Impact of Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Inflammatory Responses and Viral Clearance in COVID-19 Patients: A Multicenter Retrospective Cohort Study

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Abstract

Objectives: To evaluate the impact of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) on coronavirus disease 2019 (COVID-19) patients.

Methods: We included 229 patients with confirmed COVID-19 in a multicenter, retrospective cohort study. Propensity score matching at a ratio of 1:4 was introduced to eliminate the potential confounders. Patients were assigned to the ACEI/ARB group (n=40) or control group (n=160) according to whether they were current users of medication.

Results: Compared to the control group, patients in the ACEI/ARB group had lower levels of plasma IL-1β [(6.27±0.50) vs. (8.23±0.39) pg/ml, *P*=0.028], IL-8 [(35.74±4.00) vs. (45.88±2.06) pg/ml, *P*=0.037] and TNF-α [(8.79±0.40) vs. (10.91±0.21) pg/ml, *P*<0.01]. Patients with the current use of ACEIs/ARBs had a higher risk of shock (23% vs. 8%, *P*<0.01). Decreased lymphocyte counts [(0.85±0.45) vs. (1.02±0.52)*10^9/L, P=0.041] and elevated plasma levels of IL-10 [(7.39±0.51) vs. (6.18±0.16) pg/ml, *P*<0.01] were also important discoveries in the ACEI/ARB group. Patients in the ACEI/ARB group had a prolonged duration of viral shedding [(25±7) vs. (20±6) days, *P*=0.031] and increased length of hospitalization [(23±12) vs. (16±8) days, *P*<0.01]. These trends were similar in patients with hypertension.

Conclusions: For patients with excessive inflammatory responses and stable hemodynamics, ACEIs or ARBs might be tried to relieve the inflammatory storm, but the antiviral treatment should be enforced and the hemodynamics should be monitored closely; for patients with low levels of proinflammatory factors or instability hemodynamics, the agents might not be used to avoid a delay in viral clearance or increase the risk of shock.

Introduction

Up to March 31, 2020, the total number of patients with coronavirus disease 2019 has risen sharply to nearly 700,000 globally, with a mortality of nearly 5%. Meanwhile, this epidemic seems to be spreading at an exponential rate and has become an urgent public health emergency of international concern.

Several large retrospective studies have revealed that pre-existing cardiovascular disease and diabetes were the most frequent comorbidities of coronavirus disease 2019 (COVID-19) patients[1-3]; these patients even had a higher risk of mortality[4,5] than those with underlying respiratory disease. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely prescribed for these patients. ACEIs/ARBs have an impact on the renin-angiotensin system (RAS) and are postulated to attenuate pulmonary and systemic inflammatory responses, reducing the severity and mortality of viral-pneumonia-related acute respiratory distress syndrome[6-8], ultimately by angiotensin-converting enzyme 2 (ACE2) upregulation through the ACE2-Ang- (1-7)-Mas axis[9].

As the molecular biology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is well established, it appears to bind to its target cells through ACE2, which is expressed by epithelial cells of the lung to enable it to infect host cells[10, 11]. The expression of ACE2 is substantially increased in patients who are treated with ACE inhibitors and ARBs[12], which promotes SARS-CoV-2 entry into the body, increasing the risk of developing COVID-19[13, 14].

The controversial pathogenesis as well as the mixed results of several clinical studies[15, 16] of pneumonia with other pathogens made it difficult for physicians to determine whether the use of ACE inhibitors or ARBs should be terminated in patients with COVID-19.

To date, the actual impact of ACE inhibitor and ARB prescriptions on COVID-19 patients has not been assessed in current studies. Therefore, we aimed to evaluate the clinical manifestations, inflammatory responses, viral clearance and outcomes by a multicenter, retrospective cohort study.

Materials And Methods

1. Study design and population

We retrospectively included patients with confirmed cases of COVID-19 according to the World Health Organization (WHO)[17] and Chinese official guidelines[18] in a multicenter retrospective cohort study performed at three tertiary hospitals in Wuhan, Hubei Province, China (Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology; Zhongnan Hospital of Wuhan University; and the Central Hospital of Wuhan) from February 15, 2020 to March 25, 2020.

Exclusion criteria

1) Patients younger than 18 years old.

2) Noncurrent users of ACE inhibitors or ARBs prior to hospitalization.

3) Patients still hospitalized at the end of the study.

All patients were treated according to the standard protocols for antiviral, antibiotic, glucocorticoid, and Chinese medicine treatments.

The ethics committee of China-Japan Friendship Hospital approved this study (2020-21-K16). Written informed consent was waived due to the rapid emergence of this infectious disease. Written informed consent was waived due to the rapid emergence of this infectious disease.

Group division

We divided the patients into two groups. The ACEI/ARB group included patients who were current users of ACE inhibitor or ARB medication, while the control group included noncurrent users. Patients in the ACEI/ARB group were further divided into subgroups of a continued medication group and a terminated medication group according to the application of ACE inhibitors or ARBs during hospitalization.

2. Data collection and analysis

We collected data on the following parameters from the hospital electronic medical record systems, nursing records, laboratory examination systems, and radiological examinations and obtained standardized data collection forms: demographic characteristics, comorbidities, medication history within one month, symptoms at admission, laboratory finding changes from day 1 to day 14, radiological manifestations, treatment during hospitalization and outcome data that contained the rate of in-hospital death and progression, the duration of viral shedding, the length of hospital stay and the time from onset to death or discharge. Patients with cardiovascular disease and diabetes often combined the medication with statins[19] and oral hypoglycemic agents, especially thiazolidinediones, which have been reported to have an impact on the level of ACE2 by several studies[14, 20]. To further control for potential confounders, data on the use of statins, thiazolidinediones and other antihypertensive agents (β receptor blocking agent and diuretics) prior to admission in each group were calculated within 90 days [6].

Two researchers also independently reviewed the data collection forms to double check the data collected. Any missing or uncertain records of the epidemiological, medication and symptom data were collected and clarified through direct communication with patients and their families.

We compared the two groups in terms of the above aspects to identify the differences between ACE inhibitor or ARB users with nonusers prior to admission. Then, a subgroup analysis was conducted by comparing the dynamic changes of indicators involved in immune status and inflammatory reactions, as well as the outcomes between patients who continued and terminated medication during hospitalization. As hypertension itself could activate the RAS, patients with hypertension were excluded to avoid potential confounders. A comparison of the immune status, inflammatory reactions and outcomes between the ACEI/ARB and control groups in patients without hypertension was conducted.

3. Cytokine and chemokine measurement

To evaluate the impact of coronavirus and additional ACE inhibitors or ARBs on the production of cytokines or chemokines in the acute phase of the illness, plasma cytokines and chemokines [interleukin 1β (IL-1β), IL-2R, IL-6, IL-8, IL-10 and tumor necrosis factor α (TNF-α)] were measured using chemiluminescent immunoassay (CLIA) (CFDA approved) by Siemens IMMULITE 1000 for patients according to the manufacturer's instructions.

4. Definitions

Medications classified as ACE inhibitors were benazepril, perindopril and fosinopril, while the ARBs of the included patients were candesartan, irbesartan, valsartan, olmesartan, telmisartan and losartan. The effective half-life period of the above agents varied from 6 to 50 hours; therefore, it took no more 10 days to achieve a stable blood drug concentration.

Patients were considered a current user of medication if they had a supply of medication to last until the date of hospitalization assuming an 80% compliance rate[6, 21]. The patients who did not meet the definition were regarded as noncurrent users. ACE inhibitors or ARBs were considered to be continued if they were given more than 50% of the days during hospitalization[8]; otherwise, they were considered to be terminated.

In-hospital progression was defined as a decline in PaO_2/FiO_2 of more than 100 mmHg or the need for invasive positive pressure ventilation (IPPV) and/or extracorporeal membrane oxygenation (ECMO) during hospitalization.

Shock was defined according to the interim guidance of the WHO for novel coronavirus[22, 23]. Acute kidney injury (AKI) was identified and classified on the basis of the highest serum creatinine level or urine output criteria according to the Kidney Disease Improving Global Outcomes Classification (KDIGO)[23, 24]. Respiratory failure, coagulation and liver failure were defined as a Sequential Organ Failure Assessment (SOFA) score greater than or equal to two points.

Statistical analysis

Descriptive statistics included proportions for categorical variables and the mean (standard deviation) or median (interquartile range) for continuous variables. Data were unadjusted unless specifically stated otherwise.

Processing of missing data

When the missing rate of vital variables involved in our study was less than 15%, we used SAS predictive mean matching imputation to replace missing values within each variable, while the variables were abandoned when the missing rate reached 20%.

Processing of the unbalanced sample size: propensity score matching

The propensity score matching (PSM) method was applied at a ratio of 1:4 between the ACEI/ARB group and the control group. Age, sex and medication history prior admission which might be potential confounders associated with ACEI/ARB were matched variables in PSM to derive the cohort.

Proportions were compared using $\chi 2$ or Fisher's exact tests, and continuous variables were compared using the t test or Wilcoxon rank sum test, as appropriate. Statistical significance was defined as a 2-tailed *P* value of $\leq .05$. SAS software, version 9.4 (SAS Institute Inc.) was used for all analyses.

Results

From February 15, 2020 to March 25, 2020, a total of 229 patients with confirmed cases of COVID-19 were admitted, and 175 patients not taking an ACE inhibitor or ARB medication. Among the 54 patients with a medication history, three of them were regarded as noncurrent users according to the definition and were excluded ultimately. The propensity score matching (PSM) method was applied at a ratio of 1:4 between the ACEI/ARB group (n=40) and the control group (n=160). Age, sex and medication history 90 days prior admission were matched variables in PSM to derive the cohort. Among the patients with the ACEI/ARB medication, 17 continued medication during hospitalization, while the other 34 terminated medication *(Figure 1)*. The mean age was 58 ± 17 years, male patients accounted for 58% (n=115), and the disease severity status[18] at admission was general for most of the study cohort (n=144, 72%).

1. Comparisons of baseline prior hospitalization between the ACEI/ARB and control groups (Table 1)

The ACEI/ARB group included more patients with hypertension (75% vs. 23%, *P*<0.01) than the control group. The demographic characteristics, other comorbidities, severity of the condition and possible medication histories might have influenced the ACE2 level but did not differ significantly between the two groups. No significant difference was found between the two groups in time from onset to hospitalization and to COVID-19 diagnosis.

2. Comparisons of clinical symptoms, laboratory examinations and radiological manifestations on admission between the ACEI/ARB and control groups *(Table 2)*

The symptoms, including fever, cough, hemoptysis, dyspnea, fatigue/myalgia and diarrhea, as well as vital signs, were not significantly different between the ACEI/ARB group and the control group. For laboratory examinations, patients with ACE inhibitor or ARB medication had lower lymphocyte counts [(0.85±0.45) vs. (1.02±0.52)*10^9/L, P=0.041] and higher levels of lactate dehydrogenase (LDH) [(377±130) vs. (289±158) IU/L, *P*<0.001] and D-dimer [(3.33±0.89) vs. (1.65±0.25) μg/ml, *P*=0.015] than the control group.

The inflammatory factors, including IL-1β, IL-2R, IL-6, IL-8, IL-10 and TNFα, were chosen from the first value within three days of admission, and as the missing rate reached 12-15%, the SAS predictive mean matching imputation was applied to replace missing values of each group. The missing rate of IL-2R, serum ferritin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were as high as 25-35%; therefore, they were abandoned in statistical analysis. Patients in the ACEI/ARB group had slightly lower levels of proinflammatory cytokines, including IL-1β [(6.27±0.50) vs. (8.23±0.39) pg/ml, *P*=0.028], IL-8 [(35.74±4.00) vs. (45.88±2.06) pg/ml, *P*=0.037] and TNF-α [(8.79±0.40) vs. (10.91±0.21) pg/ml, *P*<0.01], and higher levels of anti-inflammatory cytokines [IL-10: (10.39±0.51) vs. (6.18±0.16) pg/ml, *P*<0.01] than the control group.

3. Comparison of organ function, treatment and outcomes during hospitalization between the ACEI/ARB and control groups *(Table 3)*

Patients with current use of ACE inhibitors or ARBs seemed to have a higher risk of developing shock (23% vs. 8%, *P*<0.01) and the application of vasoconstrictive agents (20% vs. 6%, *P*<0.01) than the control group; however, the percentages of respiratory failure, AKI, coagulation failure and liver failure were not different from those of the control group. In addition, the necessities for invasive IPPV and ECMO were not decreased in the ACEI/ARB group.

The duration of viral shedding [(25±7) vs. (20±6) days, *P*=0.031], length of hospital stay [(23±12) vs. (16±8) days, *P*<0.01] and time from onset to death or discharge [(33±14) vs. (27±10) days, *P*<0.01] were longer in the ACEI/ARB group than in the control group, while no difference was found in the rate of in-hospital progression or death.

4. Subgroup analyses: comparison between patients who continued and terminated medication during hospitalization

Among the patients with ACEI/ARB medication, 17 continued medication during hospitalization, while the other 34 terminated medication for several reasons. The dynamic changes in indicators involved in immune status and inflammatory reactions at the first, seventh, and fourteenth days of hospitalization as well as the outcomes were compared between the two groups. The missing rates of IL-2R and IL-8 at seven days and fourteen days after admission were extremely high and were not included in the analysis. Patients with continued use of ACE inhibitor or ARB had a consistently lower level of IL-1β and TNF-α at seventh day; while maintained higher level of the IL-10 from the seventh day to the fourteenth day than patients terminated the medication. However, the patients who terminated the medication had a trend of elevated lymphocyte counts [day 1, day 7, day 14: (1.09±0.52) vs. (1.30±0.86) vs. (1.60±0.52)*10^9/L, *P*<0.01] from the first day to the fourteenth day, had a trend of higher levels of IL-1β [day 1, day 7, day 14: (6.03±3.19) vs. (10.78±6.88) vs. (6.52±3.33) pg/ml, *P*<0.01] and TNF-α [day 1, day 7, day 14: (9.19±2.86) vs. (18.39±8.47) vs. (6.15±2.15) pg/ml, *P*<0.01] at the seventh day, which returned to the baseline level on the fourteenth day (*Table 4, Figure 2*).

The duration of viral shedding [(27±7) vs. (21±7) days, *P*=0.042], length of hospital stay [(27±9) vs. (21±11) days, *P*=0.037] and time from onset to death or discharge [(33±13) vs. (29±14) days, *P*=0.038] were longer in the continued medication group than in the terminated medication group. The rate of in-hospital progression and death were not significantly different between the two groups (*Table 5*).

5. Subgroup analyses: a comparison of the immune status, inflammatory reactions and outcomes between the ACEI/ARB and control groups in patients with hypertension

Among 66 patients with hypertension, 30 patients were divided into the study group (ACEIs/ARBs group) and the other 36 patients were in the control group.

Compared with the control group, the patients in the study group had lower levels of IL-1β [(6.41±0.34) vs. (8.36±0.21) pg/ml, *P*=0.039] and IL-8 [(33.2±3.64) vs. (42.39±1.21) pg/ml, *P*=0.027] on admission. Regarding clinical outcomes, the duration of viral shedding [(26±9) vs. (19±7) days, *P*=0.024] and time from onset to death or discharge [(31±11) vs. (25±9) days, *P*=0.032] was longer in the study group than in the control group; however, no difference was detected in the rate of in-hospital progression and death between the two groups.

Discussion

To our knowledge, this is the first study to evaluate the clinical manifestations, inflammatory responses, and viral clearance of COVID-19 patients treated with ACE inhibitor and ARB medication by a multicenter, retrospective cohort control study and to allow a dynamic observation of inflammatory responses by continuous monitoring from the first to fourteenth day.

The major findings of our study were that ACE inhibitor or ARB medication had an impact on inhibiting the proinflammatory response but promoted the anti-inflammatory response persistently and extended the duration of viral shedding, had an impact on hemodynamics as well. The inflammatory factors of COVID-19 patients should be monitored as route examination. For patients with excessive inflammatory responses and stable hemodynamics, ACEIs or ARBs might be tried to relieve the inflammatory storm, but the antiviral treatment should be enforced and the hemodynamics should be monitored closely; for patients with low levels of proinflammatory factors or instability hemodynamics, the agents might not be used to avoid a delay in viral clearance or increase the risk of shock.

Inflammation is mediated by proinflammatory cytokines and anti-inflammatory cytokines. Inappropriate elevated expression of proinflammatory cytokines can result in sepsis, tissue destruction, or death[21, 25]. Our study revealed that the plasma levels of IL-1β, IL-8 and TNF-α in patients taking ACE inhibitor or ARB were lower than those in patients not taking medication; in addition, persistently lower levels of proinflammatory factors were maintained in patients who continued medication during hospitalization, which was consistent with the previous experimental results by Gullestad L and his colleagues[26] with the conclusion that high-dose enalapril was associated with a significant decrease in IL-6 activity in patients with severe chronic heart failure. The specific organ and systemic inflammatory responses were postulated to attenuate through a reduction in the level of cytokines, which might be explained by the attenuating effects of ACE inhibitors through the deactivation of the ACE-AngII-AT1 axis but the stimulation of the ACE2-Ang- (1-7)-Mas axis in a feedback mechanism[9, 27, 28] as a negative regulator with attenuated cytokines and thus protecting the patients from organ injury. Consequently, some authors[29, 30] have speculated that the use of ACEIs/ARBs might actually be a potentially beneficial intervention in those with COVID-19.

Apart from organ protection by attenuating the inflammatory response, basic investigation has shown that bradykinin and substance P produced by ACE inhibitors sensitize the sensory nerves of the airways and enhance the cough reflex[31, 32], which plays a protective role against pathogens. These two mechanics made it possible to improve the outcome in patients with pneumonia. Mortensen et al[6] found a significant decrease in mortality, the length of hospital stay, and mechanical ventilation in patients taking ACE inhibitors or ARBs who were hospitalized with pneumonia compared to a matched cohort. A meta-analysis[33] that included 19 studies noted that patients taking ACE inhibitors were associated with a significant approximately one-third reduction in the risk of pneumonia compared with controls. In addition, a recent study[8] by Christopher Henry also observed lower rates of death and intubation with continued use of ACE inhibitors than with terminated use (OR=0.25; 95% CI, 0.09-0.64) throughout the hospital stay in cases of viral pneumonia not due to coronavirus. Unfortunately, our study did not find decreased mortality in patients with current use of ACE inhibitors or ARBs, even though we analyzed patients with continued medication during hospitalization and without hypertension to avoid potential confounding factors. The most likely explanation was that our study included a small number of patients, while most of their patients had mild cases as determined by diseases severity status and without excessive inflammatory reactions, which was the target for ACE inhibitors or ARBs.

What is noteworthy is that ACE inhibitors or ARBs increased the risk of shock and the necessity of vasoconstrictive agents. It could be explained by the nature of the antihypertensive agents and came as a revelation to us that it should be avoided in patients with instability hemodynamics.

Our research also revealed that ACE inhibitors or ARBs led to prolonged viral shedding and extended the length of hospitalization. SARS-CoV-2 appears to bind to its target cells through angiotensin-converting enzyme 2 (ACE2). ACE inhibitors or ARBs upregulate ACE2 receptor expression in humans[34] by blocking the classic ACE pathway; thus, it is theoretically possible that the pre-existing use of these drugs might predispose a person to infection with a greater viral load of SARS-CoV-2[13]. This hypothesis was supported by the evidence of Ferrario that there was a 4.7-fold increase in cardiac ACE2 mRNA by an ACE inhibitor[35]. Decreased lymphocyte counts and elevated plasma levels of IL-10 were also important discoveries in patients with ACE inhibitors or ARBs. Moreover, the lymphocyte counts in patients with continued use of an ACE inhibitor or ARB during hospitalization recovered slowly, as observed by successive monitoring on the first to fourteenth days. The immune status was weakened by lymphocytopenia and elevated anti-inflammatory cytokines in patients taking ACEIs, which might be another reason for the slow viral clearance. As the important criterion for discharge was the negative conversion of the SARS-CoV-2, prolonged viral shedding led to an extended length of hospitalization. This might be the defect of the ACE inhibitor or ARB and could explain the mixed results and controversy about their prescription in COVID-19 patients. For this reason, antiviral therapy in patients taking ACE inhibitors or ARBs for the purpose of relieving the inflammatory response should be reinforced, and their viral load should be monitored closely; however, in patients with low levels of proinflammatory factors, ACE inhibitors or ARBs should be not be used to avoid a delay in viral clearance.

An autopsy report revealed that mononuclear inflammatory infiltration dominated by lymphocytes was observed in the lungs, but no virus inclusion bodies were found[36]. We could then propose a hypothesis that cytokines released by inflammatory storms secondary to viral infection might be more important in the death of critically ill patients with COVID-19 than the viral infection itself in a certain period. From this perspective, it is possible that ACE inhibitors or ARBs might improve the outcome in critically ill patients with excessive inflammatory responses or severe multiple organ failure; when the inflammatory storm gradually diminishes, the focus of therapy should be on clearance of the virus and the enhancement of the immune system; and ACE inhibitors or ARBs with the adverse effect of prolonged viral shedding and weakening the defense of the immune system to some degree should be terminated. Prospective cohort and randomized controlled trials are needed to confirm this hypothesis and examine potential mechanisms of action.

Our study was limited by the small number of patients included and by not strictly excluding confounding factors, such as other medications, diabetes, coronary heart disease and chronic heart failure that might influence the RAS[37]. However, the PSM method was applied to eliminate bias. We also noticed that the number of patients with hypertension was much higher in the ACEI/ARB group, which might be an important confounding factor. By subgroup

analyze, we found a similar result. We encourage further prospective randomized controlled studies designed by increasing the sample size and strictly excluding potential confounders to explore the impact of ACE inhibitors or ARBs on inflammatory responses, viral clearance and mortality in COVID-19 patients.

Declarations

Consent for publication

Not applicable.

Ethics approval and consent to participate

The ethics committee of China-Japan Friendship Hospital approved this study (2020-21-K16). Written informed consent was waived due to the rapid emergence of this infectious disease.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors made substantial contributions to the conception and design of the study or to the data acquisition, analysis or interpretation; reviewed and approved the final manuscript; and significantly contributed to this study. Dr. Zhan took full responsibility for the integrity of the submission and publication and was involved in the study design. Drs. Linna Huang and Ziying Chen involved in data collection, had full access to all of the data in the study, took responsibility for the integrity of the data and were responsible for data verification, as well as the drafting of the manuscript. Pro. Lin Hua took the responsibility for statistical analysis and the accuracy of the data analysis. Others involved in in data collection, had full access to all of the data in the study, and took responsibility for the integrity of the data.

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Tables

Table 1. Baseline variables in the two groups prior to admission

	All (n=200)	ACEI/ARB group (n=40)	Control group (n=160)	*P*
Age, years, mean ± SD	58±17	58±15	58±17	0.872
Gender (men), number (%)	115 (%)	23 (58%)	92 (58%)	1
Comorbidities, number (%)				
Hypertension	66 (33%)	30 (75%)	36 (23%)	<0.001[b]
Diabetes	33 (17%)	10 (25%)	23 (14%)	0.105
Coronary heart disease	20 (10%)	7 (18%)	13 (8%)	0.077
Chronic heart failure	5 (3%)	2 (5%)	3 (2%)	0.258
Underlying lung disease	19 (10%)	6 (15%)	13 (8%)	0.185
Chronic kidney disease	2 (1%)	0 (0%)	2 (1%)	0.477
Chronic liver dysfunction	4 (2%)	0 (0%)	4 (3%)	0.383
Malignancy	4 (2%)	0 (0%)	4 (3%)	0.383
History of smoking, number (%)	26 (13%)	7 (18%)	19 (12%)	0.344
Other medication history within 90 days, number (%)				
Corticosteroids	0 (0%)	0 (0%)	0 (0%)	1
Immunosuppressants	0 (0%)	0 (0%)	0 (0%)	1
Statins	25 (13%)	5 (13%)	20 (13%)	1
Thiazolidinediones	5 (3%)	1 (3%)	4 (3%)	1
β receptor blocking agent	25 (13%)	5 (13%)	20 (13%)	1
Diuretics	20 (10%)	4 (10%)	16 (10%)	1
Diseases severity status*				
General	144 (72%)	24 (60%)	120 (75%)	0.103
Severe	31 (16%)	9 (23%)	22 (14%)	0.171
Critical	25 (13%)	7 (18%)	18 (11%)	0.285
Treatment before hospital, number (%)				
Methylprednisolone	15 (8%)	5 (13%)	10 (6%)	0.179
Antibiotic therapy	109 (55%)	26 (65%)	83 (52%)	0.136
Antiviral therapy	113 (57%)	23 (58%)	90 (56%)	0.887
Time from onset to hospital admission, days, mean ± SD	10±6	11±6	10±6	0.405
Time from onset to diagnosis, days, mean ± SD	8±6	6±5	8±6	0.187

[a]: *P*<0.05; [b]: *P*<0.01; *defined according to the Chinese management guideline for COVID-19 (version 7.0)[18].

Table 2. Clinical, laboratory findings and radiological manifestations in the two groups on admission

	All (n=200)	ACEI/ARB group (n=40)	Control group (n=160)	P
l symptoms, number (%)				
ver (≥37.3℃)	188 (94%)	36 (90%)	152 (95%)	0.234
ugh	141 (71%)	30 (75%)	111 (69%)	0.485
oductive cough	79 (40%)	17 (43%)	62 (39%)	0.664
moptysis	6 (3%)	2 (5%)	4 (3%)	0.407
	89 (%)	23 (58%)	66 (41%)	0.064

spnea	89 (%)	23 (58%)	66 (41%)	0.064
igue or myalgia	94 (47%)	18 (45%)	76 (48%)	0.777
arrhea	51 (26%)	13 (33%)	38 (24%)	0.256
l signs, mean ± SD				
hest temperature, °C	38.5±0.7	38.6±0.7	38.5±0.6	0.207
spiratory rate, breaths/min	23±5	24±6	23±5	0.179
art rate, beats/min	96±13	99±13	95±13	0.059
stolic blood pressure, mmHg	124±18	118±17	126±20	0.033[a]
O_2, %	94±7	93±6	94±7	0.451
$)_2$, %	42±18	43±17	41±18	0.511
ratory examination, mean ± SD				
l routine				
BC, *10^9/L	6.16±3.80	7.01±3.96	5.98±3.75	0.084
utrophil count, *10^9/L	4.62±3.82	5.39±3.75	4.45±3.82	0.117
mphocytes, *10^9/L	0.98±0.51	0.85±0.45	1.02±0.52	0.041[a]
emical examination				
T, U/L	43±3	52±9	41±2	0.085
T, U/L	40±2	48±9	39±2	0.135
IL, mmol/L	10.9±6.8	11.1±6.6	10.9±6.8	0.852	
:, μmol/L	80.4±5.6	74.2±3.4	81.8±6.8	0.609
H, U/L	305±157	377±130	289±158	<0.001[b]
T, pg/ml	11±1	13±2	11±1	0.498
'-proBNP, pg/ml	372±87	437±92	332±61	0.096
nmatory factors				
1β, pg/ml	7.89±0.34	6.27±0.50	8.23±0.39	0.028[a]
2R, U/ml	796.30±25.1	696.22±55.69	817.57±28.44	0.070
6, pg/ml	42.48±2.50	40.37±7.55	42.95±2.58	0.684
8, pg/ml	44.10±1.85	35.74±4.00	45.88±2.06	0.037[a]
10, pg/ml	7.69±0.14	9.39±0.51	6.18±0.16	0.005[b]
F-α, pg/ml	10.54±0.92	8.79±0.40	10.91±0.21	<0.001[b]
T, ng/ml	0.28±0.09	0.12±0.03	0.32±0.11	0.408
ulation function				
, s	13±1	14±1	13±1	0.148
TT, s	36±9	37±8	36±10	0.528
Dimer, μg/ml	1.94±0.26	3.33±0.89	1.65±0.25	0.015[a]
t CT manifestations, number (%)				
ateral lesion	113 (57%)	18 (45%)	95 (59%)	0.101
GO	115 (58%)	18 (45%)	97 (61%)	0.074
nsolidation	51 (26%)	12 (30%)	39 (24%)	0.465

[a]: $P<0.05$; [b]: $P<0.01$; SpO_2: saturation of peripheral oxygen; FiO_2: fraction of inspiration; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; Scr: creatinine; LDH; lactate dehydrogenase; TnT: troponin T; NT-proBNP: N-terminal pro-brain natriuretic peptide; IL-1β: interleukin-1β; IL-2R: interleukin-2R; IL-6: interleukin-6; IL-8: interleukin-8; IL-10: interleukin-10; TNF-α: tumor necrosis factor-α; PCT: procalcitonin; PT: prothrombin time; APTT: activated partial thromboplastin time; GGO: ground-glass opacity

Table 3. Organ function, treatments and outcomes in the two groups during hospitalization

	All (n=200)	ACEI/ARB group (n=40)	Control group (n=160)	*P*
n failure*, number (%)				
spiratory failure	28 (14%)	8 (20%)	20 (13%)	0.221
ock	22 (11%)	9 (23%)	13 (8%)	<0.01[b]
I	18 (9%)	4 (10%)	14 (9%)	0.805
agulation failure	6 (3%)	1 (3%)	5 (3%)	0.836
er failure	20 (10%)	5 (13%)	15 (9%)	0.556
ment, number (%)				
tibiotics	141 (71%)	24 (60%)	117 (73%)	0.104
tiviral treatment	188 (94%)	38 (95%)	150 (94%)	0.766
rticocorticoids	68 (34%)	10 (25%)	58 (36%)	0.179
travenous immunoglobin	47 (24%)	9 (23%)	38 (24%)	0.868
ndard oxygen therapy	169 (85%)	36 (90%)	133 (83%)	0.283
NO	32 (16%)	7 (18%)	25 (16%)	0.772
PV	17 (9%)	5 (13%)	12 (8%)	0.310
V	17 (9%)	6 (15%)	11 (7%)	0.099
MO	4 (2%)	1 (3%)	3 (2%)	0.801
soconstrictive agents	17 (9%)	8 (20%)	9 (6%)	<0.01[b]
ome				
hospital progression#, number (%)	33 (17%)	6 (15%)	27 (17%)	0.775
hospital death, number (%)	21 (11%)	4 (10%)	17 (11%)	0.908
spital length of stay, days, mean ± SD	18±9	23±12	16±8	<0.001[b]
ration of viral shedding, ys, mean ± SD	22±8	25±7	20±6	0.031[a]
ne from onset to death or discharge, days, mean ± SD	28±11	33±14	27±10	<0.001[b]

me from onset to death or discharge, days, mean ± SD	28±11	33±11	27±10	<0.001

[a]: $P<0.05$; [b]: $P<0.01$; [*], Shock was defined according to the interim guidance of the WHO for novel coronavirus[22, 23]. AKI was identified and classified on the basis of the highest serum creatinine level or urine output criteria according to kidney disease, improving global outcome classification[23, 24]. Respiratory failure, coagulation and liver failure were defined as a SOFA score greater than or equal to two points. [#], defined as a decline in PaO_2/FiO_2 greater than 100 mmHg or the need for IPPV and/or ECMO during hospitalization. AKI: acute kidney injury; HFNO: high flow nasal oxygenation; NPPV: noninvasive positive pressure ventilation; IPPV: invasive positive pressure ventilation; ECMO: extracorporeal membrane oxygenation

Table 4. The dynamic changes in the lymphocytes and inflammatory factors in patients continued and terminated ACEI/ARB during hospitalization

	D1	D7	D14	*P*
tinued medication group, mean ± SD				
ymphocytes, *10^9/L	0.82±0.59	1.33±0.36	1.33±0.41	0.265
-1β, pg/mL	6.85±4.37	6.35±2.84	5.01±0.52	0.153
-10, pg/mL	9.21±4.14	14.69±9.41	9.82±4.02	0.095
NF-α, pg/mL	7.85±2.83	8.17±2.45	6.82±2.17	0.639
minated medication group, n ± SD				
ymphocyte count, *10^9/L	1.09±0.52	1.30±0.86	1.60±0.52	0.003 [b]
-1β, pg/mL	6.03±3.19	10.78±6.88	6.52±3.33	0.002 [b]
-10, pg/mL	8.08±3.40	7.71±3.94	5.53±1.52	0.09
NF-α, pg/mL	9.19±2.86	18.39±8.47	6.15±2.15	<0.001 [b]

[b]: $P<0.01$; IL-1β, interleukin 1β; TNF-α, tumor necrosis factor α; D1, the first day after admission; D7, the seventh day after admission; D14, the fourteenth day after admission

Table 5. Outcomes in patients who continued and those who terminated ACEIs/ARBs during hospitalization

Outcomes	Continued ACEIs/ARBs (n=17)	Terminated ACEIs/ARBs (n=34)	*P*
In-hospital progression[#]	2 (12%)	5 (15%)	0.774
In-hospital death	0 (0%)	2 (6%)	0.308
Hospital length of stay, days	27±9	21±11	0.037[a]
Duration of viral shedding, days	27±7	21±7	0.042[a]
Time from onset to death or discharge, days	33±13	29±14	0.038[a]

[a]: $P<0.05$; [#], defined as a decline in PaO_2/FiO_2 greater than 100 mmHg or the need for IPPV and/or ECMO during hospitalization.

Figures

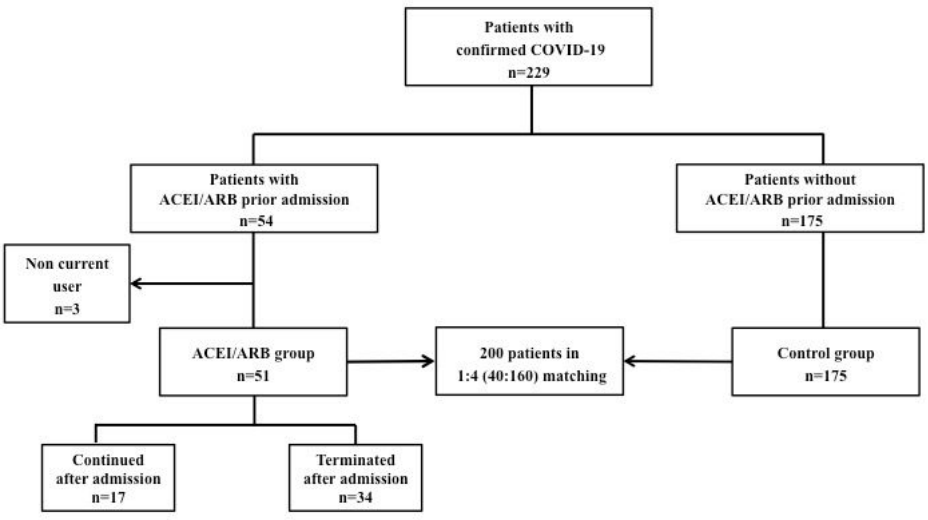

Figure 1

Flowchart. A flowchart illustrated the enrollment of patients in our study. From February 15, 2020 to March 25, 2020, a total of 217 patients with confirmed cases of COVID-19 were admitted, and 171 patients not taking an ACE inhibitor or ARB medication were designated as the control group. Among the 46 patients with a medication history, three of them were regarded as noncurrent users according to the definition, and 43 patients were ultimately divided into the ACEI/ARB group. Among the patients in the ACEI/ARB group, 15 continued medication during hospitalization, while the other 28 terminated medication.

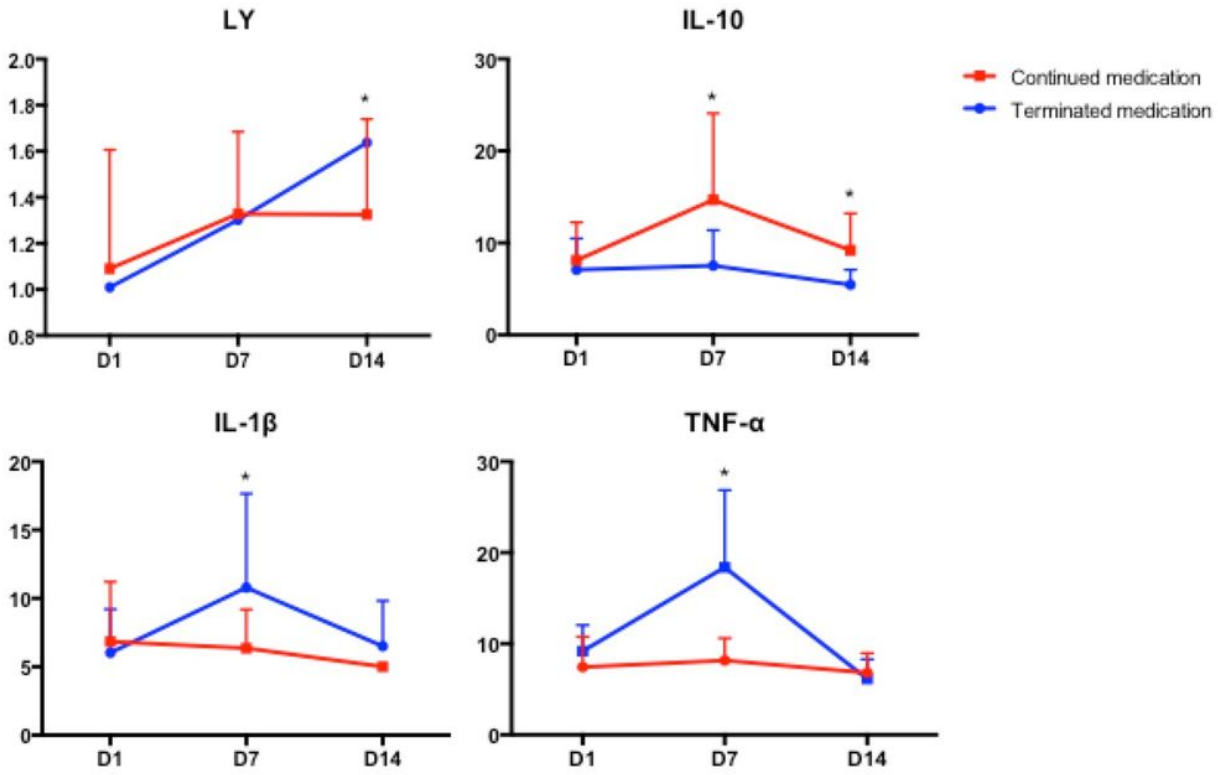

Figure 2

The dynamic changes in the lymphocyte counts and inflammatory factors between patients who continued and those who terminated ACEIs/ARBs during hospitalization. Patients with continued use of ACE inhibitor or ARB had a consistently lower level of IL-1β and TNF-α at seventh day; while maintains higher level of the IL-10 from the seventh day to the fourteenth day than patients terminated the medication. The patients who terminated the medication had a trend of elevated lymphocyte counts from the first day to the fourteenth day, while they had a trend of higher levels of IL-1β and TNF-α at the seventh day and returned to the baseline level on the fourteenth day.