59 (21.1%)	237 (9.5%)	<0.001
Acute myocardial infarction	250 (9.0%)	41 (14.6%)	209 (8.4%)	<0.001
Acute kidney injury	107 (3.9%)	22 (7.9%)	85 (3.4%)	<0.001
Multiple organ dysfunction syndrome	265 (9.6%)	52 (18.6%)	213 (8.6%)	<0.001
Treatment, n (%)				
Anti-virus drug	1861 (67.2%)	198 (70.7%)	1663 (66.8%)	0.180
Glucocorticoid	625 (22.6%)	73 (26.1%)	552 (22.2%)	0.140
Chloroquine/hydroxychloroquine	293 (10.6%)	37 (13.2%)	256 (10.3%)	0.130
Tocilizumab	41 (1.5%)	10 (3.6%)	31 (1.2%)	0.002
NPPV	316 (11.4%)	49 (17.5%)	267 (10.7%)	<0.001
IPPV	129 (4.7%)	19 (6.8%)	110 (4.4%)	0.074
CRRT	51 (1.8%)	15 (5.4%)	36 (1.4%)	<0.001
Severity, n (%)				<0.001
Mild cases	109 (3.9%)	5 (1.8%)	104 (4.2%)	
Moderate cases	1247 (45.0%)	96 (34.3%)	1151 (46.2%)	
Severe cases	1012 (36.5%)	119 (42.5%)	893 (35.8%)	
Critical	403 (14.5%)	60 (21.4%)	343 (13.8%)	
Outcome, n (%)				0.072
Recovery	2576 (93.0%)	253 (90.4%)	2323 (93.3%)	
Death	195 (7.0%)	27 (9.6%)	168 (6.7%)	

Abbreviations: RAS-I, renin–angiotensin system inhibitor; WBC, while blood cell; LYM, lymphocyte count; hs-CRP, hyper-sensitive C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; hs-cTn, hyper-sensitive cardiac troponin; SCr, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; NPPV, noninvasive positive pressure mechanical ventilation; IPPV, invasive positive pressure mechanical ventilation; CRRT, continuous renal replacement therapy.

criteria: (1) respiratory distress (respiratory rate $\geqslant$ 30 count/min); (2) oxygen saturation $\leqslant$ 93% at rest; and (3) arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) $\leqslant$ 300 mmHg. Critical cases were defined as experiencing respiratory failure and requiring mechanical ventilation, shock, or other organ failures that requires intensive care unit (ICU) care.

This study was conducted with the authorization of National Health Commission of China and was approved by the Ethics Committee of Peking University Health Science Center (IRB00001052-20032) .

RAS-I use and hypertension

ACEI (including benazepril, imidapril, captopril, perindopril, enalapril, and fosinopril) and ARB (including valsartan, irbesartan, losartan, candesartan, olmesartan, allisartan, and telmisartan) administrations were documented in the electronic medical records during hospitalization. The use of any kind of ACEI or ARB during hospitalization were defined as RAS-I administration.

Comorbidities and complications

Comorbidities including hypertension, diabetes, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and cancer were recorded. Hypertension was defined as: (1) with the diagnosis of hypertension in the medical records with ICD-10 codes I10–I15; (2) receiving antihypertensive therapy; and (3) systolic blood pressure (SBP)/diastolic blood pressure (DBP) $>$ 140/90 mmHg. Diabetes was defined as: (1) with the diagnosis of diabetes in the medical records with ICD-10 codes E11–E14; (2) receiving hypoglycemic therapy; (3) HbA1c $\geqslant$ 6.5%; and (4) fasting plasma glucose $\geqslant$ 7.0 mmol/L. CHD (ICD-10 code: I25.9), COPD (ICD-10 code: J44), and CKD (ICD-10 code: N00- N19, N25) were defined based on the diagnosis criteria in medical records.

Complications including acute respiratory distress syndrome (ARDS; ICD-10 codes: J80), heart failure (ICD-10 codes: I13.0, I13.2, I25.5, I43.8, I50.0, and I51.5), acute myocardial infarction (AMI; ICD-10 codes: I21, I22.8), acute kidney injury (AKI; ICD-10 codes: N17), and multiple organ dysfunction syndrome (MODS) were also analyzed and defined according to the diagnosis in the medical records based on related ICD-10 codes or respective criteria as follows. (1) ARDS was defined according to the Berlin definition [16]. (2) Heart failure was defined as the clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality [17]. (3) AMI was defined as hypersensitive cardiac troponin (hs-cTn) $>$ 99th percentile of normal reference values in the absence of any clinical features of myocardial ischemia [18]. (4) AKI was defined according to KDIGO clinical guidelines [19]. (5) MODS was defined as the progressive, potentially reversible dysfunction of two or more organ systems following acute, life-threatening disruption of systemic homeostasis.

Other variables

Information was collected regarding demographic characteristics, medications including anti-virus treatment, glucocorticoid, chloroquine/hydroxychloroquine and tocilizumab, mechanical ventilation including noninvasive positive pressure mechanical ventilation (NPPV) and invasive positive pressure mechanical ventilation (IPPV), and continuous renal replacement therapy (CRRT).

Laboratory tests included white blood cell (WBC, $\times$ 10^9 cells/L), lymphocyte count (LYM, $\times$ 10^9 cells/L), hyper-sensitive C-reactive protein (hs-CRP, mg/L), procalcitonin (PCT, ng/L), interleukin-6 (IL-6, pg/mL), hypersensitive cardiac troponin (hs-cTn, ng/mL), and serum creatinine (SCr, $\pm$ mol/L).

Statistical methods

Demographic characteristics, comorbidities, laboratory tests, treatments, complications, and outcomes were compared according to RAS-I administration. Normal and skewed distribution variables were presented by mean $\pm$ standard deviation (SD) and median (interquartile range, IQR), respectively. Categorical variables were presented as proportions. Student's t test, Mann–Whitney test, and Chi-square test were applied to compare the normally distributed, skewed distributed, and categorical variables between RAS-I administration groups, respectively. Subgroup analyses were conducted among patients with hypertension.

Cox proportional hazards regression models were applied to evaluate the association between RAS-I administration and all-cause mortality among patients with COVID-19. The results were presented as hazard ratio (HR) and 95% confident interval (CI). Covariates including age (continuous), gender (female vs. male), comorbidities (hypertension, diabetes, CHD; yes or no), lymphocyte count (continuous), treatments (anti-virus drugs, glucocorticoid, tocilizumab, chloroquine/hydroxychloroquine; yes or no), and complications (ARDS, heart failure, AMI, AKI; yes or no) were included in these models. Subgroup survival analyses were performed among patients with hypertension. The proportional hazard assumption was fulfilled for all analyses tested using the time-dependent covariate method [20].

All statistical analyses were two-tailed, and P value $<$ 0.05 indicated statistical significance. All analyses were

conducted using Stata version 14.0 (Stata Corp LP, College Station, TX, USA).

Results

Demographic and clinical characteristics

A total of 4058 patients with COVID-19 with confirmed real-time fluorescent PT-PCR or SARS-CoV-2 IgG/IgM test were admitted to Jinyintan, Tongji and Taikang Tongji hospitals, Wuhan, China from January 1, 2020 to March 23, 2020. Among these patients, 1263 were not discharged at the end of the study, and 24 had incomplete data of medical records and thus were excluded in the present analyses. Finally, 2771 patients were eligible (Fig. 1) .The majority of the studied population aged 45 years or older (82.2%), and 47.9% of them were males. Most patients were labeled as moderate (45.0%) and severe (36.5%) cases. Hypertension was the most common comorbidity (n = 590, 21.5%). A total of 416 (15.0%) patients developed ARDS, and 316 (11.4%) and 129 (4.7%) patients received NPPV and IPPV, respectively. The median duration of follow-up was 20 (12, 29) days. At the end of the study period, 2576 (93.0%) patients recovered, and 195 (7.0%) patients died.

A total of 280 patients received RAS-I during hospitalization, and 50.4% of them had hypertension. Among these patients, 43 (15.4%) used ACEI only, 225 (80.4%) used ARB only, and 12 (4.3%) used ACEI and ARB. Compared with the patients who did not receive RAS-I, those who received RAS-I were older and had higher proportion of comorbidities (hypertension: 50.4% vs. 18.2%; diabetes: 20.0% vs. 9.8%; CHD: 11.1% vs. 4.1%) and complications including ARDS, heart failure, AMI, AKI, and MODS ($P < 0.001$) (Table 1) .

RAS-I administration and all-cause mortality

A total of 195 patients died during hospitalization, 27 of them received RAS-I (Table 1). After the adjustment for potential confounders, Cox proportional hazards regression models showed that RAS-I (HR = 0.499, 95% CI 0.325–0.767) and ARB (HR = 0.410, 95% CI 0.240–0.700) administrations were associated with a reduced risk of all-cause mortality among patients with COVID-19. However, no significant association was found between ACEI use and all-cause mortality (HR = 0.892, 95% CI 0.473–1.682) (Table 2) .

Subgroup analyses among patients with hypertension

Among the 590 patients with hypertension, 141 (23.9%) received RAS-I with the predominance of ARB use (n = 116, 82.3%), and 64 (10.8%) died during hospitalization. The mortality of patients receiving RAS-I was lower than that of patients not receiving RAS-I (5.7% vs. 12.5%) (Table 3).

RAS-I (HR = 0.352, 95% CI 0.162–0.764) and ARB (HR = 0.279, 95% CI 0.115–0.677) applications were

Table 2 Association between RAS-I administration and all-cause mortality

Variable	Unadjusted model		Model 1		Model 2		Model 3	
	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
RAS-I administration								
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1.160 (0.771–1.743)	0.477	0.845 (0.561–1.272)	0.419	0.562 (0.371–0.852)	0.007	0.499 (0.325–0.767)	0.002
ACEI administration								
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	2.767 (1.542–4.967)	0.001	1.962 (1.091–3.528)	0.024	0.885 (0.488–1.605)	0.688	0.892 (0.473–1.682)	0.724
ARB administration								
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.775 (0.464–1.295)	0.331	0.579 (0.346–0.967)	0.037	0.457 (0.272–0.770)	0.003	0.410 (0.240–0.700)	0.001

Model 1: adjusted for age and gender. Model 2: model 1, hypertension, diabetes, CHD, LYM. Model 3: model 2, anti-virus drugs, glucocorticoid, tocilizumab, chloroquine/ hydroxychloroquine, ARDS, heart failure, AMI, AKI.
Abbreviations: RAS-I, renin–angiotensin inhibitor; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; CHD, coronary heart disease; LYM, lymphocyte count; ARDS, acute respiratory distress syndrome; AMI, acute myocardial infarction; AKI, acute kidney injury.

associated with a reduced risk of all-cause mortality among patients with COVID-19 and hypertension. No significant association was found between ACEI use and all-cause mortality (HR = 1.008, 95% CI 0.231–4.391) (Table 4).

Discussion

This study revealed the protective effects of RAS-I administration for all-cause mortality among hospitalized patients with COVID-19. ARB use was significantly associated with a reduced risk of mortality among patients with COVID-19. A similar observation was found in the subgroup analyses of patients with hypertension. This work provided evidence supporting RAS-I use, especially ARB use, for patients with COVID-19.

Inconsistent results have been reported regarding the association between RAS-I use and COVID-19 outcome. Mehta *et al.* analyzed the association between RAS-I use and clinical outcomes among 1735 patients with COVID-19 in the United States and reported higher mortality among patients receiving RAS-I (n = 8, 3.8%) than those not receiving RAS-I (n = 34, 2.1%) [13]. In Asia, several relevant studies were conducted among patients with hypertension or diabetes. By collecting data from 1178 hypertensive patients with COVID-19, Li *et al.* did not observe differences in RAS-I use between non-survivors and survivors (27.3% vs. 33.0%; P = 0.34) [9]. Chen *et al.* compared the clinical characteristics of patients with diabetes who are receiving or not receiving RAS-I and found no significant difference [21]. Zhang *et al.* reported a decreased risk for all-cause mortality with an adjusted HR

Table 3 Demographic characteristics among patients with COVID-19 with hypertension

Factors	Overall (n = 590)	RAS-I administration		P value
		Yes (n = 141)	No (n = 449)	
Age, n (%)				0.540
<18 years	0 (0.0%)	0 (0.0%)	0 (0.0%)	
18–44 years	21 (3.6%)	7 (5.0%)	14 (3.1%)	
45–64 years	230 (39.0%)	55 (39.0%)	175 (39.0%)	
⩾ 65 years	339 (57.5%)	79 (56.0%)	260 (57.9%)	
Male, n (%)	293 (49.7%)	68 (48.2%)	225 (50.1%)	0.700
Laboratory test				
WBC ($\times 10^9$ cells/L)	7.1 (5.6, 9.5)	6.4 (5.3, 9.0)	7.2 (5.6, 9.5)	0.260
LYM ($\times 10^9$ cells/L)	1.1 (0.7, 1.6)	1.1 (0.6, 1.5)	1.1 (0.7, 1.6)	0.690
hs-CRP (mg/L)	38.0 (4.5, 102.1)	22.2 (4.6, 72.3)	42.8 (4.5, 111.3)	0.980
PCT (ng/L)	0.09 (0.05, 0.24)	0.08 (0.04, 0.23)	0.09 (0.05, 0.24)	0.340
IL-6 (pg/mL)	8.3 (3.2, 15.6)	9.7 (3.0, 15.5)	8.3 (3.3, 15.6)	0.790
hs-cTn (ng/mL)	7.9 (3.3, 20.6)	8.6 (4.1, 14.3)	7.8 (3.3, 20.6)	0.780
SCr (μmol/L)	73.4 (61.0, 92.0)	86.0 (69.0, 103.0)	73.0 (60.1, 92.0)	0.100
SBP (mmHg)	129.7 (122.3, 137.0)	135.6 (124.6, 141.9)	129.6 (122.3, 137.0)	0.220
DBP (mmHg)	76.6 (72.1, 82.3)	80.5 (74.1, 86.2)	76.5 (72.1, 82.3)	0.180
Complication, n (%)				
Acute respiratory distress syndrome	84 (14.2%)	13 (9.2%)	71 (15.8%)	0.051
Heart failure	85 (14.4%)	18 (12.8%)	67 (14.9%)	0.520
Acute myocardial infarction	98 (16.6%)	19 (13.5%)	79 (17.6%)	0.250
Acute kidney injury	38 (6.4%)	8 (5.7%)	30 (6.7%)	0.840
Multiple organ dysfunction syndrome	76 (12.9%)	12 (8.5%)	64 (14.3%)	0.076
Severity, n (%)				0.730
Mild cases	10 (1.7%)	2 (1.4%)	8 (1.8%)	
Moderate cases	209 (35.4%)	53 (37.6%)	156 (34.7%)	
Severe cases	265 (44.9%)	65 (46.1%)	200 (44.5%)	
Critical	106 (18.0%)	21 (14.9%)	85 (18.9%)	
Outcome, n (%)				0.029
Recovery	526 (89.2%)	133 (94.3%)	393 (87.5%)	
Death	64 (10.8%)	8 (5.7%)	56 (12.5%)	

Abbreviations: RAS-I, renin–angiotensin system inhibitor; WBC, while blood cell; LYM, lymphocyte count; hs-CRP, hyper-sensitive C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; hs-cTn, hyper-sensitive cardiac troponin; SCr, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 4 Association between RAS-I administration and all-cause mortality among patients with hypertension

Variable	Unadjusted model		Model 1		Model 2	
	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
RAS-I administration						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.402 (0.192–0.845)	0.016	0.433 (0.206–0.909)	0.027	0.352 (0.162–0.764)	0.008
ACEI administration						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.691 (0.169–2.824)	0.606	0.663 (0.162–2.713)	0.567	1.008 (0.231–4.391)	0.992
ARB administration						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	0.353 (0.152–0.818)	0.015	0.381 (0.164–0.884)	0.025	0.279 (0.115–0.677)	0.005

Model 1: adjusted for age and gender. Model 2: model 1, LYM, anti-virus drugs, glucocorticoid, ARDS, heart failure, AMI, AKI.
Abbreviations: RAS-I, renin–angiotensin system inhibitor; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; LYM, lymphocyte count; ARDS, acute respiratory distress syndrome; AMI, acute myocardial infarction; AKI, acute kidney injury.

of 0.42 (95% CI 0.19–0.92) among hypertensive patients with COVID-19 who received RAS-I [22]. However, no stratified results on ACEI and ARB use were provided. By using a relatively large sample size of patients with COVID-19 and after adjusting for extensive covariates, the present study supported the protective effects of RAS-I and ARB on survival outcomes among patients with COVID-19 with or without hypertension.

As a major hormonal system, RAS plays pathogenetic and protective roles in complex regulation mechanisms [5,23–25]. In this system, angiotensin I could be converted into angiotensin II by ACE-induced vasoconstriction, inflammation, and fibrosis through the ACE-AT_1 axis; angiotensin II can either directly interact with AT_2 receptor or be catalyzed by ACE2 into angiotensin 1–7 and interact with Mas receptor, thus promoting vasodilatation, anti-inflammation, and anti-fibrosis [5,24]. ARBs inhibit the risk effects by blocking the AT_1 receptor; hence, the counter-regulatory increased angiotensin II could interact with AT_2 receptor and be catalyzed into angiotensin 1–7 [5,24,26]. Ultimately, the protective effects would be promoted through multiple approaches to maintain physiological homeostasis. The benefits of ARB on the all-cause mortality of patients with COVID-19 are speculated to originate from the physiological homeostasis. In theory, ACEI could also inhibit the risk effects of RAS, though the pathway is different from that of ARB [24]. However, this study found no significant association between the use of ACEI and the survival outcome of patients with COVID-19. The result might be influenced by the small sample size (43 patients used ACEI). A recent work reported the potentially harmful effects of ACEI on the outcome of patients with COVID-19 and diabetes in Iran [27]. Hence, further research with a large sample size of ACEI users with COVID-19 in different populations is still needed to verify the association between ACEI use and survival outcome.

Hypertension is a risk factor of lower respiratory tract infections and community-acquired pneumonia, especially among the elderly [28,29]. High prevalence of hypertension was observed among patients with COVID-19 [2,11], though robust evidence supporting the association between hypertension and COVID-19 risk is lacking. The inflammatory activation in hypertension is its pathogenetic linkage to COVID-19 [24]. Similar lymphocyte loss and cytokine overproduction such as IL-6 were observed in hypertension and COVID-19 [15,30,31]. The activated RAS in hypertension further augmented the lung injury through the angiotensin II-ACE-AT_1 receptor axis [7,32]. ACEI and ARB could block the angiotensin II-ACE-AT_1 receptor axis, though their target molecules are different [24]. Attenuated inflammation and few ARDS cases were observed among patients with hypertension who received RAS-I. Meng *et al.* also reported mild inflammation among patients with COVID-19 receiving RAS-I [10]. This phenomenon may partly lead to the beneficial effect of RAS-I administration on all-cause mortality among hypertensive patients.

This study has several limitations. First, given the observational nature of this work and the use of electronic medical records as the basis, the possibility of residual confounding exists. Second, only in-hospital all-cause mortality was documented. Third, due to the relatively low percentage of ACEI use in China, the analyses regarding the association between ACEI and COVID-19 outcome might be underpowered. Finally, the observational design limited the ability to generate causal inference in the analyses. Further prospective randomized trials are needed to reveal the protective effects of RAS-I on the survival outcome of patients with COVID-19.

In conclusion, this work provides evidence that ARB administration is strongly associated with a reduced risk of in-hospital all-cause mortality among patients with COVID-19 and thus could be preferably considered for

patients with COVID-19 independent of hypertension comorbidity. Further investigations using large sample sizes and interventional studies are needed to illustrate the effects of ACEI use among patients with COVID-19.

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Compliance with ethics guidelines

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