Effects of Renin-Angiotensin-Aldosterone Inhibitors on Early Outcomes of Hypertensive COVID-19 Patients: A Randomized Triple-Blind Clinical Trial

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Data availability statement: Data are available upon a reasonable request to the corresponding author.

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- *Concept and design*: Haleh Ashraf, Maryam Bahreini, Farhad Najmeddin, Morteza Goghaei, Fatemeh Rasooli, Abbas Soleimani, Mohammadreza Salehi, Maedeh Solhjoo
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- **Key Words:** Angiotensin Receptor Antagonists; Angiotensin-Converting Enzyme Inhibitors; Blood Pressure; Coronavirus Disease-2019; Hypertension; Adverse Outcome

Abstract

Background. The role of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) has been addressed in some studies related to the current coronavirus disease-2019 (COVID-19) pandemic with possible higher severity and mortality in patients with hypertension. A triple-blind randomized controlled trial was designed to evaluate the effects of these medications on the COVID-19 progression.

Methods. Patients were enrolled in this trial between April and September 2020. They were randomized in two groups. The former dosage of ACEis/ARBs was continued in one group while in another group, the ACEis/ARBs were replaced by amlodipine ± carvedilol according to the dose equivalents. The primary outcomes were length of stay in hospitals and intensive care units. Other outcomes include mechanical ventilation, non-invasive ventilation, readmission, and COVID-19 symptoms after discharge.

Results. We randomized 64 patients with COVID-19 into two groups. Most patients were aged 66-80 and 46-65 years-old, 33 (51.6%) and 27 (42.2%), respectively. The study groups were nearly similar in baseline vital signs and characteristics. In addition, there was no significant difference in terms of recorded systolic and diastolic blood pressure measurements between groups. Furthermore, we did not find a significant difference between the days of intensive care unit or ward admission, the discharge rate, or readmission rates between the two groups.

Conclusions. This randomized triple-blind multi-centric clinical trial did not show any deleterious effects of ACEi/ARB medications in hypertensive COVID-19 patients.

Key Words: Angiotensin Receptor Antagonists; Angiotensin-Converting Enzyme Inhibitors; Blood Pressure; Coronavirus Disease-2019; Hypertension; Adverse Outcome

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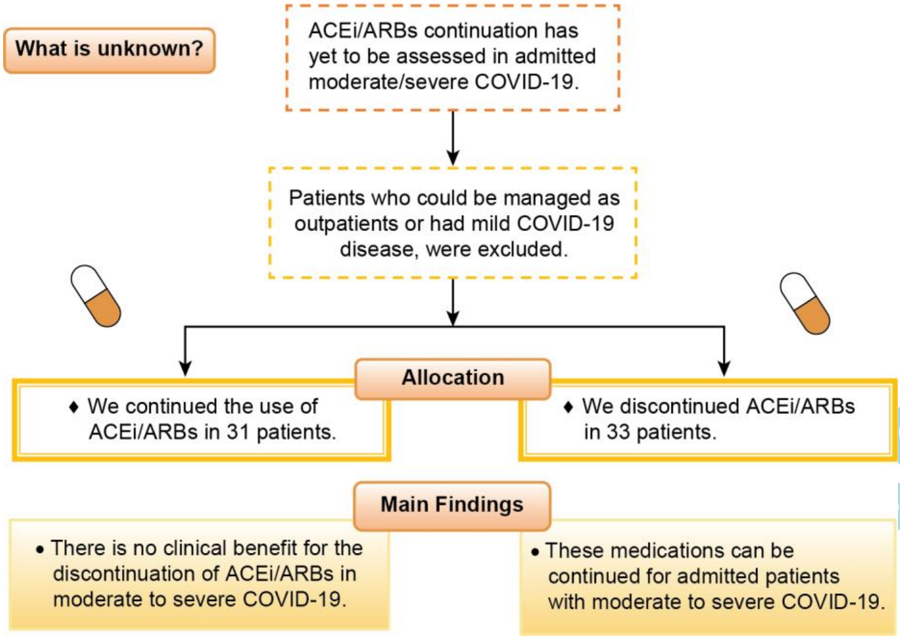

Introduction

1.1. Background

Early concerns for the use of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) in patients with coronavirus disease-2019 (COVID-19) raised from studies describing higher severity and mortality rates in the elderly and patients with hypertension [1, 2].

1.2. Importance

On one hand, overexpression of angiotensin-converting enzyme2 (ACE2) in these categories has been reported in multiple studies which may be due to pathological changes of the disease or high prevalence of ACEi/ARB use [3]. ACE2 acts as a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-COV2) and there is growing evidence on the correlation between viral tissue damage and ACE2 presentation on tissue cells' membrane [4].

On the other hand, patients consuming ACEi/ARB medications have higher levels of ACE2 which has a protective effect against endothelial, myocardial, and lung injury. The mechanism is known to be the conversion of Angiotensin II to Angiotensin (Ang) 1-7 which is a peptide with potential protective anti-inflammatory effects against the pro-inflammatory activity of Ang II [5].

1.3. Goals of This Investigation

As most studies in this field are limited to retrospective findings and no clinical trial has exclusively addressed this issue in moderate to severe COVID-19 patients, we designed a randomized controlled trial in hospitalized patients with moderate to severe involvement who were on ACEi/ARB medications to evaluate the disease progress and adverse outcomes.

Methods

2.1. Study Design and Setting

This is a prospective, triple-blind, randomized clinical trial to assess the clinical outcomes of hypertensive patients who consume renin-angiotensin-aldosterone system inhibitors and infected with COVID -19 requiring inpatient care. Generally, moderate to severe patients require hospital admission in the COVID-19 wards or intensive care units in our setting. The extent of severity and the need for admission was based on the national triage algorithm [6]. The clinical trial was conducted in three academic hospitals affiliated with our university with 40,000 to 70,000 annual ED visits.

Our University of Medical Sciences institutional Ethical review board has approved the trial IR.TUMS.VCR.REC.1399.028 and the study was registered in the randomized controlled trial system (registration No.: IRCT20151113025025N3). Informed written consent was obtained from patients or their relatives.

2.2. Selection of Participants

Inclusion criteria: Adult patients (18 year or older) were included with previously diagnosed essential hypertension consuming angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The definite diagnosis of COVID-19 was defined by positive oro/nasopharyngeal real-time polymerase chain reaction (PCR) and moderate to severe involvement of COVID-19 in their chest computed tomography scan according to the World Health Organization's interim guidance and national guidelines [7, 8].

Exclusion criteria: Uncontrolled hypertension with systolic blood pressure (BP) more than 180 mmHg or diastolic BP more than 120 mmHg; past history of congestive heart failure or arrhythmia of various severity; sensitivity to the newly prescribed medications; a history of severe asthma; a history of known depression; consuming medications with interactions such as lithium, antiepileptic drugs, chemotherapy; the treating physician's concern or patient unwillingness to enter the study; patients whose prognosis is influenced by another disease; pregnancy or breastfeeding, and unstable vital signs (systolic blood pressure <90 mmHg; pulse rate<50 or >150 beats/min).

Patients were enrolled between April 2020 and September 2020. Consecutive patients presenting to the emergency departments (ED) on the investigators' shifts (MS, MB, FR) were screened for eligibility. The shifts were randomly assigned to the three investigators during the study period among 24/7 shifts.

2.3. Interventions

2.3.1. Study Groups

Group 1: Patients continuing to consume renin-angiotensin-aldosterone system inhibitors including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with the previous dose unless mandating adjustment to control blood pressure.

Group 2: Patients whose medications of renin-angiotensin-aldosterone system inhibitors are discontinued and substituted by a calcium channel blocker (amlodipine) with or without a beta blocker (carvedilol), if not well-controlled, according to the dose equivalents. Supplementary table 1 shows the dose equivalents, developed by an expert panel of cardiologists and clinical pharmacists based on the baseline blood pressure and also the dose of previous medications of patients.

2.3.2. Blinding

The Investigators, outcome assessors, and the data analyzer were blinded to the antihypertensive medications as well as the enrolled participants. Patients received two capsules a day of similar shapes. The principle dose of anti-hypertensive medication was filled in one capsule, provided for each patient, and the other was filled with starch. Patients received capsules at day and night time episodes. Capsules were filled by a pharmacotherapist who was not involved in patient enrollment and data recruitment. Thus, a pharmacotherapist (FN) and a cardiologist (HA) were not blinded to patients to observe the process and monitor the status of blood pressure control, to confirm the safety of (dis)continuation of antihypertensive medications, and to prescribe the medications for a total of 14 days if patients were discharged before this time limit according to the instructions explained in the supplementary table 1.

2.3.3. Randomization

Patients consuming renin-angiotensin-aldosterone system inhibitors were randomized to two groups using computerized-sequence random codes with a 1:1 allocation. The process was supervised by MB.

After inclusion, a thorough medical history, habits, and comorbidities were asked from patients including but not limited to cardiovascular disease, previous lung diseases, renal/ hepatic insufficiency, diabetes, and allergy to medications.

Vital signs were examined and documented including heart rate, respiratory rate, blood pressure, body temperature and O2 saturation at the time of admission and then, daily until discharge. Registered nurses in COVID-19 wards or intensive care units (ICUs) have given the similar-shaped capsules to patients. Vital sign monitoring was performed as per routine clinical practice. Furthermore, patients were followed up by phone 14 days after discharge if they had consented. They were asked for the adherence to medications, remaining signs and symptoms of COVID-19, and possible adverse effects of medications.

2.4. Outcome measures

Primary outcomes included length of stay in the hospital and ICU. Other outcomes consisted of days on (non)invasive mechanical ventilation, readmission, change in O2 saturation between baseline and discharge time, maximum change in troponin from baseline, change in serum creatinine between baseline and discharge or time of death, acute kidney injury during hospitalization, and World Health Organization (WHO) COVID-19 ordinal endpoint ≥ 6 [9]. Adverse effects of antihypertensive medications were monitored during and after discharge including headache, dizziness, nausea, vomiting, pruritus, and abdominal pain for a total of 14 days as after this time, many patients with COVID-19 can be dispositioned. The prescribed medications for COVID-19 during admission were documented and a subgroup analysis was performed to compare the two groups regarding the outcomes.

2.4.1. Definitions

The severity of CT scan findings was estimated by visual assessment; mild: ≤ 25%, moderate: 26-49%, severe: 50-74%, very severe: ≥75% involvement of both lungs. The clinical classifications are as follows: (a) mild to moderate: with mild symptoms up to mild pneumonia, (b) severe: presence of any of the followings: dyspnea, oxygen saturation ≤ 93%, or >50% lung involvement on imaging, and (c) critical: one of the following conditions: respiratory failure, shock, or multiorgan system dysfunction [10]. Patients with at least two complications were considered to have multiorgan damage.

Acute kidney injury (AKI) was defined according to the KDIGO criteria as any of the followings: 1) increase in serum creatinine (SCr) to ≥ 1.5 times of baseline occurred within the previous 7 days or an increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours (criteria for urine volume < 0.5 ml/kg/hour for 6 hours was excluded since there were no records of patients' urine volume in electronic health data) [11]. Furthermore, the WHO Clinical Progression Scale was calculated [9]. In addition, the systemic immune inflammation index (SII) was calculated as (platelet count × neutrophil count)/(lymphocyte count) [12].

2.5. Statistical Analysis

Categorical variables are reported as frequency and percentage while continuous variables are expressed as mean ± standard deviation or median (interquartile range) according to normality of distribution. Categorical variables were compared using chi-square or fisher exact test and continuous variables were compared using independent Student’s t-test or Mann-Whitney U test, as appropriate. A univariate logistic regression analysis was performed to identify predictors of outcome measures. Besides, variables with a p value of less than 0.1 in the univariate analysis were further assessed in a multivariable logistic regression analysis. Considering one day reduction in the length of stay of patients with a standard deviation of 1.5, and one day reduction in the length of ICU stay, a sample size of 27 per group was calculated to achieve 95% power. All analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, Illinois, USA) and a p-value of less than 0.05 as the statistical significance level and a two-sided 95% confidence interval were considered for all the analyses.

Results

In this clinical trial, 66 patients who met the inclusion criteria were enrolled. Two enrolled patients die early after inclusion and thus, not allocated. Twelve patients were excluded due to acute kidney injury, acute coronary syndrome, unwillingness of the treating physician or patient refusal to consent. We finally randomized 64 patients with COVID-19 to two groups who completed the study protocol for 14 days. The flowchart of the study participants is demonstrated in Figure 1. Most patients were aged 66-80 and 46-65 years-old, 33 (51.6%) and 27 (42.2%), respectively. The study groups were nearly similar in baseline vital signs and characteristics (Table 1). In addition, there was no significant difference in terms of recorded mean systolic and diastolic blood pressure measurements between the groups (Supplementary figure). Table 2 depicts baseline laboratory data and COVID-19 medications of the study groups.

Table 3 provides an overview of the primary outcome measures and also some influential factors that may lead to adverse outcomes. The odds ratio of ischemic heart disease, 95 % CI was 0.61 (0.1 – 3.8) and for diabetes 2.22 (0.42 – 11.60) in the study participants. Table 4 reports the odds ratio of COVID-19 clinical outcomes in the ACEi/ARB change vs. the

ACEi/ARB continuation group. Furthermore, the detailed presenting signs and symptoms are depicted in the supplementary table 2 as well as the remaining symptoms after 14 days, asked by phone follow-up. The most common symptoms of COVID-19 after the 2-week follow-up were fatigue ($P = 0.088$), cough ($P = 0.939$), and anosmia ($P = 0.170$) with no difference between the two groups. Regarding the adverse effects of medications, they were not completely distinguished from the remaining COVID-19 symptoms on phone follow-up. The overall rate of the remaining symptoms was low.

The total admission days were 5.3 ± 3.9 and 8.0 ± 15.9 for the continued and changed medication groups, respectively ($P = 0.184$). The study participants were not different regarding blood groups ($P = 0.721$). Only 9 (14.1) had a history of flu vaccination.

Discussion

We conducted a randomized triple-blind clinical trial, assessing the paradoxical effects of ACEis and ARBs on outcomes in admitted patients with moderate to severe COVID-19. Few studies with controversial results and only two clinical trials have yet discussed this issue, mostly evaluating mild to moderate COVID-19. In the present study, there was no significant difference between the demographic characteristics, past medical history, medications utilized for the treatment of COVID-19, and the remaining signs and symptoms of the two groups as we followed the participants in the course of disease on admission and after discharge. The comparison of the outcomes of ICU/ward admission days, invasive ventilation necessities, and laboratory prognostic factors showed no clinical or statistical difference whether the ACEi/ARBs were continued or discontinued in moderate to severe admitted patients. Furthermore, blood pressure of patients on admission days were not different among the study groups.

The very recent REPLACE COVID trial was implemented in 53% mild and 35% moderate COVID-19 patients who were probably prescribed ACEi/ARB before admission. They concluded that the discontinuation of these medications did not significantly affect acute hospitalization outcomes which is consistent with our findings [13]. Recently, in the BRACE CORONA trial in mild to moderate COVID-19, the proportion of out-of-hospital alive patients by the end of 30 days was 91.8 % vs. 95.0 % in the discontinuation vs. continued groups (P = NA) and the 30-day mortality was 2.8 % vs. 2.7 %, respectively (P = NA). They concluded that there is no clinical benefit from changing these medications in hospitalized patients [14].

A retrospective study evaluated the effect of continuation vs. discontinuation of ACEi/ARB in COVID-19 on blood pressure control and mortality [15]. The mortality rate was described to be lower in patients using ACEi/ARB (12.5 % and 27.5 % with adjusted OR of 0.1 CI 0.0-0.6 for ACEi/ARB continuation vs. discontinuation/no therapy). However, this study was a cohort with no randomization strategy and a lack of rationales for ACEi/ARB discontinuation [15]. Zhang et al. evaluated the association between in-hospital use of ACEi/ARB and all-cause mortality in hospitalized patients with COVID-19 and hypertension in a multicenter retrospective setting. They demonstrated a lower risk of mortality in patients using ACEi/ARB compared with the non-ACEi/ARB group (adjusted hazard ratio 0.4 [95% CI, 0.1-0.9] (P=0.030)). However, the use of antihypertensive medications in the non-ACEi/ARB group raises concern with medication underuse and there is not enough data about blood pressure control during hospital stay [16].

Besides, K.W. Lam et al. published a retrospective study on three groups: group A included patients who did not take ACEi/ARB before admission, group B for whom ACEi/ARB was discontinued on admission, and group C who continued to receive ACEi/ARB in the hospital. The mortality did not differ between groups A and C (22.2 % vs. 17.3%, respectively, P =

0.336) while group B had significantly higher mortality rate. They reported higher ICU admission rates in patients in group B vs. group C (26.3 % vs. 12.2 %, adjusted P = 0.001) [17]. Also in a study by Soleimani et al., after adjustment of possible confounders, no independent association was found 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. They found that discontinuation of ARBs during hospitalization was associated with a greater risk of mortality, invasive ventilation, and AKI (all P < 0.002) [18].

Moreover, X. Zhang et al. implemented a systematic review and meta-analysis of 12 retrospective studies and described no significant association between taking ACEi/ARB and the risk of mortality from COVID-19 (OR 0.7, CI 0.5 - 1.07, P = 0.110) while the mortality rate was lower in patients using ACEi/ARB (OR 0.6 CI 0.4 - 1.0, P = 0.059) [19].

Overall, most of the previous retrospective/observational studies have concluded that there is no benefit to withhold ACEi/ARBs in hypertensive COVID-19 patients regarding clinical outcomes. Some studies reported a protective effect in these patients [15]. Finally, one clinical trial in mild to moderate COVID-19 patients reported no worse outcome to discontinue these medications [14] similar to what we have concluded in our trial on patients suffering from moderate to severe involvement.

Limitations

We managed to include and follow patients till 14 days although it was inevitable to exclude patients due to early deterioration, hypotension, early death, multi-organ failures, unwillingness of the treating physicians, acute kidney injury, electrolyte imbalance, acute coronary syndrome, patient failure to consent or to continue the antihypertensive medications until 14 days. This study was underpowered to compare death rates. Further studies with larger sample sizes can be implemented exclusively addressing moderate to severe patients. During the early months of the COVID-19 pandemics, admitted patients received several regimens according to the possibly introduced treatment options at the time of data recruitment and thus, some effective medications such as corticosteroids were prescribed for patients as soon as suggestive data showed the efficacy and obviated possible harm.

Conclusion

This randomized triple-blind multi-centric clinical trial did not show any deleterious effects of ACEi/ARB medications in hypertensive patients with moderate to severe COVID-19.

Disclosures:

Declaration of Interests: The authors declare that they have no conflict of interest.

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Data availability statement: Data are available upon a reasonable request to the corresponding author.

Figure Legend

Figure 1. The flow diagram of the study participants.

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Table 1. Detailed characteristics of the study groups.

Characteristics of study groups	**Total (n = 64)**	**ACEi/ARB continued (n = 31)**	**ACEi/ARB changed (n = 33)**	**P value**
Age, years, mean ± SD	66.3 ± 9.9	65.0 ± 9.9	67.5 ± 9.8	0.313
Age groups, n (%)				0.385
< 65 years	27 (42.2%)	12 (38.7%)	15 (45.5%)	
≥65 years	37 (57.8%)	19 (61.3%)	18 (54.5%)	
Gender (Male), n (%)	30 (46.9%)	17 (26.6%)	13 (20.3%)	0.216
Medications, n (%)				
ACEI	6 (9.4%)	2 (3.1%)	4 (6.2%)	
ARB	58 0.6%)	29 (45.3%)	29 (45.3%)	0.437
Past medical history, n (%)				
Diabetes	32 (50.0%)	15 (23.8%)	17 (26.9%)	0.707
Ischemic heart disease	16 (25%)	13 (20.6%)	3 (4.7%)	0.003
Kidney Transplant	1 (1.6%)	0	1 (1.5%)	-
End-stage renal disease	1 (1.6%)	1 (1.5%)	0	-
Cancer, active chemotherapy	3 (4.7%)	2 (3.1%)	1 (1.5%)	0.488
Chronic obstructive pulmonary disease	1 (1.6%)	0	1 (1.5%)	-
Positive present substance use	4 (6.2%)	2 (3.2%)	2 (3.2%)	0.947
Positive past substance use	5 (7.8%)	4 (6.4%)	1 (1.6%)	0.140
Positive current smoking	4 (6.2%)	2 (3.2%)	2 (3.2%)	0.947
Positive past smoking habit	16 (25%)	11 (17.7%)	5 (8.1%)	0.058
Presenting symptoms, n (%)				
Fever	37 (57.8%)	19 (61.3%)	18 (54.5%)	0.440
Cough	44 (68.8%)	21 (67.7%)	23 (69.7%)	0.467
Dyspnea	37 (57.8%)	17 (54.8%)	20 (60.6%)	0.359
Anorexia	23 (35.9%)	11(35.5%)	12 (36.4%)	0.538
Fatigue	26 (40.6%)	8 (25.8%)	18 (54.5%)	0.014
Chills	23 (35.9%)	13 (20.6%)	10 (30.3%)	0.268

Myalgia	25 (39.1%)	11(35.5%)	14 (42.4%)	0.340
Anosmia	5 (7.8%)	2 (3.2%)	3 (9.1%)	0.515
Chest pain	5 (7.8%)	3 (9.7%)	2 (3.2%)	0.485
Headache	9 (14.1%)	6 (19.3%)	3 (9.1%)	0.221
Sore throat	3 (4.7%)	3 (9.7%)	0	0.113
Nausea & vomiting	18 (28.1%)	11(35.5%)	7 (21.2%)	0.180
Diarrhea	8 (12.5%)	5 (16.1%)	3 (9.1%)	0.336
Dizziness	3 (4.7%)	2 (3.2%)	1 (1.5%)	0.488
Sweating	5 (7.8%)	3 (9.7%)	2 (6.1%)	0.452
Altered mental status	1 (1.6%)	0	1 (1.5%)	-
Seizure	1 (1.6%)	0	1 (1.5%)	-
Hemiparesis and dysphasia	1 (1.6%)	1 (1.5%)	0	-
Presenting vital signs				
Temperature, ^{oc}	37.0 (36.6 - 38.0)	36.9 (36.4 -37.3)	37.2 (36.8 -38.3)	0.028
Systolic blood pressure, mmHg	130.0 (120.0-140.0)	130.0 (120.0-140.0)	120.0 (130.0-140.0)	0.558
Diastolic blood pressure, mmHg	80.0 (70.0-85.0)	80.0 (75.0-80.0)	80.0 (70.0-90.0)	0.786
Pulse rate, beats/minute	82.0 (75.0-92.0)	81.0 (75.0-94.0)	82.0 (75.2-91.7)	0.736
Respiratory rate, beats/minute	20.0 (18.0-25.0)	16.7 (19.5-25.0)	20.0 (18.0-24.2)	0.328
Saturation o2 in room air, %	90.0 (85.5-92.0)	90.0 (87.0-92.0)	88.0 (83.0-91.2)	0.097
Saturation o2 with oxygenation, %	96.0 (93.0-98.0)	97.0 (93.7-98.0)	95.0 (93.0-98.0)	0.280
Severe disease	58 (90.6%)	29 (93.5%)	29 (87.9%)	0.367

n (%): number (percent); ACEi/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; SD: Standard deviation

Table 2. Baseline laboratory data and treatment options between the study groups.

Laboratory data and treatment options	**Total (n = 64)**	**ACEi/ARB continued (n = 31)**	**ACEi/ARB changed (n = 33)**	**P value**
Baseline laboratory data				
WBC ($\times 10^9$/l)	6.9 (5.0 -9.3)	7.0 (5.2 -9.4)	6.6 (4.6 -9.0)	0.328
Neutrophil ($\times 10^9$/l)	4.8 (3.3-7.4)	5.4 (3.7-7.8)	4.5 (2.8-6.7)	0.192
Lymphocyte ($\times 10^9$/l)	1.1 (0.9-1.5)	1.2 (0.9-1.9)	1.1 (0.9-1.5)	0.710
Platelets ($\times 10^9$/l)	203.0 (150.7 - 286.7)	206.0 (148.5 - 280.5)	201.5 (165.5 - 303.0)	0.625
Neutrophil-to-lymphocyte ratio	3.7 (2.3-7.6)	5.6 (2.5-8.3)	3.4 (2.3-5.5)	0.182
Platelet-to-lymphocyte ratio	175.9 (138.3- 257.2)	157.2 (105.5-267.4)	193.5 (149.2- 224.9)	0.415
SII *	470.6 (780.8- 1562.8)	490.4 (1055.0- 2209.9)	365.0 (682.2- 1077.7)	0.153
RBC (×1012/l) †	4.1 4.6 5.0	4.3 4.8 5.1	3.8 4.3 4.8	0.013
Hemoglobin (g/dl) †	11.2 13.1 14.5	11.8 13.8 15.2	10.9 12.9 13.5	0.127
RDW †	13.5 13.9 15.0	13.5 13.8 14.4	13.4 14.6 15.9	0.265
Urea (mg/dl) †	39.8 56.0 72.3	36.5 49.0 65.3	44.0 58.0 74.0	0.178

Creatinine (mg/dl)	1.1 (0.9 -1.3)	1.1 (0.9 -1.3)	1.0 (0.9 -1.3)	0.643
BUN/creatinine †	16.4 21.6 27.2	16.3 20.4 24.9	24.9 30.3 10.1	0.078
Sodium (mmol/l) †	137.4 141.0 143.9	137.1 140.0 143.9	138.5 141.0 143.7	0.527
Potassium (mmol/l) †	4.6 4.9 5.2	4.4 4.8 5.1	4.7 5.1 5.3	0.04
CRP (mg/l) †	30.1 66.2 101.8	29.8 61.9 137.8	27.4 73.2 99.2	0.868
ESR (mm/hour)	70.5 (51.0-89.7)	66.3 (33.8-90.5)	70.5 (53.3-91.0)	0.404
LDH (U/l) †	529.3 664.5 792.8	596.3 714.5 829.8	498.0 642.0 766.0	0.160
hs-cTnI (pg/ml) †	2.9 7.4 17.1	3.3 11.0 19.2	1.8 6.4 13.5	0.266
Pro-BNP †	10.0 24.9 90.6	10.0 30.3 88.7	10.0 18.1 784.5	0.979
SGOT (U/l) †	43.0 59.0 80.0	43.0 60.0 73.0	43.3 57.0 86.5	0.676
SGPT (U/l) †	37.0 51.0 69.0	33.0 49.0 66.8	37.3 51.5 74.0	0.503
ALP (U/l) †	148.0	141.5	149.5	0.387

	182.0 250.0	177.5 215.0	185.0 300.3	
Vitamin D	27.9 (17.0-46.0)	25.6 (12.0-38.2)	32.1 (19.7-54.2)	0.199
D-Dimer	1000.0 (797.2-3456.7)	1173.0 (789.0-3274.4)	1000.0 (822.0-4591.7)	1.000
Accompanying medications, n (%)				
Lipid lowering agents – Statins	30 (46.9)	20 (71.4)	10 (34.5)	0.008
Interferon-beta-1a	19 (29.7)	9 (32.1)	10 (34.5)	0.848
Hydroxychloroquine	30 (46.9)	13 (46.4)	17 (58.6)	0.374
Corticosteroid	27 (42.2)	11 (39.3)	16 (55.2)	0.244
Naproxen	5 (7.8)	4 (14.3)	1 (3.4)	0.151
Azithromycin	6 (9.4)	0	6 (20.7)	0.011
Remdesivir	7 (10.9)	4 (14.3)	3 (10.3)	0.525
First-day oxygenation and ventilation, n (%)				
No device	7 (10.9)	3 (10.7)	4 (13.8)	0.659
Nasal Cannula	1 (1.6)	1 (3.6)	0	0.459
Simple face mask	16 (25.0)	9 (32.1)	7 (24.1)	
Face mask with reservoir	37 (57.8)	18 (64.3)	19 (65.5)	
Non-invasive ventilation in total	3 (4.7)	1 (3.6)	2 (6.9)	
Invasive mechanical ventilation	5 (7.8)	3 (10.7)	2 (6.9)	

n (%): number (percent); ACEi/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; WBC: White blood cell; RBC: Red blood cell; RDW: Red cell distribution width; BUN: Blood urea nitrogen; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; LDH: Lactate dehydrogenase; hs-cTnI: High sensitivity troponin I; Pro-BNP: pro B-type natriuretic peptide; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; ALP: Alkaline phosphatase

* SII: Systemic immune inflammation index (Platelet count × neutrophil count)/lymphocyte count

† Figures are 25th percentile, median, and 75th percentiles, respectively.

Table 3. Patient outcomes between the study groups.

Outcomes	**ACEi/ARB continued (n =28)**	**ACEi/ARB changed (n = 29)**	**P value**
Intensive care unit admission, n (%)	4 (14.3)	7 (24.1)	0.293
Length of intensive care unit stay, days	7.0 (3.5-11.2)	4.0 (3.0-16.0)	0.691
Length of hospital stay, days	4.0 (2.0-8.0)	4.0 (2.0-5.0)	1.0
Invasive mechanical ventilation, n (%)	4 (14.3)	3 (10.3)	0.464
Intensive care unit admission or respiratory failure requiring mechanical ventilation, n (%)	5 (17.8)	7 (24.1)	0.422
Change in saturation of O2 between baseline and discharge or time of death, mean (SD)	-9.6 ± 7.9	-7.4 ± 12.5	1.0
Maximum change in troponin from baseline, n (%)	2.56 ± 5.72	34.41 ± 67.68	0.421
Change in serum creatinine between baseline and discharge or time of death, n (%)	0.38 ± 1.17	1.33 ± 1.85	0.151
Acute kidney injury during hospitalization (defined as Kidney Disease Improving Global Outcomes stage 2 or higher), n (%)	4 (14.3)	4 (13.8)	0.610
WHO COVID-19 ordinal endpoint ≥ 6 *	19 (67.8)	20 (68.9)	0.579
Death, n (%)	5 (17.8)	4 (13.8)	
Days to all-cause death during hospitalization, mean (SD)	8.0 (4.5-13.5)	5.5 (6.0-50.0)	0.591
Readmission, n (%)	1 (3.6)	3 (10.3)	

* World Health organization clinical progression scale

n (%): number (percent); ACEi/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ICU: Intensive care unit; SD: Standard deviation

Table 4. Odds ratio of COVID-19 clinical outcomes in the angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) change vs. the ACEi/ARB continuation group.

	Unadjusted			*Adjusted **		
Clinical outcomes	**Odds ratio**	**95% CI (lower, upper)**	**P value**	**Odds ratio**	**95% CI (lower, upper)**	**P value**
ICU admission or respiratory failure requiring mechanical ventilation	1.400	0.393-4.985	0.604	1.756	0.354-8.699	0.491
WHO COVID-19 ordinal endpoint ≥ 6 †	0.972	0.356-2.654	0.955	0.470	0.114-1.939	0.297
Death	0.929	0.241-3.581	0.914	0.864	0.154-4.860	0.869

CI: Confidence interval; ICU: Intensive care unit

*Adjusted for gender, having ischemic heart disease, saturation o2 and temperature at admission

† World Health organization clinical progression scale

Figure 1

CONSORT Flow Diagram