Effects of angiotensin receptor blockers (ARBs) on in-hospital outcomes of patients with hypertension and confirmed or clinically suspected COVID-19

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Abstract

Background: There is an ongoing controversy about harms and benefits of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in hypertensive patients with coronavirus disease 2019 (COVID-19). Given the unresolved debate, we investigated the association of ARBs with in-hospital outcomes of these patients.

Methods: In this retrospective observational study, we studied patients with COVID-19 who referred to Sina Hospital in Tehran, Iran, from February 20 to May 29, 2020. Patients with either positive real-time reverse-transcriptase polymerase-chain-reaction test of swab specimens, or high clinical suspicion according to the World Health Organization's interim guidance were included. We followed-up patients for incurring death, severe COVID-19, and in-hospital complications.

Results: We evaluated 681 patients with COVID-19 of whom 37 patients were excluded due to incomplete medical records and 8 patients who used ACEIs which left 636 patients in the analysis. In this cohort, 108 (17.0%) patients expired and 407 (64.0%) patients incurred severe COVID-19. Of 254 (39.9%) patients with hypertension, 122 (48.0%) patients were receiving an ARB. After adjustment for possible confounders, we found no independent association between taking ARBs and in-hospital outcomes except for acute kidney injury (AKI), in patients with confirmed or clinically suspected COVID-19, either hypertensive or not-hypertensive. We found that discontinuation of ARBs during hospitalization was associated with a greater risk of mortality, invasive ventilation, and AKI (All $P<0.002$).

Conclusions: We found that taking ARBs by patients with hypertension and confirmed or clinically suspected COVID-19 is not associated with poorer in-hospital outcomes after adjustment for possible confounders.

Keywords: COVID-19; SARS-CoV-2; Angiotensin-Converting Enzyme Inhibitors; Angiotensin Receptor Antagonists; Renin-Angiotensin System; Hypertension.

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) which is a pandemic first discovered in Wuhan, China, in December 2019.[1] Up to August 14, 2020, it affected more than 21.2 million persons worldwide with more than 338 thousand confirmed cases in Iran.[2]

Given that angiotensin-converting enzyme 2 (ACE2) serves as the main receptor for SARS-CoV-2, ACE2-expressing cells are more prone to COVID-19 infection.[3,4] According to the greater mortality of COVID-19 in patients with hypertension,[5] there is an ongoing controversy about potential harms and benefits of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in patients with hypertension and COVID-19 which caused uncertainties in clinical practice.[6-9] It is a major challenge to change or continue these medications in patients with hypertension and COVID-19. Hence, the mechanistic speculations have been evaluated in some clinical studies; nonetheless, they are not conclusive. Some studies demonstrated beneficial effects of ACEI/ARBs in hypertensive patients with COVID-19 in terms of mortality and severity of the disease;[10-12] however, other ones did not find any beneficial or harmful effects.[13-16] Moreover, no study investigated the effects of these medications separately.

In this observational study, we aim to evaluate the association of ARBs with in-hospital outcomes of patients with confirmed or clinically suspected COVID-19 from a tertiary referral center in Tehran, Iran.

Methods

Ethical considerations

The protocol of this study corresponds to the 2013 Helsinki declaration and was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.018). All participants gave written informed consent before inclusion in the study.

Study design and participants

We reported this study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[17] Sina Hospital is one of the major tertiary teaching hospitals affiliated by Tehran University of Medical Sciences which is designated for treatment of COVID-19 in the capital Tehran. We

evaluated patients who were admitted to Sina Hospital from February 20 to May 29, 2020. We included patients≥18 years of age with a diagnosis of COVID-19 who met one of the following criteria: 1) Positive real-time reverse-transcriptase polymerase-chain-reaction (PCR) test of oropharyngeal or endotracheal swab specimens. 2) Highly suspicious patients according to the World Health Organization's interim guidance[18] and Iranian national committee of COVID-19,[19] including patients with ground-glass opacity, either isolated or with consolidation in chest computed tomography scan, which cannot be fully explained by volume overload, lobar or lung collapse, or nodules along with the history compatible with COVID-19. The details of patient care for individuals presenting with respiratory symptoms to Sina Hospital emergency department has been published previously.[20]

We collected demographic data, present, drug and past medical history, admission vital signs and physical examination, baseline laboratory parameters, imaging findings, and in-hospital treatments from electronic medical records. We followed-up patients for in-hospital acute respiratory distress syndrome (ARDS), invasive ventilation, acute cardiac injury (ACI), acute kidney injury (AKI), acute liver injury (ALI), multiorgan damage, the severity of the disease, and mortality. Moreover, we compared in-hospital outcomes between four groups of patients with hypertension categorized based on the history of ARB usage during hospitalization: 1) Continued: Patients who continued their ARBs at least for seven days after admission. 2) Discontinued: Patients who discontinued their ARBs within seven days after admission. 3) Newly started: Patients who were newly started on an ARB after hospitalization. 4) Never used: Patients who never used any ARB.

Definitions

Hypertension was defined as systolic blood pressure≥140 mmHg, diastolic blood pressure≥90 mmHg, or anti-hypertensive treatment. We defined diabetes mellitus (DM) in case of fasting blood sugar≥126 mg/dL on two occasions, or blood sugar≥200 mg/dL on two occasions, or treatment with oral antidiabetic agents or insulin. History of coronary artery disease (≥50% stenosis on coronary angiography), heart failure, or receiving treatment for these conditions were designated as cardiac disease. Cerebrovascular disease was defined as a history of transient ischemic attack or stroke. We defined chronic lung disease as a history of asthma, chronic obstructive pulmonary disease, or interstitial lung disease. Patients with a glomerular filtration rate<30 mL/h or the need for renal replacement therapy were designated to have chronic kidney disease. History of malignancy was defined as a history of a treated neoplasm. The systemic immune-inflammation index (SII) was calculated as (platelet count×neutrophil count)/(lymphocyte count).

ARDS was defined according to the Berlin definition criteria.[21] We defined ACI as an increased serum level of high-sensitivity cardiac troponin I (hs-cTnI) above the 99th percentile upper limit normal (ULN).[22,23] AKI was diagnosed if serum creatinine increased by≥0.3 mg/dL within 48 hours except for patients with known end-stage renal disease.[24] Serum transaminases≥3×ULN or alkaline phosphatase≥2×ULN, or total bilirubin≥2×ULN were designated as ALI.[25] Patients with at least two complications including ACI, AKI, ALI, or ARDS were considered to have multiorgan damage. We defined severe COVID-19 in the presence of at least one of the following criteria: dyspnea, respiratory rate≥30/min, oxygen saturation≤93%, >50% lung involvement on imaging, respiratory failure, shock, or multiorgan damage. The rest of the patients were categorized as non-severe COVID-19. We employed this definition similar to Wu and co-workers[26] and modified it to introduce a binary outcome, severe versus non-severe COVID-19.

Statistical analysis

We reported the data as mean±standard deviation or median [interquartile range] for continuous variables with normal or skewed distribution, respectively. Means of continuous variables were compared using independent group t-test if the data were normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were demonstrated by number (%) and compared using the chi-square test. We compared in-hospital outcomes between four groups of hypertensive patients based on the history of taking ARBs by the chi-square post-hoc test, in which we assumed P≤0.00625 as statistically significant according to the Bonferroni correction. We fitted binary logistic regression models to the data to predict in-hospital outcomes of the whole cohort and hypertensive patients based on the usage of ARBs. Moreover, we used Cox proportional hazard models for prediction of mortality to take the effect of the time into account. We employed a standard entry method to adjust these models for possible confounders. Other than age and sex, we adjusted for the comorbidities and laboratory data that were significantly (P<0.05) associated with mortality and severity, and were not missed in more than 10% of cases. Additionally, we performed a sensitivity analysis to investigate the prognostic value of ARB usage in patients with positive PCR tests. All statistical analyses were performed using IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. P≤0.05 was considered statistically significant.

Results

Baseline characteristics of patients

We evaluated 681 patients with confirmed or clinically suspected COVID-19 of whom 37 patients were excluded due to inter-hospital transfer or lack of key information in their medical records. Furthermore, we excluded 8 patients who used ACEIs to be more focused on the effects of ARBs because the number of ACEI-users was far less than the number of ARB-users. Eventually, we included 636 patients including 254 hypertensive patients in the analysis. Although all patients were highly suspicious for COVID-19 based on the national and international guidelines,[18,19] 348 (54.7%) patients underwent PCR test of whom 145 (41.7%) patients were definitely diagnosed with COVID-19. PCR test was done for 165 (65.0%) hypertensive patients of whom 67 (40.6%) specimens were positive for COVID-19. Overall, 145 (22.8%) patients in the whole cohort and 67 (26.4%) hypertensive patients were definitely diagnosed with COVID-19 based on a positive PCR test. The mean age was 57.2 years (interquartile range: 45-69 years) and 397 (62.4%) were male. The most common comorbidities in all patients were hypertension (39.9%), DM, and cardiac disease (Supplementary Table 1). In this cohort, 108 (17.0%) patients expired and 407 (64.0%) patients incurred severe COVID-19. Although the data of history, mortality, severity, ARDS, and invasive ventilation were complete and the rate of missing data for most of the laboratory data is less than 5%, we had not the data of lactate dehydrogenase (LDH), hs-cTnI, liver transaminases, and erythrocyte sedimentation rate (ESR) in 29.1%%, 27.1%, 20.8%, and 15.0% of the patients. In comparison with non-hypertensive patients, patients with hypertension were significantly older and more likely to have comorbidities except for malignancy. Furthermore, they were at increased risk of mortality, severe COVID-19, invasive ventilation, ACI, AKI, and multiorgan damage (Supplementary Table 1). Of 254 hypertensive patients, 122 (48.0%) patients were receiving an ARB (Losartan: N=105 and Valsartan: N=17). In comparison with non-ARB users, ARB users were more likely to be older, have cardiac disease, receive cardiovascular medications, have higher serum creatinine, have longer hospital length of stay, and incur AKI during hospitalization (Table 1).

Predictors of mortality and severity in hypertensive patients

In hypertensive patients, the severe form of COVID-19 was associated with lower serum sodium and higher ESR (Table 2). We found history of cerebrovascular and chronic lung diseases, history of metformin use, lower lymphocyte counts and hemoglobin, and higher white blood cells count, neutrophil count, platelet-to-lymphocyte ratio, SII and creatinine as risk factors of mortality in these patients (Table 2). Moreover, older age,

history of DM, and higher neutrophil-to-lymphocyte ratio, urea, C-reactive protein (CRP), LDH, hs-cTnI and liver transaminases were associated with increased risk of both severity and mortality of COVID-19 in hypertensive patients (Table 2).

Discontinuation of ARBs and in-hospital outcomes

During the hospitalization of hypertensive patients, 79 patients continued and 43 patients discontinued their ARBs, 36 patients were newly started on an ARB, and 96 patients never used any ARB (Table 3). The most common reason for discontinuation was the inclusion in an ongoing randomized controlled trial in Sina Hospital in which we aim to investigate the effects of ACEI/ARBs on in-hospital outcomes of patients with COVID-19. The reason for discontinuation was the inclusion in the trial in 23 (53.5%), both AKI and shock in 11 (25.6%), AKI in 6 (14.0%), and shock in 3 (7.0%) patients. There were statistically significant differences between these groups regarding mortality, invasive ventilation, and AKI (Table 3). Chi-square post-hoc analysis showed that patients who discontinued their ARBs were more likely to die (P=0.0000171), be invasively ventilated (P=0.00194), and incur AKI (P=0.000216) in comparison with the other three groups.

History of ARB usage and in-hospital outcomes

We determined the independent effects of ARB usage on in-hospital outcomes of the whole cohort and hypertensive patients by using logistic regression analysis and taking possible confounders into account (Table 4). In the all patients' model, we adjusted for age, sex, DM, hypertension, cardiac disease, cerebrovascular disease, chronic lung disease, chronic kidney disease, neutrophil-to-lymphocyte ratio, urea, and CRP. In the hypertensive patients' model, we employed age, sex, DM, cerebrovascular disease, chronic lung disease, chronic kidney disease, neutrophil-to-lymphocyte ratio, urea, and CRP as confounders. After these adjustments, we found no independent association between taking ARBs and in-hospital outcomes except for the higher incidence of AKI, in patients with confirmed or clinically suspected COVID-19, either hypertensive or not-hypertensive (Table 4). After adjustment for the same confounders in the whole cohort and hypertensive patients, Cox proportional hazard models (Figure 1 and Supplementary Table 2) revealed that taking ARBs is not associated with greater mortality either in the whole cohort (hazard ratio (HR)=1.00, 95% confidence interval (CI): 0.57-1.77; P=0.997) or hypertensive patients (HR=0.89, 95% CI: 0.51-1.54; P=0.679). In the sensitivity analysis for patients with positive PCR tests, we found similar findings except that in patients with positive PCR tests, there was no significant association between history of ARB usage and in-hospital AKI (Supplementary Table 3).

Sex disparities in in-hospital outcomes

We observed no significant difference between female and male patients, either in the whole cohort or hypertensive patients, in terms of in-hospital outcomes; however, female hypertensive patients were more likely to incur ARDS rather than male hypertensive patients (P=0.014) (Supplementary Table 4). Furthermore, ARB usage was not associated with worse clinical outcomes in men and women with confirmed or clinically suspected COVID-19 (Supplementary Tables 5 and 6).

Discussion

In this study, we found that taking ARBs in hypertensive patients with confirmed or clinically suspected COVID-19 was not associated with mortality, severity, or any other in-hospital complication except for AKI. After adjustment for possible confounders, we found that ARB usage in patients with confirmed or clinically suspected COVID-19 was not an independent risk factor for worse in-hospital outcomes but AKI. Moreover, we observed poorer outcomes in patients who discontinued their ARBs during hospitalization.

Studies have demonstrated that SARS-CoV-2 enters the cell via ACE2[3,4] which has a 40% identity and 61% similarity to ACE; however, this homology is not in their active sites which means that they are two different enzymes with different functions.[27] Thus, ACEIs do not inhibit ACE2 and cannot interfere with the entrance of SARS-CoV-2 to the cell through this mechanism.

There are two forms of ACE2 in the human body, membrane-bound ACE2 (mACE2) and soluble ACE2 (sACE2). The former exerts beneficial effects including cardioprotective effects through converting angiotensin Ⅱ to angiotensin 1-7. The latter constitutes a very small portion of the total body ACE2 which is not functional and its level is inversely correlated with mACE2.[28,29] Angiotensin Ⅱ through angiotensin Ⅱ type 1 receptor (AT_1R) and activation of ADAM17 results in cleavage of mACE2 from the membrane to produce sACE2. Although studies have shown that ARBs may upregulate mACE2 through this mechanism, this effect varies widely between different ARBs and different organs. Moreover, such an effect has not been observed by ACEIs which is attributed to the fact that this upregulation is done through blockade of AT_1Rs which is achieved by ARBs and not ACEIs.[28] Moreover, even if we accept that this upregulation happens in vivo, it is suggested to be of minimal clinical significance regarding the infectivity of SARS-CoV-2 because most of the total body ACE2 is as mACE2 and cannot vary significantly through these changes. Furthermore, the virus can enter the cell via

small amounts of ACE2.[28,29] Therefore, we may conclude that ACEI/ARBs do not facilitate virus entry and its infectivity. Additionally, it should be emphasized that some evidence shows that increased expression of ACE2 can be protective against acute lung injuries by its anti-inflammatory and anti-fibrotic effects on the lung.[3,28,30]

We found that taking ARBs is not independently associated with poorer in-hospital outcomes, except for AKI, after adjustment for confounders which is in line with several previous reports;[13-16] nevertheless, some studies suggest that ACEI/ARBs were associated with improved outcomes in COVID-19 patients.[10-12] Zhang and colleagues[11] studied 1128 hypertensive patients with COVID-19 of whom 17% were taking ACEI/ARBs and the medications were continued during hospitalization in two-thirds of them. They showed that treatment with ACEI/ARBs is associated with a remarkably lower 28-day all-cause mortality (HR=0.37, 95% CI: 0.15-0.89; P=0.03) and a borderline-significantly lower incidence rate of ARDS (HR=0.65, 95% CI: 0.41-1.04; P=0.07).[11] In contrast, we, not only, found no beneficial effects of ARBs on in-hospital outcomes, but also demonstrated remarkably greater in-hospital mortality and invasive ventilation in patients who discontinued ARBs during hospitalization which is a novel finding. These conflicting results may be attributed to the differences in sample sizes, follow-up durations, statistical approaches, and ethnicity of the patients; however, it should be noted that discontinuation is linked with poorer outcomes. Although this is an observational study with its inherent biases and we cannot generalize this finding, it supports the statement that discontinuing ARBs in COVID-19 patients can be potentially harmful.[30-33] Furthermore, there is no study implying detrimental effects of ARBs on the clinical outcomes of hypertensive patients with COVID-19. Therefore, the current debate is that if ARBs have neutral or beneficial effects on outcomes of patients with hypertension and COVID-19. Future multicenter studies, randomized controlled trials, and meta-analyses will help to respond to this question.

We found that usage of ARBs is associated with an increased risk of AKI both in the whole cohort and hypertensive patients. Furthermore, we observed that the prevalence of AKI was significantly higher in patients who discontinued their ARBs during hospitalization. These findings may be attributed to the fact that AKI can be an adverse event of ARBs. In a population-based cohort study, Mansfield and colleagues[34] demonstrated that treatment with ACEI/ARBs is associated with a 12% increased risk of AKI. Moreover, our patients must be managed with a conservative approach for fluid therapy for the treatment of ARDS which might contribute to the occurrence of AKI.[35]

We found no sex disparity in terms of in-hospital outcomes, except for the higher prevalence of ARDS in female hypertensive patients similar to some studies;[15] nevertheless, other studies demonstrated poorer outcomes in

male patients with COVID-19.[13,36] These discrepancies may arise from differences in methodologies, sample sizes, or ethnic differences which necessitate future studies.

Limitations

Despite the several strengths of this study including its focus on the effects of ARBs alone rather than combined ACEI/ARBs, we emphasize that it has several limitations. First, this is an observational study with possible inherent biases that calls for caution to extrapolate its results. Future randomized studies are warranted. Second, it is a single-center study on the Iranian population, and future multicenter studies on different ethnicities are needed. Third, survival cox regression analysis appears to be the best approach for evaluating associations between the characteristics and outcomes of the patients; however, we employed binary logistic regression models rather than this approach because we did not record the exact occurrence time of each outcome except for mortality. Another limitation is the rate of missing data in some laboratory data, especially hs-cTnI and liver transaminases, which might result in under- or overestimation in the rate of the ACI and ALI.

Conclusions

In this single-center observational study, we found that taking ARBs by patients with hypertension and confirmed or clinically suspected COVID-19 is not associated with poorer in-hospital outcomes after adjustment for possible confounders. We found that discontinuation of these medications during hospitalization was associated with a greater risk of mortality and invasive ventilation. All studies reported so far, along with the results of this article, provide tentative reassurance that taking ARBs is not harmful in COVID-19 patients. The hypothesis that these medications may be beneficial or not needs more prospective and clinical trials. Our findings support the recommendations of cardiology societies of continuing treatment with their anti-hypertensive medications.[32,33]

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Contributors: Concept and design: AS, SKS, ZS, HS, and HA. Acquisition, analysis, or interpretation of data: AS, SK, SKS, AA, ZS, AH, MT, HS, PP, MS, MB, FN, EZ, and HA. Statistical analysis: SK, AA, and HA. Drafting of the manuscript: SK, AA, ZS, and EZ. Critical revision of the manuscript: AS, SKS, AH, MT, HS, PP, MS, MB, FN, and HA. Supervision: AS and HA. All authors have read and approved the manuscript and are responsible for its content.

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Figure legend

Figure 1. Cumulative survival of patients based on the history of ARB usage in the **A.** All patients model and the **B.** Hypertensive patients model. ARB: angiotensin II receptor blockers.

Table 1. Baseline characteristics and clinical outcomes of hypertensive patients with and without ARB treatment.

Characteristic*	Total (N=254)	ARB users (N=122)	Non-ARB users (N=132)	P†
Demographics				
Age (year)	66.4±12.9	68.0±11.7	64.9±13.8	0.051
Sex Female	105 (41.3%)	50 (41.0%)	55 (41.7%)	0.912
Male	149 (58.7%)	72 (59.0%)	77 (58.3%)	
Comorbidities				
DM	119 (46.9%)	57 (46.7%)	62 (47.0%)	0.968
Cardiac disease	89 (35.0%)	56 (45.9%)	33 (25.0%)	**<0.001**
Cerebrovascular disease	21 (8.3%)	10 (8.2%)	11 (8.3%)	0.968
Chronic lung disease	22 (8.7%)	10 (8.2%)	12 (9.1%)	0.800
Chronic kidney disease	26 (10.2%)	15 (12.3%)	11 (8.3%)	0.298
Malignancy	8 (3.1%)	4 (3.3%)	4 (3.0%)	0.910
Drug history				
Statin	66 (26.0%)	54 (44.3%)	12 (9.1%)	**<0.001**
Aspirin	69 (27.2%)	54 (44.3%)	15 (11.4%)	**<0.001**
Metformin	53 (20.9%)	29 (23.8%)	24 (18.2%)	0.273
Beta blocker	58 (22.8%)	42 (34.4%)	16 (12.1%)	**<0.001**
Calcium channel blocker	33 (13.0%)	23 (18.9%)	10 (7.6%)	**0.008**
Baseline laboratory data				

WBC ($x10^9$/L)	7.3 [5.4-10.0]	7.3 [5.2-9.9]	7.4 [5.4-10.0]	0.640
Neutrophil ($x10^9$/L)	5.4 [3.6-8.2]	5.3 [3.6-8.2]	5.6 [3.6-8.2]	0.903
Lymphocyte ($x10^9$/L)	1.3 [0.9-1.8]	1.2 [0.8-1.8]	1.3 [1.0-1.8]	0.180
Platelets ($x10^9$/L)	192.0 [149.0-263.0]	196.0 [145.7-267.0]	191.0 [149.5-260.0]	0.875
Neutrophil-to-lymphocyte ratio	4.0 [2.6-7.7]	4.4 [2.5-8.7]	3.9 [2.6-6.6]	0.476
Platelet-to-lymphocyte ratio	154.4 [113.4-220.0]	160.9 [118.7-255.5]	146.6 [107.8-216.8]	0.206
SII	816.6 [445.4-1590.8]	825.8 [473.9-1809.7]	778.5 [433.4-1459.4]	0.329
RBC ($x10^{12}$/L)	4.6 [4.1-5.0]	4.5 [4.0-5.0]	4.6 [4.1-5.0]	0.365
Hemoglobin (g/dL)	13.3 [12.1-15.0]	13.2 [11.8-14.9]	13.4 [12.1-15.0]	0.389
Urea (mg/dL)	41.0 [27.0-66.2]	45.5 [30.0-76.0]	39.0 [25.2-58.7]	0.060
Creatinine (mg/dL)	1.2 [0.9-1.5]	1.2 [1.0-1.7]	1.1 [0.9-1.4]	**0.037**
BUN/Creatinine	17.6 [12.8-28.7]	17.8 [36.7-13.2]	16.9 [12.7-24.4]	0.330
Sodium (mmol/L)	136.2 [132.5-140.2]	136.1 [132.4-139.6]	136.7 [132.4-140.5]	0.386
Potassium (mmol/L)	4.3 [4.0-4.6]	4.3 [4.1-4.6]	4.3 [3.9-4.7]	0.260
CRP (mg/L)	60.9 [25.1-116.8]	66.5 [27.0-126.9]	57.6 [23.6-98.4]	0.122
ESR (mm/h)	50.0 [28.0-83.0]	52.5 [33.5-87.2]	41.0 [27.0-77.5]	0.068
LDH (U/L)	550.0 [443.2-686.5]	565.0 [441.5-691.0]	531.0 [443.0-688.0]	0.926
hs-cTnI (pg/mL)	8.0 [2.2-35.4]	8.1 [2.3-41.0]	8.0 [1.9-28.8]	0.578
AST (U/L)	50.0 [37.0-69.0]	53.5 [38.0-67.7]	48.0 [36.0-71.5]	0.500
ALT (U/L)	36.0 [26.5-50.0]	36.0 [25.0-47.0]	37.0 [28.5-56.5]	0.126
ALP (U/L)	176.0 [140.7-228.0]	176.5 [142.2-232.5]	175.0 [140.2-223.5]	0.807

In-hospital outcomes				
Hospital length of stay (day)	4.0 [3.0-8.0]	5.0 [3.0-9.0]	4.0 [2.0-6.0]	**0.008**
Severity	182 (71.7%)	91 (74.6%)	91 (68.9%)	0.318
Mortality	68 (26.8%)	33 (27.0%)	35 (26.5%)	0.923
ARDS	80 (31.5%)	41 (33.6%)	39 (29.5%)	0.486
Invasive ventilation	42 (16.5%)	20 (16.4%)	22 (16.7%)	0.953
ACI	73 (28.7%)	38 (31.1%)	35 (26.5%)	0.415
AKI	49 (19.3%)	31 (25.4%)	18 (13.6%)	**0.018**
ALI	29 (11.4%)	11 (9.0%)	18 (13.6%)	0.247
Multiorgan damage	67 (26.4%)	36 (29.5%)	31 (23.5%)	0.276

* Data are presented as mean±standard deviation, number (%), or median [interquartile range].

† Statistically significant P-values are bolded.

ACI: acute cardiac injury; AKI: acute kidney injury; ALI: acute liver injury; ALP: alkaline phosphatase; ALT: alanine aminotransferase; ARDS: acute respiratory distress syndrome; AST: aspartate aminotransferase; ARB: angiotensin II receptor blockers; BUN: blood urea nitrogen; CRP: C-reactive protein; DM: diabetes mellitus; ESR: erythrocyte sedimentation rate; hs-cTnI: high-sensitivity cardiac troponin I; LDH: lactate dehydrogenase; RBC: red blood cells; SII: systemic immune-inflammation index; WBC: white blood cells.

Table 2. Severity and mortality rates of confirmed or clinically suspected COVID-19 in hypertensive patients.

Characteristic *		Total (N=254)	Severity			Mortality		
			Severe (N=182)	Non-severe (N=72)	P†	Deceased (N=68)	Survived (N=186)	P†
Demographics								
Age (years)		66.4±12.9	67.7±12.4	62.9±13.5	**0.007**	73.3±11.0	63.8±12.8	**<0.001**
Sex	Female	105 (41.3%)	81 (44.5%)	24 (33.3%)	0.103	30 (44.1%)	75 (40.3%)	0.587
	Male	149 (58.7%)	101 (55.5%)	48 (66.7%)		38 (55.9%)	111 (59.7%)	
Comorbidities								
DM		119 (46.9%)	96 (52.7%)	23 (31.9%)	**0.003**	39 (57.4%)	80 (43.0%)	**0.043**
Cardiac disease		89 (35.0%)	64 (35.2%)	25 (34.7%)	0.947	27 (39.7%)	62 (33.3%)	0.346
Cerebrovascular disease		21 (8.3%)	18 (9.9%)	3 (4.2%)	0.136	13 (19.1%)	8 (4.3%)	**<0.001**
Chronic lung disease		22 (8.7%)	19 (10.4%)	3 (4.2%)	0.109	10 (14.7%)	12 (6.5%)	**0.038**
Chronic kidney disease		26 (10.2%)	19 (10.4%)	7 (9.7%)	0.865	8 (11.8%)	18 (9.7%)	0.627

Malignancy	8 (3.1%)	5 (2.7%)	3 (4.2%)	0.559	4 (5.9%)	4 (2.2%)	0.132
Drug history							
Statin	66 (26.0%)	52 (28.6%)	14 (19.4%)	0.135	17 (25.0%)	49 (26.3%)	0.829
Aspirin	69 (27.2%)	51 (28.0%)	18 (25.0%)	0.626	21 (30.9%)	48 (25.8%)	0.421
Metformin	53 (20.9%)	41 (22.5%)	12 (16.7%)	0.300	20 (29.4%)	33 (17.7%)	**0.043**
Beta blocker	58 (22.8%)	42 (23.1%)	16 (22.2%)	0.884	18 (26.5%)	40 (21.5%)	0.404
ARB	112 (48.0%)	91 (50.0%)	31 (43.1%)	0.318	33 (485%)	89 (47.8%)	0.923
Calcium channel blocker	33 (13.0%)	25 (13.7%)	8 (11.1%)	0.575	9 (13.2%)	24 (12.9%)	0.944
Baseline laboratory data							
WBC (x10^9/L)	7.3 [5.4-10.0]	7.8 [5.4-10.5]	7.0 [5.3-9.3]	0.227	9.7 [6.5-14.1]	6.7 [5.1-9.3]	**<0.001**
Neutrophil (x10^9/L)	5.4 [3.6-8.2]	5.6 [3.8-8.4]	5.1 [3.3-6.9]	0.072	7.8 [5.5-10.6]	4.5 [3.4-7.2]	**<0.001**
Lymphocyte (x10^9/L)	1.3 [0.9-1.8]	1.2 [0.8-1.8]	1.4 [1.0-1.8]	0.091	1.0 [0.7-1.6]	1.3 [1.0-1.8]	**<0.001**
Platelets (x10^9/L)	192.0 [149.0-	189.5 [147.7-	200.0 [150.5-	0.667	207.0 [151.0-	190.0 [148.0-	0.356

	263.0]	275.0]	252.5]		277.0]	256.7]	
Neutrophil-to-lymphocyte ratio	4.0 [2.6-7.7]	4.4 [2.8-8.7]	3.5 [2.3-6.0]	**0.011**	6.7 [4.1-10.9]	3.5 [2.4-6.0]	**<0.001**
Platelet-to-lymphocyte ratio	154.4 [113.4-220.0]	156.5 [109.3-247.7]	149.0 [117.0-192.8]	0.336	206.1 [126.0-268.9]	143.2 [107.5-201.3]	**0.002**
SII	816.6 [445.4-1590.8]	881.1 [444.8-1745.5]	713.3 [449.3-1150.2]	0.065	1375.7 [783.2-3093.1]	740.6 [407.6-1234.6]	**<0.001**
RBC (x10^{12}/L)	4.6 [4.1-5.0]	4.5 [4.0-5.0]	4.7 [4.1-5.0]	0.334	4.4 [3.9-4.9]	4.6 [4.1-5.0]	0.112
Hemoglobin (g/dL)	13.3 [12.1-15.0]	13.1 [12.0-14.9]	13.8 [12.3-15.0]	0.328	13.1 [11.2-14.7]	13.5 [12.2-15.1]	**0.045**
Urea (mg/dL)	41.0 [27.0-66.2]	45.5 [28.0-73.2]	35.0 [26.0-57.0]	**0.044**	59.0 [38.0-107.0]	36.0 [25.0-54.0]	**<0.001**
Creatinine (mg/dL)	1.2 [0.9-1.5]	1.2 [1.0-1.6]	1.1 [0.9-1.4]	0.122	1.4 [1.1-2.1]	1.1 [0.9-1.4]	**<0.001**
BUN/Creatinine	17.6 [12.8-28.7]	18.8 [13.5-33.3]	14.8 [11.6-21.3]	**0.016**	23.1 [15.5-61.8]	16.5 [11.6-22.2]	**<0.001**
Sodium (mmol/L)	136.2 [132.5-	135.6 [132.0-	138.1 [134.7-	**0.003**	135.9 [132.7-	136.7 [132.4-	0.881

	140.2]	139.2]	141.1]		139.7]	140.4]	
Potassium (mmol/L)	4.3 [4.0-4.6]	4.3 [4.0-4.7]	4.3 [4.0-4.6]	0.753	4.3 [3.8-4.7]	4.3 [4.0-4.6]	0.591
CRP (mg/L)	60.9 [25.1-116.8]	67.5 [33.6-126.6]	47.2 [10.9-78.2]	**0.001**	80.2 [57.7-140.7]	53.4 [14.9-97.9]	**<0.001**
ESR (mm/h)	50.0 [28.0-83.0]	51.5 [30.0-87.0]	40.5 [21.0-76.2]	**0.021**	59.0 [27.0-90.0]	46.0 [29.0-79.0]	0.176
LDH (U/L)	550.0 [443.2-686.5]	598.5 [485.5-745.2]	460.0 [347.2-551.5]	**<0.001**	677.0 [498.5-837.2]	528.5 [436.0-644.2]	**0.001**
hs-cTnI (pg/mL)	8.0 [2.2-35.4]	11.0 [3.1-52.9]	3.9 [1.5-8.0]	**<0.001**	34.7 [7.2-144.5]	6.1 [1.7-18.0]	**<0.001**
AST (U/L)	50.0 [37.0-69.0]	57.5 [42.2-75.0]	38.0 [30.5-43.0]	**<0.001**	66.5 [49.5-90.7]	44.0 [36.0-60.5]	**<0.001**
ALT (U/L)	36.0 [26.5-50.0]	38.0 [28.0-53.0]	30.0 [24.0-40.0]	**<0.001**	45.5 [31.0-62.0]	34.0 [25.0-45.0]	**<0.001**
ALP (U/L)	176.0 [140.7-228.0]	177.0 [140.7-230.5]	169.5 [140.7-215.0]	0.686	186.0 [140.0-248.0]	174.0 [141.0-222.0]	0.272
In-hospital outcomes							

Hospital length of stay (day)	4.0 [3.0-8.0]	5.0 [3.0-8.5]	3.0 [2.0-5.0]	**<0.001**	7.0 [3.0-10.0]	4.0 [3.0-7.0]	**0.048**
ARDS	80 (31.5%)	80 (44.0%)	0	**<0.001**	49 (72.1%)	31 (16.7%)	**<0.001**
Invasive ventilation	42 (16.5%)	42 (23.1%)	0	**<0.001**	42 (61.8%)	0	**<0.001**
ACI	73 (28.7%)	69 (37.9%)	4 (5.6%)	**<0.001**	34 (50.0%)	39 (21.0%)	**<0.001**
AKI	49 (19.3%)	46 (25.3%)	3 (4.2%)	**<0.001**	36 (52.9%)	13 (7.0%)	**<0.001**
ALI	29 (11.4%)	25 (13.7%)	4 (5.6%)	0.065	18 (26.5%)	11 (5.9%)	**<0.001**
Multiorgan damage	67 (26.4%)	67 (36.8%)	0	**<0.001**	48 (70.6%)	19 (10.2%)	**<0.001**

* Data are presented as mean±standard deviation, number (%), or median [interquartile range].

† Statistically significant P-values are bolded.

ACI: acute cardiac injury; AKI: acute kidney injury; ALI: acute liver injury; ALP: alkaline phosphatase; ALT: alanine aminotransferase; ARDS: acute respiratory distress syndrome; AST: aspartate aminotransferase; ARB: angiotensin II receptor blockers; BUN: blood urea nitrogen; CRP: C-reactive protein; DM: diabetes mellitus; ESR: erythrocyte sedimentation rate; hs-cTnI: high-sensitivity cardiac troponin I; LDH: lactate dehydrogenase; RBC: red blood cells; SII: systemic immune-inflammation index; WBC: white blood cells.

Table 3. Comparison of in-hospital outcomes of hypertensive patients with confirmed or clinically suspected COVID-19 based on the history of ARBs usage.

In-hospital outcomes*	Continued (N=79)	Discontinued (N=43)	Newly started (N=36)	Never used (N=96)	P†
Hospital length of stay (day)	5.0 [3.0-8.0]	7.0 [3.0-11.0]	6.0 [3.0-10.0]	4.0 [2.0-6.0]	0.069
Mortality	10 (12.7%)	23 (53.5%)‡	7 (19.4%)	28 (29.2%)	**<0.001**
ARDS	22 (27.8%)	19 (44.2%)	14 (38.9%)	25 (26.0%)	0.115
Invasive ventilation	6 (7.6%)	14 (32.6%)‡	5 (13.9%)	17 (17.7%)	**0.005**
ACI	21 (26.6%)	17 (39.5%)	11 (30.6%)	24 (25.0%)	0.342
AKI	14 (17.7%)	17 (39.5%)‡	5 (13.9%)	13 (13.5%)	**0.003**
ALI	7 (8.9%)	4 (9.3%)	5 (13.9%)	13 (13.5%)	0.718
Multiorgan damage	18 (22.8%)	18 (41.9%)	10 (27.8%)	21 (21.9%)	0.076

* Data are presented as number (%) or median [interquartile range].

† Statistically significant P-values are bolded.

‡ Chi-square post-hoc P-value<0.00625

ACI: acute cardiac injury; AKI: acute kidney injury; ALI: acute liver injury; ARDS: acute respiratory distress syndrome.

Table 4. Prognostic value of ARB usage for prediction of in-hospital outcomes of patients with confirmed or clinically suspected COVID-19.

In-hospital outcomes	All patients†			Hypertensive patients‡		
	OR	**95% CI**	**P***	**OR**	**95% CI**	**P***
Mortality	1.00	0.48-2.06	0.996	0.86	0.42-1.78	0.689
Severity	1.21	0.65-2.24	0.553	1.23	0.66-2.30	0.522
ARDS	1.06	0.58-1.94	0.844	1.12	0.61-2.06	0.709
Invasive ventilation	0.92	0.41-2.06	0.842	0.88	0.41-1.90	0.749
ACI	1.24	0.67-2.29	0.492	1.36	0.75-2.47	0.315
AKI	2.17	1.06-4.44	**0.034**	2.26	1.13-4.56	**0.022**
ALI	0.54	0.21-1.40	0.207	0.54	0.21-1.42	0.214
Multiorgan damage	1.50	0.77-2.90	0.230	1.53	0.80-2.94	0.200

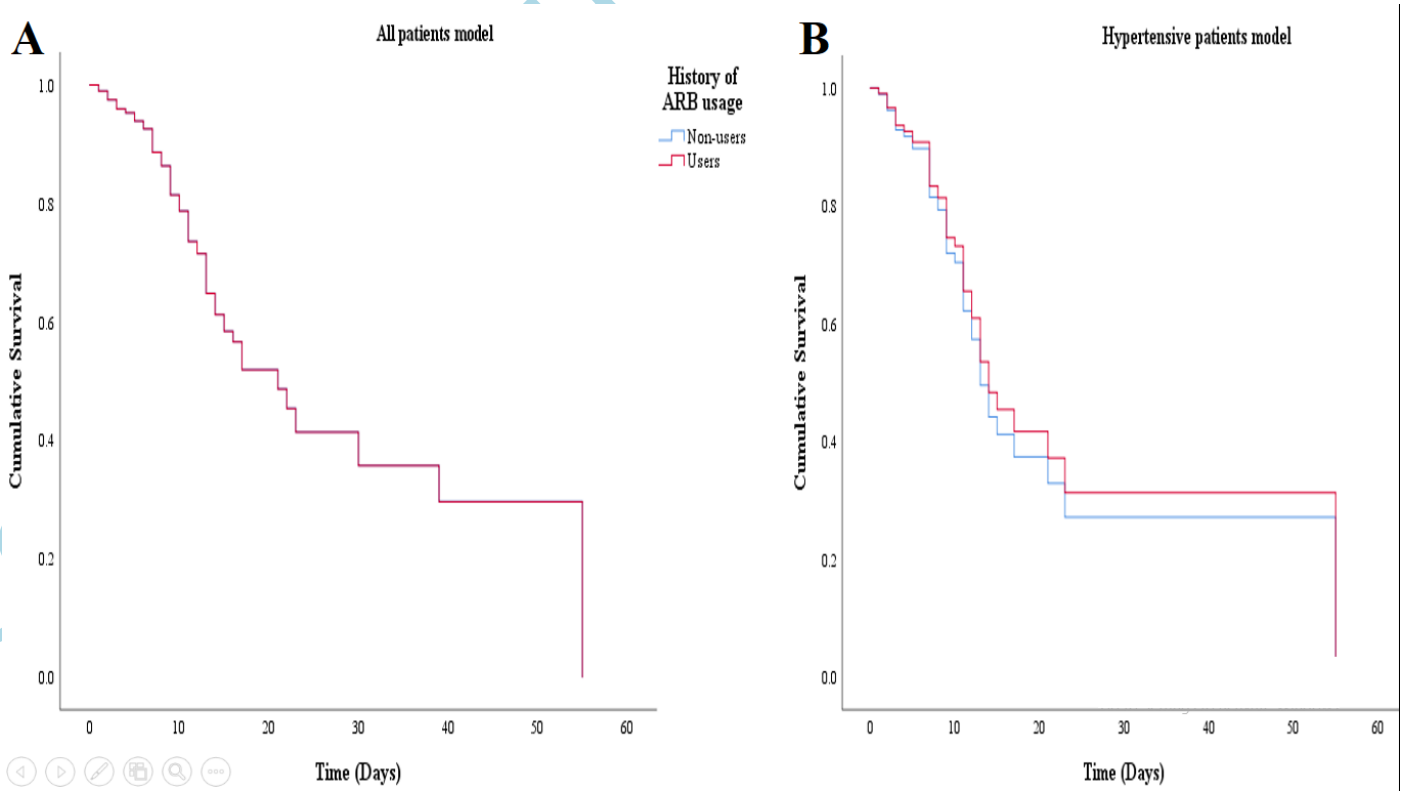
† Multivariate logistic regression adjusted for age, sex, diabetes mellitus, hypertension, cardiac disease, cerebrovascular disease, chronic lung disease, chronic kidney disease, neutrophil-to-lymphocyte ratio, urea, and C-reactive protein.

‡ Multivariate logistic regression adjusted for age, sex, diabetes mellitus, cerebrovascular disease, chronic lung disease, chronic kidney disease, neutrophil-to-lymphocyte ratio, urea, and C-reactive protein.

* Statistically significant P-values are bolded.

ACI: acute cardiac injury; AKI: acute kidney injury; ALI: acute liver injury; ARDS: acute respiratory distress syndrome.

Figure 1


A
All patients model
History of ARB usage
Non-users
Users
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Time (Days)
B
Hypertensive patients model
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Time (Days)