Calcium channel blockers improve prognosis of patients with coronavirus disease 2019 and hypertension

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Abstract

Background: Hypertension is considered an important risk factor for the coronavirus disease 2019 (COVID-19). The commonly anti-hypertensive drugs are the renin-angiotensin-aldosterone system (RAAS) inhibitors, calcium channel blockers (CCBs), and beta-blockers. The association between commonly used anti-hypertensive medications and the clinical outcome of COVID-19 patients with hypertension has not been well studied.

Methods: We conducted a retrospective cohort study that included all patients admitted with COVID-19 to Huo Shen Shan Hospital and Guanggu District of the Maternal and Child Health Hospital of Hubei Province, Wuhan, China. Clinical and laboratory characteristics were extracted from electronic medical records. Hypertension and anti-hypertensive treatment were confirmed by medical history and clinical records. The primary clinical endpoint was all-cause mortality. Secondary endpoints included the rates of patients in common wards transferred to the intensive care unit and hospital stay duration. Logistic regression was used to explore the risk factors associated with mortality and prognosis. Propensity score matching was used to balance the confounders between different anti-hypertensive treatments. Kaplan-Meier curves were used to compare the cumulative recovery rate. Log-rank tests were performed to test for differences in Kaplan-Meier curves between different groups.

Results: Among 4569 hospitalized patients with COVID-19, 31.7% (1449/4569) had a history of hypertension. There were significant differences in mortality rates between hypertensive patients with CCBs (7/359) and those without (21/359) (1.95% vs. 5.85%, risk ratio [RR]: 0.32, 95% confidence interval [CI]: 0.13–0.76, χ² = 7.61, P = 0.0058). After matching for confounders, the mortality rates were similar between the RAAS inhibitor (4/236) and non-RAAS inhibitor (9/236) cohorts (1.69% vs. 3.81%, RR: 0.43, 95% CI: 0.13–1.43, χ² = 1.98, P = 0.1596). Hypertensive patients with beta-blockers (13/340) showed no statistical difference in mortality compared with those without (11/340) (3.82% vs. 3.24%, RR: 1.19, 95% CI: 0.53–2.69, χ² = 0.17, P = 0.6777).

Conclusions: In our study, we did not find any positive or negative effects of RAAS inhibitors or beta-blockers in COVID-19 patients with hypertension, while CCBs could improve prognosis.

Keywords: Calcium channel blockers; COVID-19; Hypertension; Renin-angiotensin-aldosterone system inhibitors; Anti-hypertensive medication; Mortality

Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide and has caused a global public health crisis.[1-3] Hypertension is considered to be the most prevalent comorbidity among COVID-19 patients. An early study conducted in China reported a comorbidity rate of 16.9% among 1590 COVID-19 patients between December 11, 2019, and January 31, 2020.[4] In addition, previous research found that COVID-19 patients with hypertension had more severe secondary infections, cardiac and renal dysfunction on admission, and were more likely to be classified as critically ill than those without hypertension.[5] Hypertension may be an independent prognostic risk factor in COVID-19 patients.

The drugs most commonly used to treat hypertension are the renin-angiotensin-aldosterone system (RAAS) inhibitors, calcium channel blockers (CCBs), and beta-blockers.[6] Theoretical studies on the association between anti-hypertensive drugs and SARS-CoV-2 are ongoing. Since 1984, it has been known that verapamil, a CCB, inhibits influenza A virus infection.[7] Furthermore, CCBs have also been effective against other viruses, including the influenza virus, respiratory syncytial virus, and rhinovirus.[8,9] The mechanism of action of CCBs in COVID-19 is not well understood.

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against several emerging viruses, including dengue fever, Zika virus, and hemorrhagic fever arenavirus infection. Angiotensin-converting enzyme 2 (ACE2) was confirmed to be crucial for the viral entry of SARS-CoV-2.\textsuperscript{[10]} Li \textit{et al.}\textsuperscript{[11]} found that 24 h after COVID-19 infection, the expression of ACE2 increased. Persistently elevated ACE2 expression has been observed after 48 h indicating the critical role of ACE2, not only in viral susceptibility but also post-infectious regulation. Their results also showed that the high expression of ACE2 increased the expression of genes involved in viral replication. Several studies have shown that treatment with RAAS inhibitors, such as ACE inhibitors (ACEIs) or angiotensin II AT1 receptor blockers (ARBs), may increase the expression of ACE2 receptors in human subjects\textsuperscript{[12]} and animal models.\textsuperscript{[13]} Consequently, this may enhance the ability of the virus to enter the host cells.

COVID-19 patients experience pneumonia, and patients with severe disease have complications such as acute respiratory distress syndrome (ARDS), respiratory failure, and septic shock with a high mortality rate.\textsuperscript{[14]} Recent studies demonstrated that beta-blockers could reduce mortality in septic shock patients.\textsuperscript{[15]} Beta-blockers also have beneficial effects on ARDS and respiratory failure patients.\textsuperscript{[16]} Patients with COVID-19 exhibit lymphopenia and high cytokine levels (such as interleukin [IL]-6, IL-1β, and tumor necrosis factor [TNF]), which can be considered as potential biomarkers for disease progression.\textsuperscript{[17]} Beta-blockers were found to be competent in inhibiting inflammatory cytokines, including IL-1β, IL-6, TNF-α in a series of experiments.\textsuperscript{[18-20]} In addition, previous studies found that beta-adrenergic blockers can reduce the activity of both arms of the RAAS pathway through its negative regulation of juxtaglomerular cells in the kidney, thereby decreasing ACE2 levels.\textsuperscript{[21]} Thus, beta-blockers may decrease SARS-CoV-2 virus entry into the host cell.

Since anti-hypertensive drugs have received an increasing amount of attention, evidence about the effect of these medications in patients with COVID-19 is urgently needed. However, the results of previous studies were mainly based on a small sample size. In this study, we carried out a large sample study to examine the clinical prognosis of COVID-19 patients with or without hypertension. We evaluated the association between anti-hypertensive drugs and the clinical outcomes of patients with COVID-19.

\section*{Methods}

\subsection*{Ethical approval}

The study was approved by the Ethical Committee of Navy Medical University. In order to protect the privacy of the individuals, any information about the patients is de-identified, without individual patient identifiers. Owing to the fact that this de-identified nature, the written informed consents are waived by our institution.

\subsection*{Study design and patient selection}

We conducted a retrospective cohort study using de-identified patient data from two military-run field hospitals for treating COVID-19 patients, Huo Shen Shan Hospital and Guanggu District of the Maternal and Child Health Hospital of Hubei Province, Wuhan, China. All data of confirmed COVID-19 patients with and without hypertension who were admitted between February 5 and April 15, 2020, were retrieved. All included patients were diagnosed with COVID-19, according to the Diagnosis and Treatment of Novel Coronavirus Pneumonia (fifth edition) guidelines published by the National Health Commission of China.\textsuperscript{[22]} The diagnosis of hypertensive patients was based on a clear medical history of hypertension, with systolic blood pressure ≥140 mmHg (1 mmHg = 0.133 kPa) or diastolic blood pressure ≥90 mmHg.\textsuperscript{[23]} The exclusion criteria included patients with repeated admissions and those with incomplete medical records (Figure 1).

\subsection*{Data collection}

Demographic characteristics, pertinent clinical features, laboratory test data on admission, complications, medications for hypertension, treatment for COVID-19, other comorbidities, and date of discharge or death were extracted. Total hospital length of stay was also recorded. Data were extracted using the hospital information systems of the two hospitals. All data were retrieved and checked independently by two investigators. Discrepancies were resolved after a consensus was reached between the investigators.

\subsection*{Clinical endpoints}

The primary clinical endpoint was all-cause mortality. Secondary endpoints included the rates of patients in common wards transferred to the intensive care unit (ICU) and hospital stay duration.

\subsection*{Propensity score-matching analysis}

Propensity score-matching analysis was used to balance the covariates between different cohorts. When comparing the outcome of specific anti-hypertensive medications, clinical characteristics (age, sex, temperature, respiratory, and pulse), comorbidities (diabetes, cancer, kidney disease, and chronic obstructive pulmonary disease), treatment (antiviral, antibacterial, antifungal, immunoglobulin, glucocorticoid, and plasma), and other anti-hypertensive medications were matched between different cohorts. A logistic model was used to calculate propensity score including all covariates. The matching ratio was 1:1 for different cohorts. The nearest neighbor matching algorithm was used with a caliper size of 0.05 based on the propensity scores for all matched pairs. The balance between covariates was evaluated by estimating standardized mean differences before and after matching. Only those with small absolute values of <0.1 were considered qualified.

\subsection*{Statistical analysis}

Continuous variables with normal distribution are represented as mean and standard deviation, and those with a skewed distribution are represented as median and...
interquartile range. Categorical variables are presented as counts and percentages. Chi-square tests or Fisher exact tests were used to compare the frequencies of categorical variables, and the independent Student’s t test or Mann-Whitney U test was used to compare the means of two continuous data. Kaplan-Meier curves were used to compare the cumulative recovery rate. Log-rank tests were performed to test for differences in Kaplan-Meier curves between different groups. Logistic regression was applied to determine the potential risk factors associated with all-cause mortality in COVID-19 patients with hypertension, and the results are reported as odds ratios and 95% confidence intervals. R 4.0.2 (R Foundation, Vienna, Austria) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA) were used for the statistical analysis. \( P < 0.05 \) were considered as statistically significant.

Result

Use of CCBs may be associated with a better prognosis in COVID-19 patients with hypertension

In total, 1078 patients (74.40%) had CCBs among the COVID-19 patients with hypertension (CCBs group), and 371 patients (25.60%) did not have CCBs (non-CCBs group). After propensity score matching, 359 patients from the CCBs group were matched with 359 patients from the non-CCBs group. As shown in Table 1, all the covariates between the two groups are balanced after matching [Figure 2A]. The results revealed that the CCBs group had lower mortality (1.95% vs. 5.85%, \( \chi^2 = 7.61, P = 0.0058 \)) and longer hospitalization days (median, 16 vs. 13 days, \( Z = -4.59, P < 0.0001 \)) than the non-CCBs group. All data are shown in Table 2. The Kaplan-Meier curves revealed that the CCBs group had a higher cumulative curative rate than non-CCBs group (\( \chi^2 = 16.03, P < 0.0001 \)) [Figure 3A].

Hypertension patients with or without RAAS inhibitors had a similar prognosis

Among the 1449 COVID-19 patients with hypertension, 259 patients (17.87%) were administered RAAS inhibitors (RAAS inhibitors group), and 1190 patients (82.13%) were prescribed other anti-hypertensive drugs (non-RAAS inhibitors group) according to their clinical records. In the propensity score matching analysis, we matched 236 patients from the RAAS inhibitor group with 236 patients from the non-RAAS inhibitor group. Clinical characteristics, comorbidities, and treatment were balanced after matching [Supplementary Table 1, http://links.lww.com/CM9/A536], and all the covariates between the two groups are balanced after matching [Figure 2B].

The RAAS inhibitors group had lower mortality (1.69% vs. 3.81%, \( \chi^2 = 1.98, P = 0.1596 \)), lower proportion of patients transferred to the ICU (1.69% vs. 3.39%, \( \chi^2 = 1.37, P = 0.2421 \)), and similar hospitalization days (median, 15 vs. 15 days, \( Z = 0.48, P = 0.6305 \)). All data are shown in Table 3. The Kaplan-Meier curves revealed no significant differences between the two groups in the cumulative recovery rate (\( \chi^2 = 0.06, P = 0.7997 \)) [Figure 3B].
Table 1: The basic clinical characteristics of hypertensive patients with or without CCBs.

| Items                        | CCBs (unmatched; n = 1078) | Non-CCBs (unmatched; n = 371) | Statistics (F/Z/x²) | P value | CCBs (matched; n = 359) | Non-CCBs (matched; n = 359) | Statistics (F/Z/x²) | P value |
|------------------------------|-----------------------------|--------------------------------|---------------------|---------|------------------------|-----------------------------|---------------------|---------|
| General condition            |                             |                                |                     |         |                        |                             |                     |         |
| Age, years                   | 66 (59, 73)                 | 65 (57, 72)                    | -1.88* 0.0596       | 0.0668  |                        |                             |                     |         |
| Male                         | 504 (46.75)                 | 199 (53.64)                    | 3.24* 0.0221        | 0.0481  | 182 (50.70)            | 188 (53.72)                 | 0.0281  | 0.9159  |
| Temperature, degree centigrade| 36.5 (36.3, 36.7)           | 36.5 (36.3, 36.7)              | 0.27* 0.7699        | 0.3614  |                        |                             |                     |         |
| Respiratory rate, breaths per min | 20.0 (19.0, 20.0)   | 20.0 (19.0, 20.0)              | 0.22* 0.8229        | 0.2819  |                        |                             |                     |         |
| Pulse rate, per min          | 84.0 (78.0, 94.0)           | 85.0 (78.0, 96.0)              | 0.88* 0.3789        | 0.3839  | 85.0 (78.0, 96.0)      | 85.0 (78.0, 96.0)            | 0.3517  | 0.7231  |
| Disease severity             |                             |                                |                     |         |                        |                             |                     |         |
| Mild type                    | 34 (3.15)                   | 8 (2.16)                       |                     |         |                        |                             |                     |         |
| Ordinary type                | 757 (70.22)                 | 262 (70.62)                    |                     |         |                        |                             |                     |         |
| Severe type                  | 254 (23.56)                 | 83 (22.37)                     |                     |         |                        |                             |                     |         |
| Critical type                | 33 (3.06)                   | 18 (4.85)                      |                     |         |                        |                             |                     |         |
| Blood pressure, mmHg         |                             |                                |                     |         |                        |                             |                     |         |
| Systolic                     | 138.0 (126.0, 150.0)        | 134.0 (124.0, 147.0)           | -3.03* 0.0025       | 0.0519  | 135.0 (124.0, 145.0)   | 134.0 (124.0, 147.0)         | 0.0414  | 0.9653  |
| Diastolic                    | 83.0 (76.0, 91.0)           | 81.0 (74.0, 90.0)              | -2.70* 0.0069       | 0.0097  | 80.0 (76.0, 90.0)      | 82.0 (75.0, 90.0)            | 0.1821  | 0.8554  |
| Medical history              |                             |                                |                     |         |                        |                             |                     |         |
| Diabetes                     | 258 (23.93)                 | 98 (26.42)                     | 0.92* 0.3382        | 0.3416  |                        |                             |                     |         |
| Coronary heart disease       | 136 (12.62)                 | 60 (16.77)                     | 2.98* 0.0841        | 0.0221  |                        |                             |                     |         |
| Kidney disease               | 45 (4.17)                   | 23 (6.20)                      | 2.53* 0.1117        | 0.1179  |                        |                             |                     |         |
| COPD                         | 12 (1.11)                   | 12 (3.23)                      | 7.63* 0.0038        | 0.0212  |                        |                             |                     |         |
| Cancer                       | 10 (0.93)                   | 5 (1.35)                       | 0.15* 0.6949        | 0.4147  |                        |                             |                     |         |
| Anti-hypertensive treatment  |                             |                                |                     |         |                        |                             |                     |         |
| RAAS inhibitors              | 193 (17.90)                 | 66 (17.79)                     | 0.001 0.9607        | 0.4487  |                        |                             |                     |         |
| Beta-blockers                | 298 (27.64)                 | 79 (21.29)                     | 5.78* 0.0162        | 0.2989  |                        |                             |                     |         |
| Diuretics                    | 149 (13.82)                 | 51 (13.75)                     | 0.001 0.9711        | 0.0517  |                        |                             |                     |         |
| Others                       | 43 (3.39)                   | 18 (4.85)                      | 0.51* 0.4753        | 0.3036  |                        |                             |                     |         |
| Treatment                    |                             |                                |                     |         |                        |                             |                     |         |
| Antiviral therapy            | 645 (59.83)                 | 202 (54.45)                    | 3.30* 0.0694        | 0.0416  | 195 (54.32)            | 196 (54.60)                 | 0.0141  | 0.9403  |
| Antibacterial                | 413 (38.31)                 | 140 (37.74)                    | 0.04* 0.8439        | 0.3131  | 129 (33.93)            | 131 (36.49)                 | 0.0220  | 0.8766  |
| Antifungal                   | 15 (1.39)                   | 5 (1.35)                       | 0.00* 0.9503        | 0.6148  | 5 (1.39)               | 5 (1.39)                    | 0.7373  |         |
| Immunoglobulin               | 220 (20.41)                 | 65 (17.52)                     | 1.46* 0.2274        | 0.1520  | 66 (18.38)             | 62 (17.27)                  | 0.0696  |         |
| Glucocorticoid               | 163 (15.12)                 | 53 (14.29)                     | 0.15* 0.4969        | 0.4000  | 56 (15.60)             | 50 (13.93)                  | 0.3279  |         |
| Plasma                       | 16 (1.09)                   | 0 (0.00)                       | 0.00* 0.5573        | 1.0000  | 0 (0.00)               | 0 (0.00)                    | 0.0000  |         |

Data are presented as median (interquartile range) or n (%). *Z-statistics; †x²-statistics; ‡F-statistics. CCBs: Calcium channel blockers; COPD: Chronic obstructive pulmonary disease; RAAS: Renin-angiotensin-aldosterone system.

Figure 2: The covariate balance analysis. (A) The covariate balance between two groups, one is hypertensive patients with CCBs in COVID-19 patients, another is without CCBs. (B) The covariate balance between two groups, one is hypertensive patients with RAAS Inhibitors in COVID-19 patients, another is without RAAS Inhibitors. (C) The covariate balance between two groups, one is hypertensive patients with beta-blockers in COVID-19 patients, another is without beta-blockers. CCBs: Calcium channel blockers; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; DBP: Diastolic blood pressure; RAAS: Renin-angiotensin-aldosterone system.
Hypertension patients with or without beta-blockers had a similar prognosis

Among the 1449 COVID-19 patients with hypertension, 377 patients (26.02%) had beta-blockers (beta-blocker group), and 1072 patients (73.98%) did not have beta-blockers (non-beta-blocker group). In the propensity score matching analysis, we matched 340 patients from the beta-blocker group with 340 patients from the non-beta-blocker group at a ratio of 1:1. Clinical characteristics, comorbidities, and treatment are balanced after matching [Supplementary Table 2, http://links.lww.com/CM9/A536]; all the covariates between the two groups are balanced after matching [Figure 2C].

The beta-blocker group had higher mortality (3.82% vs. 3.24%, \( \chi^2 = 0.17, P = 0.6777 \)), higher proportion of patients transferred to the ICU (4.41% vs. 2.35%, \( \chi^2 = 2.32, P = 0.1376 \)) than the non-beta-blocker group, and similar hospitalization days (median, 16 vs. 15 days, \( Z = -0.89, P = 0.3740 \)). All data are shown in Table 4. The Kaplan-Meier curves revealed no significant differences between the two groups in the cumulative recovery rate (\( \chi^2 = 2.36, P = 0.1248 \)) [Figure 3C].

Comparison of characteristics between hypertension patients who survived and those who died

To further explore the potential risk factors for mortality in COVID-19 patients with hypertension, we performed multivariable logistic regression analysis with the stepwise regression method to explore the predictors of death. The results are shown in Table 5. Age, disease severity, medical history of kidney disease, and use of CCBs, antibacterial therapy, antifungal therapy, and glucocorticoid therapy were statistically significant. It is worth noting that whether these relationships are causal is unknown.

Discussion

Our study evaluated the effect of anti-hypertensive medications on the prognosis and clinical outcome of COVID-19 patients with hypertension. We demonstrated that after propensity score-matching analysis, CCBs were associated with lower all-cause mortality, while RAAS inhibitors and beta-blockers had no apparent effect on the main clinical outcomes.

From the pathophysiologic perspective, the protective effect of CCBs should be considered. Viruses use the host

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**Table 2: The clinical outcomes of hypertensive patients with or without CCBs in COVID-19 patients.**

| Clinical outcome | CCBs (\( n = 1078 \) for unmatched; \( n = 359 \) for matched) | Non-CCBs (\( n = 371 \) for unmatched; \( n = 359 \) for matched) | RR (95% CI) | Statistics (\( Z/\chi^2 \)) | \( P \) value |
|------------------|--------------------------------------------------|--------------------------------------------------|-------------|------------------------|------------|
| Death, \( n \) (%)  |
| Unmatched        | 25 (2.23)                                       | 23 (6.20)                                       | 0.36 (0.20–0.64) | 12.98\(^5\)     | 0.0003     |
| Matched          | 7 (1.95)                                        | 21 (5.85)                                       | 0.32 (0.13–0.76) | 7.61\(^1\)      | 0.0058     |
| Transfer to ICU, \( n \) (%)  |
| Unmatched        | 27 (2.50)                                       | 15 (4.04)                                       | 0.61 (0.32–1.16) | 2.32\(^7\)      | 0.1276     |
| Matched          | 6 (1.67)                                        | 14 (3.90)                                       | 0.42 (0.16–1.10) | 3.38\(^8\)      | 0.0696     |
| Time after admission, days, median (IQR)  |
| Unmatched        | 15 (10, 21)                                     | 13 (8, 18)                                      | NA          | -6.21\(^7\)     | <0.0001    |
| Matched          | 16 (10, 21)                                     | 13 (8, 18)                                      | NA          | -4.59\(^7\)     | <0.0001    |

\( ^5 \chi^2 \)-statistics; \(^7 Z \)-statistics. CCBs: Calcium channel blockers; CI: Confidence interval; ICU: Intensive care unit; IQR: Interquartile range; NA: Not applicable; RR: Risk ratio.

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**Figure 3:** Kaplan-Meier curves for patients. (A) The cumulative recovery rates of two matched-groups, one is hypertensive patients with CCBs in COVID-19 patients (red), another is without CCBs (blue). (B) The cumulative recovery rates of two matched-groups, one is hypertensive patients with RAAS inhibitors in COVID-19 patients (red), another is without RAAS inhibitors (blue). (C) The cumulative recovery rates of two-matched groups, one is hypertensive patients with beta-blockers in COVID-19 patients (red), another is without beta-blockers (blue). CCBs: Calcium channel blockers; COVID-19: Coronavirus disease 2019; RAAS: Renin-angiotensin-aldosterone system.
cell environment to replicate, thereby causing host cell dysfunction. Virus-host interaction is a key to disease pathogenesis and is closely related to disease severity and incidence. Regulations of the intracellular environment have become an important strategy in antiviral drug development. Calcium ion (Ca^{2+}) is an important second messenger in mammalian cells involved in the mediation of the sensor input and response output for almost every known cellular processes, such as stress responses, synaptic plasticity, immune defenses, protein transport, and endosome formation.\(^{[24,25]}\) It has been proven that host cell dysfunction following viral infection is accompanied by abnormal intracellular Ca^{2+} concentration.\(^{[26]}\) The virus can influence the host intracellular Ca^{2+} system to achieve replication via multiple paths, while previous research suggested that Ca^{2+} plays an important role in virion structure formation, virus entry, viral gene expression, post-translational processing of viral proteins, and virion maturation and release.\(^{[27]}\)

A recent study on the fusion peptide (FP) of SARS-CoV showed that the FP region began immediately from downstream of the S2 cleavage site and could be separated into two distinct domains, FP1 and FP2.\(^{[28]}\) FP1 and FP2 together form an extended FP that acts as a bipartite fusion platform. Both FP subdomains require Ca^{2+} to influence

### Table 3: Clinical outcomes of hypertensive patients with or without RAAS inhibitors in COVID-19 patients.

| Clinical outcome | RAAS inhibitors (n=259 for unmatched; n=359 for matched) | Non-RAAS-inhibitors (n=1190 for unmatched; n=359 for matched) | RR (95% CI) | Statistics (Z/\(\chi^2\)) | P value |
|-----------------|----------------------------------------------------------|---------------------------------------------------------------|-------------|-----------------------------|---------|
| Death, n (%)    |                                                          |                                                               |             |                             |         |
| Unmatched       | 6 (2.32)                                                 | 42 (3.53)                                                     | 0.65 (0.27–1.54) | 0.98\(^*\)                   | 0.3230  |
| Matched         | 4 (1.69)                                                 | 9 (3.81)                                                      | 0.43 (0.13–1.43) | 1.98\(^*\)                   | 0.1596  |
| Transfer to ICU, n (%) |                                                          |                                                               |             |                             |         |
| Unmatched       | 7 (2.70)                                                 | 35 (2.94)                                                     | 0.92 (0.40–2.09) | 0.04\(^*\)                   | 0.8358  |
| Matched         | 4 (1.69)                                                 | 8 (3.39)                                                      | 0.49 (0.15–1.66) | 1.37\(^*\)                   | 0.2421  |
| Times after admission, days, median (IQR) |                                                          |                                                               |             |                             |         |
| Unmatched       | 16 (10, 20)                                              | 14 (10, 20)                                                   | NA          | 1.93\(^*\)                   | 0.0536  |
| Matched         | 15 (10, 20)                                              | 15 (10, 20)                                                   | NA          | 0.48\(^*\)                   | 0.6305  |

\(*\chi^2\)-statistics; \(\chi^2\)-statistics. CI: Confidence interval; ICU: Intensive care unit; IQR: Interquartile range; NA: Not applicable; RAAS: Renin-angiotensin-aldosterone system; RR: Risk ratio.

### Table 4: Clinical outcomes of hypertensive patients with or without beta-blockers in COVID-19 patients.

| Clinical outcome | Beta-blockers (n=377 for unmatched; n=340 for matched) | Non-beta-blockers (n=1072 for unmatched; n=359 for matched) | RR (95% CI) | Statistics (Z/\(\chi^2\)) | P value |
|-----------------|---------------------------------------------------------|--------------------------------------------------------------|-------------|-----------------------------|---------|
| Death, n (%)    |                                                          |                                                               |             |                             |         |
| Unmatched       | 25 (6.63)                                                | 23 (2.15)                                                     | 3.24 (1.82–5.78) | 17.52\(^*\)                 | <0.0001 |
| Matched         | 13 (3.82)                                                | 11 (3.24)                                                     | 1.19 (0.53–2.69) | 0.17\(^*\)                   | 0.6777  |
| Transfer to ICU, n (%) |                                                          |                                                               |             |                             |         |
| Unmatched       | 24 (6.37)                                                | 18 (1.68)                                                     | 3.98 (2.14–7.42) | 21.77\(^*\)                 | <0.0001 |
| Matched         | 15 (4.41)                                                | 8 (2.35)                                                      | 1.92 (0.80–4.58) | 2.21\(^*\)                   | 0.1376  |
| Times after admission, days, median (IQR) |                                                          |                                                               |             |                             |         |
| Unmatched       | 16 (10, 22)                                              | 14 (10, 20)                                                   | NA          | 3.21\(^*\)                   | <0.0001 |
| Matched         | 16 (10, 21)                                              | 15 (10, 20.5)                                                 | NA          | −0.89\(^*\)                  | 0.3740  |

\(*\chi^2\)-statistics; \(\chi^2\)-statistics. CI: Confidence interval; ICU: Intensive care unit; IQR: Interquartile range; NA: Not applicable; RR: Risk ratio.

### Table 5: Logistic regression analysis on the risk factors associated with mortality in COVID-19 patients with hypertension.

| Factors           | Wald \(\chi^2\) | OR (95% CI) | P value |
|-------------------|-----------------|-------------|---------|
| Age               | 7.78            | 2.54 (1.22–5.31) | 0.0131  |
| Severity          | 13.76           | 3.04 (1.73–5.32) | 0.0001  |
| Kidney disease    | 6.35            | 4.41 (1.61–12.07) | 0.0040  |
| CCBs              | 16.24           | 0.20 (0.09–0.46) | <0.0001 |
| Antibacterial therapy | 7.13          | 17.77 (2.30–137.47) | 0.0058  |
| Antifungal therapy | 10.41           | 6.70 (1.99–25.58) | 0.0022  |
| Glucocorticoid therapy | 21.68         | 8.61 (3.41–21.74) | <0.0001 |

CI: Confidence interval; CCBs: Calcium channel blockers; OR: Odds ratio.
their function in membrane entry and fusion. Straus et al. also found that consumption of extracellular and intracellular Ca²⁺ pools resulted in obviously reduced infectivity of SARS-CoV pseudo-particles, indicating that Ca²⁺ could regulate both the plasma membrane and endosomal cell entry pathways. Furthermore, the genome sequences of SARS-CoV-2 were demonstrated to share a 79.6% sequence identity to SARS-CoV. In addition, Ca²⁺ may play a similar role in the effect on human bodies caused by SARS-CoV-2. Furthermore, the genome sequences of SARS-CoV-2 were demonstrated to share a 79.6% sequence identity to SARS-CoV. In addition, Ca²⁺ may play a similar role in the effect on human bodies caused by SARS-CoV-2.

Zhang et al. retrospectively analyzed the medical record of 487 adult COVID-19 patients with hypertension. A beneficial effect in reducing mortality was observed in patients receiving CCB (amlodipine besylate). In addition, in one multicenter study involving 39 hospitals, after using natural language processing, CCBs can effectively decrease all-cause mortality in patients with COVID-19 and hypertension.

These results are consistent with that of our study. Previous studies have reported that the RAAS inhibitors could increase ACE2 receptor expression in the body, which may enhance the viral entry. Meanwhile, ACE2 enzyme activity may have a positive effect on cardiovascular disease. Experiments indicated that ACEI/ARBs could play a protective role by activating the ACE2/angiotensin1-7/Mas axis, which may be associated with rising ACE2 levels in the body. Our studies show RAAS inhibitors have no discernible effect on prognosis.

Prior studies have shown that beta-blockers may improve clinical outcomes of patients with COVID-19 by suppressing inflammatory factors and the expression of ACE2 receptor. However, in our study, beta-blockers did not significantly affect prognosis.

There are several limitations to this study. First, although our study adjusted for multiple confounding factors, other confounders, such as body mass index and arterial blood gas analysis, could affect our results. These data were not recorded in detail in the study owing to the admission status of patients and the urgency of limiting COVID-19 transmission. Second, multiple logistic regression analysis was performed in an attempt to estimate the propensity score and examine the risk factors for all-cause mortality in COVID-19 patients with hypertension. However, the usual deficiency of similar studies exists, such as the inability to include all relevant confounders. Third, because of the statistical power, we did not take the interaction between different kinds of anti-hypertensive medications into consideration. Fourth, part of the sample size was lost after propensity score matching when comparing different anti-hypertensive medications, which may cause bias. Last, considering the nature of such retrospective studies, these results should be interpreted with caution, and further prospective studies are required to validate our results.

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Conflicts of interest

None.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–1242. doi: 10.1001/jama.2020.2648.
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565–574. doi: 10.1016/s0140-6736(20)30251-8.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–733. doi: 10.1056/NEJMoa2001017.
4. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55:2000547. doi: 10.1183/13993003.00547-2020.
5. Pan W, Zhang J, Wang M, Ye J, Xu Y, Shen B, et al. Clinical features of COVID-19 in patients with essential hypertension and the impacts of renin-angiotensin-aldosterone system inhibitors on the prognosis of COVID-19 patients. Hypertension 2020;76:732–741. doi: 10.1161/hypertensionaha.120.15289.
6. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2018;138:e426–e493. doi: 10.1161/CIR.0000000000000597.
7. Nugent KM, Stanley JD. Verapamil inhibits influenza A virus replication. Arch Virol 1984;81:163–170. doi: 10.1007/bf01309305.
8. Lavanya M, Cuevas CD, Thomas M, Cherry S, Ross SR. sRNA screen for genes that affect Junin virus entry uncovers voltage-gated calcium channels as a therapeutic target. Sci Transl Med 2013;5:204ra131. doi: 10.1126/scitranslmed.3006827.
9. Doñate-Macián P, Jungflesch J, Pérez-Vilaró G, Rubio-Moscardo F, Perálvarez-Marín A, Díez J, et al. The TRPV4 channel links calcium influx to DDX3X activity and viral infectivity. Nat Commun 2018;9:2307. doi: 10.1038/s41467-018-04776-7.
10. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–273. doi: 10.1038/s41586-020-20127-7.

11. Li G, He X, Zhang L, Ran Q, Wang J, Xiong A, et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. J Autonommn 2020;112:102463. doi: 10.1016/j.jaut.2020.102463.

12. Vuille-dit-Bille RN, Camargo SM, Emmenegger L, Sasse T, Kummer E, Jando J, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino Acids 2015;47:693–705. doi: 10.1007/s00726-014-1889-6.

13. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2003;111:2605–2610. doi: 10.1161/circulationaha.104.510461.

14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–1062. doi: 10.1016/s0140-6736(20)30566-3.

15. Tan K, Harazim M, Tang B, McLean A, Nalos M. The association between preambirol beta blocker exposure and mortality in sepsis-a systematic review. Crit Care 2019;23:298. doi: 10.1186/s13054-019-2362-y.

16. Noveau M, Breidhardt T, Reichlin T, Gayat E, Potocki M, Pargger H, et al. Effect of oral f β-blocker on short and long-term mortality in patients with acute respiratory failure: results from the BASEL-II-ICU study. Crit Care 2010;14:R198. doi: 10.1186/cc9317.

17. Yang L, Liu S, Liu J, Zhang Z, Wu X, Huang R, et al. COVID-19: immunopathogenesis and immunotherapeutics. Signal Transduct Target Ther 2020;5:128. doi: 10.1038/s41392-020-00243-2.

18. Doo YC, Kim DM, Oh DJ, Ryu KH, Rhim CY, Lee Y. Effect of beta blockers on expression of interleukin-6 and C-reactive protein in patients with unstable angina pectoris. Am J Cardiol 2001;88:422–424. doi: 10.1016/s0002-9149(01)01693-9.

19. Deten A, Volz HC, Holzl A, Briest W, Zimmer HG. Effect of propranolol on cardiac cytokine expression after myocardial infarction in rats. Mol Cell Biochem 2005;231:127–137. doi: 10.1023/a:1025498319598.

20. Tatlı E, Kurum T, Aktoz M, Buyuk M. Effects of carvedilol on right ventricular ejection fraction and cytokines levels in patients with systolic heart failure. Int J Cardiol 2008;125:273–276. doi: 10.1016/j.ijcard.2007.07.166.

21. Vasanthakumar N. Beta-adrenergic blockers as a potential treatment for COVID-19 patients. Bioessays 2020;42:e2000394. doi: 10.1002/bies.202000394.

22. National Health Commission of China. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Fifth Edition). Available from: http://www.nhc.gov.cn/yzygj/s7653p/202002/3b9b894ac9b204a7b5b3b912d4d440e8a77260301a39384c87e876d52963ec08.pdf. Accessed February 5, 2020.

23. Flack JM, Adefola B. Blood pressure and the new ACC/AHA hypertension guidelines. Trends Cardiovasc Med 2020;30:160–164. doi: 10.1016/j.tcm.2019.05.003.

24. Martínez de Victoria E. Calcium, essential for health (in Spanish). Nutr Hosp 2016;33:341.

25. Berridge MJ, Bootman MD, Lipp P. Calcium—a life and death signal. Nature 1998;395:645–648. doi: 10.1038/27094.

26. Olivier M. Modulation of host cell intracellular Ca2+. Parasitol 2015;47:693–705.

27. Zhou Y, Frey TK, Yang J. Viral calciosics: interplays between Ca2+ and virus. Cell Calcium 2009;46:1–17. doi: 10.1016/j.ceca.2009.05.003.

28. Lai AL, Miller JK, Daniel S, Freed JH, Whittaker GR. The SARS-CoV fusion peptide forms an extended bipartite fusion platform that perturbs membrane order in a calcium-dependent manner. J Mol Biol 2017;429:3875–3892. doi: 10.1016/j.jmb.2017.10.017.

29. Straus MR, Tang T, Lai AL, Pegel A, Bidon M, Freed JH, et al. Ca(2+) ions promote fusion of Middle East respiratory syndrome coronavirus with host cells and increase infectivity. J Virol 2020;94:e00246–e00320. doi: 10.1128/jvi.00246-20.

30. Horng T. Calcium signaling and mitochondrial destabilization in the triggering of the NLRP3 inflammasome. Trends Immunol 2014;35:253–261. doi: 10.1016/j.it.2014.02.007.

31. Silva IVG, de Figueiredo RC, Dias RA. Effect of different classes of antihypertensive drugs on endothelial function and inflammation. Int J Mol Sci 2019;20:3458. doi: 10.3390/ijms20143458.

32. Zhang LK, Sun Y, Zeng H, Wang Q, Jiang X, Shang WJ, et al. COVID-19: Ca2+ homeostasis and virus. Cell Calcium 2009;46:1–17. doi: 10.1016/j.ceca.2009.05.003.

33. Neuraz A, Lerner I, Digan W, Paris N, Tsopra R, Rogier A, et al. Natural language processing for rapid response to emergent diseases: case study of calcium channel blockers and hypertension in the COVID-19 pandemic. J Med Internet Res 2020;22:e20773. doi: 10.2196/20773.

34. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension 2004;43:970–976. doi: 10.1161/01.HYP.0000124667.34632.1a.

35. Carey RM. Angiotensin type-1 receptor blockade increases ACE 2 expression in the heart. Hypertension 2004;43:943–944. doi: 10.1161/01.HYP.0000124669.02394.72.

36. Gallagher PE, Ferrario CM, Tallant EA. Regulation of ACE2 in cardiac myocytes and fibroblasts. Am J Physiol Heart Circ Physiol 2008;295:H2373–H2379. doi: 10.1152/ajpheart.00426.2008.

37. Callera GE, Antunes TT, Correa JW, Moorman D, Gutsol A, He Y, et al. Differential renal effects of candesartan at high and ultra-high doses in diabetic mice-potent role of the ACE2/AT2R/Mas axis. Biosci Rep 2016;36:e00398. doi: 10.1042/bsr20160344.

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