Efficacy of ACEIs/ARBs vs CCBs on the progression of COVID-19 patients with hypertension in Wuhan: A hospital-based retrospective cohort study

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Abstract
To evaluate the efficacy of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) vs calcium channel blockers (CCBs) on the progression of Corona Virus Disease 2019 (COVID-19) patients with hypertension in Wuhan. This retrospective single-center case series analyzed COVID-19 patients with hypertension, treated with ACEIs/ARBs or CCBs at the Tongji Hospital of Wuhan City, China from 25th January to 15th March 2020. After propensity score matching analysis, 76 patients were selected into two groups. Univariate and multivariable analyses were conducted to determine factors related to improvement measures and outcome measures by Cox proportional hazard regression models. Among 157 patients with confirmed COVID-19 combined hypertension, including 73 males and 84 females, a median age of 67.28 ± 9.11 vs 65.39 ± 10.85 years. A univariable analysis indicated that clinical classification, lymphocyte count, and interleukin-2 receptor were associated with a lengthened negative time of nucleic acid, with a significant difference between two groups (P = .036). Furthermore, we found no obvious difference in nucleic acid conversion time between ACEIs/ARBs and CCBs groups (hazard ratio [HR]: 0.70; 95% confidence interval [CI]: [0.97, 3.38]; P = .18) in the multivariable analysis as well as chest computed tomography improved time (HR: 0.73; 95% CI [0.45, 1.2]; P = .87), and hospitalization time between ACEIs/ARBs and CCBs groups (HR: 1.06; 95% CI [0.44, 1.1]; P = .83). Our study provided additional evidence of no obvious difference in progress and prognosis between ACEIs/ACEIs and CCBs group, which may suggest ACEIs/ARBs may have scarcely influence on increasing the clinical severe situations of COVID-19 patients with hypertension.

KEYWORDS
ACEIs, ARBs, CCBs, COVID-19, hypertension, RAS blockers

Abbreviations: ACE2, angiotensin-converting enzyme 2; ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; COVID-19, Corona Virus Disease 2019; RAS blockers, renin-angiotensin system blockers; RT-PCR, real-time reverse-transcription-polymerase chain reaction; SARS, severe acute respiratory syndrome; WHO, World Health Organization.
INTRODUCTION

Corona Virus Disease 2019 (COVID-19) is a new respiratory illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), first reported in Wuhan, China, in December 2019. The outbreak of COVID-19 is currently continuously evolving globally, resulting in 1,133,758 confirmed cases including in healthcare workers, worldwide by 5 April 2020.1 On 20 January 2020, the National Health Commission issued No. 1 announcement, which included COVID-19 as an acute respiratory infectious disease into the class B infectious disease specified in the law of the people's Republic of China on the prevention and control of infectious diseases, and then managed it as class A infectious disease. The COVID-19 epidemic situation was classified as "public health emergencies of international concern" on 31st January, the highest level in the World Health Organization (WHO) infectious disease emergency mechanism by WHO.

There was of particular interest to clinicians and investigators with a major interest in cardiovascular disease and mortality on infected patients, particularly in elderly people with comorbidities. Thereby, in an analysis of 45,000 confirmed cases in China,2,3 the crude case fatality rate was 0.9% for patients without any documented comorbidities, whereas the case fatality rate was much higher for patients with cardiovascular disease (10.5%), diabetes (7.3%), or hypertension (6.3%).

Well, now the current study reports that hypertension may be associated with an increased risk of severe in hospitalized COVID-19 patients. Previous experimental data2,4 revealed angiotensin-converting enzyme 2 (ACE2) receptors serve as binding sites for the anchoring spike (S) proteins on the exterior surfaces of beta coronaviruses. The beta coronavirus SARS-CoV causes the severe acute respiratory syndrome (SARS). The phylogenetically related beta coronavirus, SARS-CoV-2, causes the novel coronavirus disease (nCoV-2019) or COVID-19. S proteins anchor both beta coronaviruses to ACE2 receptors in the lower respiratory tract of infected patients to gain entry into the lungs. Viral pneumonia and potentially fatal respiratory failure may result in susceptible persons after 10 to 14 days.

Currently, the hypertension patients are basically treated with blood pressure-lowering drugs, mainly including renin-angiotensin system (RAS) blockers-angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), β-blockers, diuretics. In Southwest China, CCBs accounted for 58.6% of hypertension treatment, followed by ACEIs/ARBs accounted for 22.4%.5 Since ACE2 was identified to the functional receptor of SARS-CoV-2, ACE2 level was increased following treatment with ACEIs and ARBs. The current research6,7,8 revealed that intravenous infusions of ACEIs and ARBs in experimental animals increased the numbers of ACE2 receptors in the cardiopulmonary circulation. Patients taking ACEIs or ARBs chronically for cardiovascular diseases are assumed to have increased numbers of ACE2 receptors throughout their cardiopulmonary circulations as observed in experimental animal models. Currently, a corollary concern needed to identify through real-world clinical studies, whether these commonly used RAS blockers—ACEIs/ARBs may increase the severity of COVID-19. The present study therefore retrospectively analyzed data from hospitalized COVID-19 patients with hypertension in a single center in Wuhan, China, to compare the difference between ACEIs/ARBs and CCB groups, which may provide clinical evidence on the impact of ACEIs/ARBs on the clinical course of COVID-19 infection.

METHODS

2.1 Study patients

We performed a retrospective study of COVID-19 patients with hypertension who were recorded in Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China from 25th January to 15th March 2020. COVID-19 was diagnosed via epidemiological history (Travel history or residence history in Wuhan and surrounding areas or other communities with case reports within 14 days before the onset of illness; history of exposure to COVID-19 case infection within 14 days before onset of illness and so on), consistent with two clinical manifestations (fever and respiratory symptoms, normal or decreased white blood cells in early onset of illness), and microbiological evidence (laboratory test for the COVID-19 from the respiratory specimens shows positive result by the real-time reverse-transcription-polymerase chain reaction [RT-PCR] assay) according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (7th edition, in Chinese) published by the National Health Commission of China. Hypertension history and blood pressure medications obtained through electronic medical record (EMR). Patients demographics as well as the use of antihypertensive drug, therapy protocol, imaging data, laboratory data, follow-up records, and prognosis were collected from EMR. Routine tests, such as chest computed tomography (CT), serum biochemical indices, and complete blood counts were conducted during hospitalization.

From 25th January to 15th March 2020, 306 patients diagnosed with COVID-19 combined hypertension using CCBs, ACEIs, or ARBs antihypertensive drugs. Patients with the following conditions were excluded from our study: (a) lung imaging was significantly improved before using antihypertensive; (b) before using antihypertensive, uleic acid was negative for two consecutive times; (c) case use both CCBs and ACEIs/ARBs. This study was approved by the institutional ethics board of the Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology (No. TJ-IRB20200338).

According to the Novel Coronavirus Pneumonia Diagnosis and Treatment Guideline (7th edition, in Chinese), clinical classification of the COVID-19 patients was classified into mild-moderate, severe, and critically ill. Baseline clinical data were collected at admission, including blood routine, such as white blood cell count (3.5-9.5)×10^9/L, lymphocyte count (1.1-3.2)×10^9/L, coagulation function such as D-dimer less than 0.5 mg/L, renal and liver function, such as alanine aminotransferase and aspartate aminotransferase less than 40 U/L,
2.2 | Statistical analysis

Continuous data accorded with normal distribution were expressed as mean ± standard deviation and compared by independent samples t test or expressed as median (25th-75th percentile) and compared by the Wilcoxon rank-sum test. Categorical variables were expressed as number (percentage) and compared by χ² test or Fisher’s exact test. Among patients diagnosed with COVID-19 combined hypertension using CCBs, ACEIs, or ARBs antihypertensive drugs, we sought to investigate the ACEIs or ARBs medication on progress and prognosis of COVID-19 patients. The main improvement measures, such as the first nucleic acid conversion time, first chest CT improved time and chest CT improved. The secondary endpoints were worsened Chest CT during hospitalization and in-hospital mortality. The outcome measures were the time from illness onset to discharge from hospital.

3 | RESULTS

3.1 | Study the selected population

In total, 306 patients with a diagnosis of COVID-19 combined hypertension using CCBs, ACEIs, or ARBs antihypertensive drugs between 25th January 2020 to 15th March 2020. The patient selection flow-chart is displayed in Figure 1. All these patients were treated with one or multiple blood pressure-lowering drugs, including RAS blockers—ACEIs/ARBs, calcium channel blockers, β-Blockers, and diuretics. The ACEIs/ARBs group consisted of ACEIs or ARBs without CCBs, as well as CCBs group. Then, we selected 157 adult hypertension patients with COVID-19 infections, including 73 males (46.50%) and 84 females (53.50%). The vast majority of patients were discharged from hospital. Unfortunately, there were five patients and one patient died from pneumonia in ACEIs/ARBs and CCBs groups, respectively. The in-hospital mortality showed no significant difference between two groups (P = .191). After PSM, we selected 76 adult hypertension patients with COVID-19 infections (Figures S1 and S2).

3.2 | Comparison of demographic and clinical characteristics

Before PSM, a total of 157 adult hypertension patients with COVID-19 infections were involved in this study. Demographic features and clinical characteristics data are shown in Table 1. There is no obvious difference between ACEIs/ARBs and CCBs groups about 49 (59.0) vs 35 (47.3) female, a median age of 67.28 ± 9.11 vs 65.39 ± 10.85 years (P >.05).
89.19 ± 17.62 bpm, respectively, we found that antihypertensive drugs in ACEIs/ARBs and CCBs groups exhibited a similarly anti-hypertensive efficacy. The underlying diseases, including diabetes mellitus and coronary disease, in ACEIs/ARBs and CCBs groups are listed in Table 2. There was no significant difference between two groups, as well as lymphocytes count (×10^9/L) 1.26 ± 0.53 vs 1.29 ± 0.60, D-dimer (mg/L) 1.43 ± 2.04 vs 1.38 ± 1.59, interleukin-6 18.51 ± 32.41 vs 24.11 ± 52.72 mmol/L, interleukin-2 receptor 32.69 ± 490.99 vs 752.82 ± 550.00 mmol/L, and CRP 29.57 ± 47.25 vs 24.25 ± 50.47 mg/L. The clinical severity was graded as mild-moderate, severe, and critically ill. There is no difference in any of grade between ACEIs/ARBs and CCBs groups. It is worth noting that the significant differences between ACEIs/ARBs group and CCBs group on temperature 36.92°C ± 0.84°C vs 37.69°C ± 0.75°C, white blood cell count (×10^9/L) 5.92 ± 2.28 vs 7.54 ± 2.31, aspartate aminotransferase 22.82 ± 13.42 vs 29.95 ± 16.61 U/L. To further

| Characteristics            | Before PSM | ACEIs/ARBs group | After PSM | ACEIs /ARBs group |
|----------------------------|------------|-------------------|-----------|-------------------|
|                            | CCBs group (n = 83) | ACEIs/ARBs group (n = 74) | P         | CCBs group (n = 38) | ACEIs /ARBs group (n = 38) | P         |
| Gender = female (%)        | 49 (59.0)  | 35 (47.3)         | .19       | 22 (57.9)         | 22 (57.9)          | 1         |
| Age (mean ± SD)            | 67.28 ± 9.11 | 65.39 ± 10.85     | .239      | 65.34 ± 9.65      | 68.16 ± 7.58       | .162      |
| Outcome = cure (%)         | 82 (98.8)  | 69 (93.2)         | .163      | 38 (100.0)        | 38 (100.0)         | 1         |
| Clinical classification (%)| .191       | .818              |           |                   |                   |           |
| Mild-moderate (%)          | 44 (53.0)  | 38 (51.4)         |           |                   |                   |           |
| Severe (%)                 | 38 (45.8)  | 31 (41.9)         |           |                   |                   |           |
| Critically ill (%)         | 1 (1.2)    | 5 (6.8)           |           |                   |                   |           |
| Diabetes (%)               | 22 (26.5)  | 21 (28.4)         | .934      | 9 (23.7)          | 12 (31.6)         | .608      |
| coronary disease (%)       | 6 (7.2)    | 10 (13.5)         | .301      | 3 (7.9)           | 5 (13.2)          | .709      |
| Temperature (mean ± SD)    | 36.92 ± 0.84 | 37.69 ± 0.75      | .012      | 36.85 ± 0.83      | 36.73 ± 0.74       | .505      |
| Respiratory rate (breaths per min) (mean ± SD) | 21.39 ± 7.22 | 19.96 ± 2.42 | .107 | 20.18 ± 2.99 | 20.11 ± 2.08 | .894 |
| diastolic BP (mean ± SD), mm Hg | 83.23 ± 11.88 | 81.81 ± 13.47 | .484 | 83.45 ± 11.72 | 82.66 ± 12.69 | .779 |
| systolic BP (mean ± SD), mm Hg | 138.66 ± 17.97 | 134.76 ± 18.53 | .182 | 140.53 ± 17.97 | 136.03 ± 18.58 | .287 |
| Heart rate (mean ± SD), bpm | 89.01 ± 14.35 | 89.19 ± 17.62 | .945 | 89.13 ± 13.71 | 88.82 ± 14.03 | .921 |
| White blood cell count (×10^9/L) (mean ± SD) | 5.92 ± 2.28 | 7.54 ± 2.31 | .019 | 6.53 ± 2.54 | 6.62 ± 2.42 | .887 |
| lymphocyte count (×10^9/L) (mean ± SD) | 1.26 ± 0.53 | 1.29 ± 0.60 | .757 | 1.38 ± 0.61 | 1.26 ± 0.55 | .38 |
| D-dimer (mean ± SD), mg/L  | 1.43 ± 2.04 | 1.38 ± 1.59       | .874      | 1.08 ± 1.55       | 1.49 ± 1.66        | .267      |
| Interleukin-6 (mean ± SD), mmol/L | 18.51 ± 32.41 | 24.11 ± 52.72 | .419 | 14.97 ± 30.09 | 15.54 ± 27.05 | .932 |
| Interleukin-2 receptor (mean ± SD), mmol/L | 732.69 ± 490.99 | 752.82 ± 550.00 | .809 | 631.87 ± 422.94 | 758.95 ± 393.16 | .179 |
| Alanine aminotransferase (mean ± SD), U/L | 26.04 ± 23.08 | 31.46 ± 21.82 | .134 | 26.03 ± 20.99 | 26.42 ± 16.25 | .927 |
| Aspartate aminotransferase (mean ± SD), U/L | 22.82 ± 13.42 | 29.95 ± 16.61 | .037 | 22.95 ± 13.44 | 22.92 ± 9.71 | .992 |
| Lung image (%)             | 75 (90.4)  | 65 (87.8)         | .802      | 32 (84.2)         | 35 (92.1)         | .478      |
| NT-ProBNP (mean ± SD), pg/L | 1305.13 ± 7258.23 | 294.00 ± 385.08 | .233 | 164.18 ± 263.02 | 306.11 ± 442.72 | .094 |
| Creatinine (mean ± SD), U/L | 93.17 ± 116.46 | 80.32 ± 43.05 | .372 | 71.16 ± 17.44 | 76.32 ± 39.31 | .462 |
| Urea (mean ± SD), mmol/L   | 5.69 ± 4.94 | 5.73 ± 3.45       | .957      | 4.79 ± 1.52       | 5.11 ± 1.96        | .431      |
| Uric acid (mean ± SD), mmol/L | 268.24 ± 82.61 | 285.67 ± 116.59 | .277 | 276.84 ± 83.11 | 264.35 ± 97.42 | .549 |
| Potassium (mean ± SD), mmol/L | 4.25 ± 0.56 | 4.22 ± 0.47       | .772      | 4.14 ± 0.44       | 4.24 ± 0.50        | .345      |
| Sodium (mean ± SD), mmol/L  | 140.10 ± 2.90 | 139.45 ± 3.83 | .223 | 140.31 ± 2.83 | 140.32 ± 3.05 | .997 |
| C-reactive protein (mean ± SD), mg/L | 29.57 ± 47.25 | 24.25 ± 50.47 | .496 | 13.45 ± 21.30 | 17.88 ± 25.46 | .413 |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; PSM, propensity score matching; SD, standard deviation.
TABLE 2 Univariate and multivariate Cox regression analysis for nucleic acid conversion time

| Characteristics                 | HR   | P value | Lower | Upper |
|---------------------------------|------|---------|-------|-------|
| Univariate                      |      |         |       |       |
| Gender                          | 0.94 | .78     | 0.59  | 1.5   |
| Age                             | 0.99 | .25     | 0.96  | 1     |
| Clinical classification         | 0.11 | 2.05E-08| 0.11  | 0.34  |
| Diabetes                        | 0.19 | 0.025   | 0.96  | 1     |
| Coronary disease                | 0.79 | .53     | 0.38  | 1.6   |
| Temperature                     | 1.1  | .68     | 0.78  | 1.5   |
| Respiratory rate (breaths/min)  | 1    | .64     | 0.92  | 1.1   |
| Diastolic BP, mm Hg             | 1    | .99     | 0.99  | 1     |
| Systolic BP, mm Hg              | 1    | .82     | 0.99  | 1     |
| Heart rate, bpm                 | 1    | .65     | 0.98  | 1     |
| White blood cell count          | 0.95 | .22     | 0.86  | 1     |
| Lymphocyte count (>10^9/L)      | 1.5  | .032    | 1     | 2.3   |
| D-dimer, mg/L                   | 0.94 | .52     | 0.79  | 1.1   |
| Interleukin-6, mmol/L           | 1    | .27     | 0.99  | 1     |
| Interleukin-2 receptor, mmol/L  | 1    | .045    | 1     | 1     |
| Alanine aminotransferase, U/L   | 1    | .47     | 0.99  | 1     |
| Aspartate aminotransferase, U/L | 1    | .69     | 0.98  | 1     |
| Lung image                      | 0.8  | .54     | 0.4   | 1.6   |
| NT-ProBNP, pg/L                 | 1    | .3      | 1     | 1     |
| Creatinine, U/L                 | 1    | .72     | 0.99  | 1     |
| Urea, mmol/L                    | 0.95 | .43     | 0.84  | 1.1   |
| Uric acid, mmol/L               | 1    | .6      | 1     | 1     |
| Potassium, mmol/L               | 1.5  | .12     | 0.89  | 2.5   |
| Sodium, mmol/L                  | 0.97 | .38     | 0.89  | 1     |
| C-reactive protein, mg/L        | 0.99 | .087    | 0.98  | 1     |
| CCBs vs ACEI/ARBs groups        | 0.6  | .036    | 0.38  | 0.97  |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio.

To evaluate the detected differences between ACEIs/ARBs and CCBs groups, we performed a 1:1 matched case-control analysis using the PSM method. PSM between the ACEIs/ARBs and CCBs groups was conducted by all variables (age, gender, clinical classification, comorbidities, temperature, respiratory rate, diastolic BP, systolic BP, heart rate, white blood cell count, lymphocytes count, D-dimer, interleukin-6, interleukin-2 receptor, alanine aminotransferase, aspartate aminotransferase, lung image, NT-ProBNP, creatinine, urea, uric acid, potassium, sodium, and CRP). After PSM, the ACEIs/ARBs and CCBs groups consisted of 38 patients, respectively. No statistical differences on demographic features and clinical characteristics data were observed between the two groups.

3.3 Comparison of nucleic acid conversion time between the ACEIs/ARBs and CCBs groups in all patients

We performed a stratified analysis according to different variables in 1:1 matched group. We used the Cox proportional hazards model to investigate the effect of baseline characteristics on nucleic acid conversion time. A univariable analysis indicated that clinical classification ($P = 1.20E-08$), lymphocyte count ($P = 0.032$), and interleukin-2 receptor ($P = 0.045$) were significantly associated with a lengthened negative time of nucleic acid (Table 2). In total, we found a significant difference in nucleic acid time between two groups in all univariable ($P = 0.036$) (Figure 2A). Furthermore, we included all variables mentioned earlier in the multivariable analysis. After adjustment for potential confounders, we found no obvious difference in nucleic acid conversion time between ACEIs/ARBs group and CCBs group (hazard ratio [HR]: 0.70; 95% confidence interval [CI]: [0.97, 3.38]; $P = 0.12$) (Table 2).

3.4 Comparison of chest CT improved time between the ACEIs/ARBs and CCBs groups in all patients

Furthermore, we used the Cox proportional hazards model to investigate the effect of baseline characteristics on chest CT improved time. Although a univariable analysis indicated that clinical classification ($P = 1.70E-08$), lymphocyte count ($P = 0.019$), and uric acid ($P = 0.024$) were significantly associated with a lengthened negative time of chest CT improved (Table 3). However, we found no difference in chest CT improved time between two groups in all univariable ($P = 0.19$) (Figure 2B). Subsequently, we included all variables mentioned earlier in the multivariable analysis. After adjustment for potential confounders, we also found no obvious difference in chest CT improved time between ACEIs/ARBs group and CCBs group (HR: 0.73; 95% CI: [0.45, 1.2]; $P = 0.87$) (Table 3).

3.5 Comparison of the hospitalization time between the ACEIs/ARBs and CCBs groups in all patients

To evaluate differences among antihypertensive drugs on the outcome measures of patients diagnosed with COVID-19 combined hypertension, Cox proportional hazards model was performed to investigate these factors in the hospitalization time between ACEIs/ARBs and CCBs groups. As showed in Table 4, univariate Cox regression analysis identified six prognosis factors for hospitalization time: clinical classification ($P < 0.001$), lymphocyte count ($P = 0.012$) and interleukin-2 receptor ($P = 0.025$), lung image ($P = 0.037$), uric acid ($P = 0.045$), potassium ($P = 0.0086$) (Figure 2C). Next, multivariate Cox regression analysis was performed to determine if these variables were independently related to hospitalization time. Multivariate Cox regression analysis revealed that no obvious difference in the hos-
Hospitalization time between ACEIs/ARBs group and CCBs group (HR: 1.06; 95% CI: [0.44, 1.1]; \( P = .83 \)) (Table 4).

### 4 | DISCUSSION

During the spread of the SARS-CoV-2, some reports of data still emerging and in need of full analysis indicated that certain groups of patients are at risk of COVID-19, especially complicated with diabetes mellitus, hypertension, and coronary artery disease.\(^{14}\) Currently, hypertension patients are basically treated with blood pressure-lowering drugs, mainly including RAS blockers—ACEIs/ARBs, CCBs, \( \beta \)-blockers, diuretics. However, it has been popularized in clinical treatment that RAS blockers might increase the risk of developing a severe and fatal SARS-CoV-2 infection.\(^{15}\) Until now, the distinct effects of antihypertensives on prognosis remains unclear. The present study therefore retrospectively analyzed data from hospitalized COVID-19 patients with hypertension in a single center in Wuhan, China, to compare the difference between ACEIs/ARBs groups and CCB groups, which may provide clinical evidence on the impact of ACEIs/ARBs on the clinical course of COVID-19 infection.

Upon sufficient consideration of the relationship that ACE2 was the receptor that allowed coronavirus entry into cells, ACE2 overexpression facilitated the replication in cells that were otherwise resistant to the virus. In the RAAS, ACE2 catalyzes the conversion of angiotensin II to angiotensin 1 to 7, which acts as a vasodilator and exerts protective effects in the cardiovascular system.\(^{5}\) In animal experiments, increased expression and activity of ACE2 in various organs including the heart were found in connection with ACEIs and ARBs administration.\(^{16}\) In addition, more recent data\(^ {7}\) showing increased urinary secretion of ACE2 in hypertensive patients treated with the ARB olmesartan suggest that the upregulation of ACE2 may also occur in humans. These observations have been reiterated in the literature and on the web in recent days and the question arose whether RAAS inhibition may increase the risk of the deleterious outcome of COVID-19 through upregulation of ACE2 and increase of viral load.

Nevertheless, we analyzed the clinical characteristics of 76 essential hypertension patients with COVID-19 and then found a significant difference in nucleic acid time between two groups in all univariable \(( P = .036 \) in the univariable analysis. Specifically, compared with CCBs, we observed that clinical classification \(( P = 1.20E-08 \) ), lymphocyte count \(( P = .032 \) ), and interleukin-2 receptor \(( P = .045 \) ) were significantly associated with a lengthened negative time of nucleic acid of ACEI and ARB in univariable analysis. For further confirmation, we included all variables mentioned earlier in the

![Figure 2](image-url)
Especially if elderly hypertensive patients suffered with cardiovascular diseases, diabetes, and renal insufficiency, with the highest level of evidence with regard to mortality reduction. Given that ACEIs/ARBs increase the risk of COVID-19 associated infections, there is no direct evidence proving a causal relationship between ACE2 activity and SARS-CoV2 infection, and the theoretically associated risk of a higher susceptibility to infection. Although the possible upregulation of ACE2 by RAAS inhibition and the theoretically associated risk of a higher susceptibility to infection, there is no direct evidence proving a causal relationship between ACE2 activity and SARS-CoV2 infection, and the theoretically associated risk of a higher susceptibility to infection.

### TABLE 3 Univariate and multivariate Cox regression analysis for chest CT improved time

| Characteristics                        | HR  | P value | Lower | Upper |
|----------------------------------------|-----|---------|-------|-------|
| **Univariate**                          |     |         |       |       |
| Gender                                 | 0.91| .7      | 0.57  | 1.5   |
| Age                                    | 0.99| .48     | 0.97  | 1     |
| Clinical classification                | 0.21| 1.70E-08| 0.12  | 0.34  |
| Diabetes                               | 1   | .96     | 0.6   | 2.6   |
| Coronary disease                       | 0.87| .74     | 0.39  | 1.6   |
| Temperature                            | 1.3 | .11     | 0.95  | 1.5   |
| Respiratory rate (breaths per min)     | 1   | .37     | 0.95  | 1.1   |
| Diastolic BP, mm Hg                    | 0.99| .4      | 0.97  | 1     |
| Systolic BP, mm Hg                     | 1   | .83     | 0.99  | 1     |
| Heart rate, bpm                        | 0.99| .48     | 0.98  | 1     |
| White blood cell count (<10⁹/L)        | 0.97| .56     | 0.89  | 1     |
| Lymphocyte count (>10⁹/L)              | 1.5 | .019    | 1.1   | 2.3   |
| D-dimer, mg/L                          | 0.88| .23     | 0.72  | 1.1   |
| Interleukin-6, mmol/L                  | 0.99| .24     | 0.99  | 1     |
| Interleukin-2 receptor, mmol/L         | 1   | .25     | 1     | 1     |
| Alanine aminotransferase, U/L          | 1   | .089    | 1     | 1     |
| Aspartate aminotransferase, U/L        | 1   | .36     | 0.99  | 1     |
| Lung image                             | 0.73| .38     | 0.36  | 1.6   |
| NT-ProBNP, pg/L                        | 1   | .37     | 1     | 1     |
| Creatinine, U/L                        | 1   | .86     | 0.99  | 1     |
| Urea, mmol/L                           | 0.94| .3      | 0.82  | 1.1   |
| Uric acid, mmol/L                      | 1   | .024    | 1     | 1     |
| Potassium, mmol/L                      | 1.1 | .82     | 0.65  | 2.5   |
| Sodium, mmol/L                         | 0.98| .62     | 0.9   | 1     |
| C-reactive protein, mg/L               | 0.99| .26     | 0.99  | 1     |
| CCBs vs ACEI/ARBs groups               | 0.73| .19     | 0.45  | 0.97  |

| **Multivariate**                        |     |         |       |       |
| Clinical classification                | 0.21| 11706   | 4.74E-08|
| Lymphocyte count (>10⁹/L)              | 1.32| 8439    | .0942  |
| Uric acid, mmol/L                      | 1.00| 3377    | .0209  |
| CCBs vs ACEI/ARBs groups               | 0.96| 2869    | .8792  |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CI, confidence interval; CT, computed tomography; HR, hazard ratio.

Our study has several limitations. First, only 76 patients with confirmed COVID-19 were included, and a larger cohort study is needed to verify our conclusions. Second, as a retrospective study, some other specific information regarding cardiovascular complications such as echocardiography were not presented in the study because the data were incomplete owing to the limited conditions in the isolation ward and the urgency of containing the COVID-19 epidemic. Third, we did not observe mild cases who were treated at home. Four, we did not observe who changed past usage of ACEIs/ARBs medication at home to CCBs in hospital.

### 4.1 Limitations
TABLE 4 Univariate and multivariate Cox regression analysis for the hospitalization time

| Characteristics                  | ID  | HR  | P value | 95% CL Lower | 95% CL Upper |
|----------------------------------|-----|-----|---------|--------------|--------------|
| Univariate                       |     |     |         |              |              |
| Gender                           | 0.83| .44 | 0.52    | 1.3          |              |
| Age                              | 0.98| .17 | 0.95    | 1            |              |
| Clinical classification          | 0.13| 3.40E-11 | 0.072 | 0.24        |              |
| Diabetes                         | 1.4 | .16 | 0.86    | 2.4          |              |
| Coronary disease                 | 1.1 | .8  | 0.52    | 2.3          |              |
| Temperature                      | 1.2 | .3  | 0.87    | 1.6          |              |
| Respiratory rate (breaths per min) | 0.97| .54 | 0.88    | 1.1          |              |
| Diastolic BP, mm Hg              | 1   | .21 | 0.99    | 1            |              |
| Systolic BP, mm Hg               | 1   | .29 | 0.99    | 1            |              |
| Heart rate, bpm                  | 1   | .91 | 0.98    | 1            |              |
| White blood cell count (×10^9/L) | 0.96| .32 | 0.87    | 1            |              |
| Lymphocyte count (×10^9/L)       | 1.7 | .012| 1.1     | 2.4          |              |
| D-dimer, mg/L                    | 0.93| .47 | 0.77    | 1.1          |              |
| Interleukin-6, mmol/L            | 1   | .64 | 0.99    | 1            |              |
| Interleukin-2 receptor, mmol/L   | 1   | .025| 1       | 1            |              |
| Alanine aminotransferase, U/L    | 1   | .33 | 0.99    | 1            |              |
| Aspartate aminotransferase, U/L  | 1   | .84 | 0.98    | 1            |              |
| Lung image                       | 0.47| .037| 0.23    | 0.95         |              |
| NT-ProBNP, pg/L                  | 1   | .86 | 1       | 1            |              |
| Creatinine, U/L                  | 1   | .68 | 0.99    | 1            |              |
| Urea, mmol/L                     | 0.92| .19 | 0.81    | 1            |              |
| Uric acid, mmol/L                | 1   | .045| 1       | 1            |              |
| Potassium, mmol/L                | 2   | .0086| 1.2     | 3.3          |              |
| Sodium, mmol/L                   | 0.95| .19 | 0.88    | 1            |              |
| C-reactive protein, mg/L         | 0.99| .066| 0.98    | 1            |              |
| CCBs vs ACEI/ARBs groups         | 0.7 | .13 | 0.44    | 1.1          |              |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio.

4.2 Conclusion

Here, the current analysis shows that as compared with CCBs, ACEIs/ARBs did not increase the risk of extended course and poor prognosis of hypertension patients with COVID-19. However, long-term observation and prospective study design on the difference between the ACEIs/ARBs and non-ACEIs/ARBs are needed.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

JL and DL conceived and designed the study. YL, SY, and XB collected clinical cases. KC performed statistical analysis and XL wrote the paper. JL, DL, and XL reviewed and edited the manuscript. All authors read and approved the manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

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

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