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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dr. Antonio Corvino is a PhD in the Motor Science and Wellness Department of University of Naples "Parthenope". After obtaining his MD degree from the School of Medicine, Second University of Naples (2008), he completed a residency in Radiology at the University of Naples Federico II (2014). Following post-graduate training at the Catholic University of Rome, yielding a second level Master's degree in "Internal Ultrasound Diagnostic and Echo-Guided Therapies" (2015), he served on the directive board of Young Directive of Italian Society of Ultrasound in Medicine and Biology (2016-2018). His ongoing research interests involve ultrasound and ultrasound contrast media in abdominal and non-abdominal applications, mainly in gastrointestinal, hepatic, vascular, and musculoskeletal imaging. (L-Editor: Filipodia)

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Retrospective Cohort Study

Angiotensin converting enzymes inhibitors or angiotensin receptor blockers should be continued in COVID-19 patients with hypertension

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Abstract

BACKGROUND

Recent studies have revealed that sustained ingestion of angiotensin converting enzymes inhibitors or angiotensin receptor blockers (ACEIs/ARBs) had no harmful effects on coronavirus disease 2019 (COVID-19) patients complicated with hypertension.

AIM

To investigate the impact on COVID-19 patients complicated with hypertension who discontinued using ACEIs/ARBs.

METHODS

All COVID-19 patients complicated with hypertension admitted to our isolated unit were consecutively recruited in this study. Some patients switched from ACEIs/ARBs to calcium channel blocker (CCBs) after admission, while others continued using non-ACEIs/ARBs. We compared characteristics and clinical outcomes between these two groups of patients.

conflict of interest.

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RESULTS

A total of 53 patients were enrolled, 27 patients switched from ACEIs/ARBs to CCBs while 26 patients continued with non-ACEIs/ARBs. After controlling potential confounding factors using the Cox proportional hazards model, hospital stay was longer in patients who discontinued ACEIs/ARBs, with a hazard ratio of 0.424 (95% confidence interval: 0.187-0.962; $P = 0.040$), upon discharge than patients using other anti-hypertensive drugs. A sub-group analysis showed that the effect of discontinuing use of ACEIs/ARBs was stronger in moderate cases [hazard ratio = 0.224 (95% confidence interval: 0.005-0.998; $P = 0.0497$)].

CONCLUSION

Patients in the discontinued ACEIs/ARBs group had longer hospital stays. Our findings suggest that COVID-19 patients complicated with hypertension should continue to use ACEIs/ARBs.

Key Words: COVID-19; Hypertension; Angiotensin converting enzymes inhibitors; Angiotensin receptor blockers; Angiotensin-converting enzyme-2; Prognosis

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Core Tip: Recent research revealed that use of angiotensin converting enzymes inhibitors or angiotensin receptor blockers (ACEIs/ARBs) had no significant harm on coronavirus disease 2019 (COVID-19) patients complicated with hypertension. However, the impact of discontinuing using ACEIs/ARBs in those patients was still unclear. In the present study, we retrospectively collected the clinical data of patients with both COVID-19 and hypertension to explore whether any difference in disease outcomes existed between patients who discontinued using ACEIs/ARBs and those who continued using other anti-hypertensive drugs.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a critical global health issue. It was first reported in December 2019, and the epidemic of the disease spread extremely rapidly since its discovery^[1].

Patients might suffer from mild, self-limiting upper airway respiratory infection, severe deteriorating pneumonia, or even fatal complications. Epidemiological surveys have shown that the proportion of patients with COVID-19 who have hypertension is between 10% and 35%, making hypertension the most common comorbidity^[2-6]. Specifically, angiotensin converting enzyme (ACE) inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are taken by 25%-50% of patients with hypertension for blood pressure control^[5-8]. As the first-line inhibitors of renin-angiotensin-aldosterone system (RAAS)^[9], they always act as a cornerstone in treatment of cardiovascular disease.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes COVID-19 infects the human body in a similar pattern as SARS coronavirus (SARS-CoV) does. They bind ACE2 in the lung *via* S protein, and subsequently enter the host alveolar cells, where they replicate and activate the immune system. The release of inflammatory factors and cytokines causes lung injury and even fatal complications in critical cases^[10-12]. Additionally, several studies^[13-15] have shown that ACEIs or angiotensin receptor blockers (ACEIs/ARBs) might upregulate level of ACE2 expression. This may confer increased susceptibility and aggravation of COVID-19. Therefore, some researchers considered that ACEIs/ARBs should be discontinued in COVID-19 patients with hypertension^[16]. However, the American Heart Association/



American College of Cardiologists and the European Society of Cardiology^[17-19] pointed out that there was no clinical evidence on worse outcomes in COVID-19 patients with previous ACEIs/ARBs prescription, and they did not recommend discontinuing ACEIs/ARBs. Moreover, most research had revealed that sustained ingestion of ACEIs/ARBs had no significant harmful effects on COVID-19 patients complicated with hypertension during hospitalization. However, few studies investigated the effect of discontinuing ACEIs/ARBs in COVID-19 patients with hypertension. Therefore, we conducted a study to investigate whether the discontinuation of ACEIs/ARBs in COVID-19 patients with hypertension had a negative impact on patient prognosis.

In the present study, we aimed to collect retrospectively the clinical data of patients with both COVID-19 and hypertension and to explore the differences between patients who discontinued using ACEIs/ARBs and those who kept using other types of anti-hypertensive medications.

MATERIALS AND METHODS

Study subjects

This study was based on the COVID-19 cohort from a patient registry of all COVID-19 patients admitted to an isolated unit in a tertiary hospital from February 8, 2020 to February 24, 2020. All patients were diagnosed with COVID-19 pneumonia according to national guidelines^[20].

The exclusion criteria were as follows: (1) Uncured malignant tumors; (2) Regular dialysis; (3) Immunosuppression therapy post transplantation; (4) Steroids or immunosuppressive agents for autoimmune diseases; (5) Chronic pulmonary diseases; (6) Active hepatitis or liver cirrhosis; (7) Pregnancy and lactation; (8) Sequelae of cerebrovascular disease; (9) Hematological diseases; and (10) Age < 18 years.

All patients were given standard care. However, due to limited resources during the initial stage of the epidemic, there was shortage of ACEIs/ARBs supply. Thus, all patients who had previously taken ACEIs/ARBs were prescribed other antihypertensive drugs, mostly calcium channel blocker (CCBs). There were 53 moderate or severe patients enrolled, 27 of which switched from ACEIs/ARBs to CCBs and 26 continued with their usual non-ACEIs/ARBs anti-hypertensive drugs.

In the majority of critical patients with multi-organ dysfunction syndrome or hemodynamic instability, oral anti-hypertensive drugs could not be administered. The prognosis of those patients was profoundly affected by severity of illness. In order to avoid potential bias, 13 critical cases were excluded from the final analysis (see Figure 1).

Study methods

The present study described the baseline characteristics of patients with moderate and severe COVID-19 who were using anti-hypertensive drugs, including their gender, age, disease severity classification, quick sequential organ failure assessment (qSOFA) score, clinical and radiological manifestations, inflammatory factors, labs, and other disease-related characteristics. In addition, those patients switched from ACEIs/ARBs to CCBs after admission were assigned to the discontinued ACEIs/ARBs group. The remaining patients who have taken non-ACEIs/ARBs anti-hypertensive drugs who maintained the previous therapeutic regime were enrolled in other anti-hypertensive drugs group. When exploring the association between the discontinuation of ACEIs/ARBs and disease prognosis, we compared baseline characteristics between the two groups.

The blood pressure on the day of admission and the 2nd, 3rd, 5th, 8th, and 12th d after admission were recorded, evaluating the consistency of blood pressure control for both groups.

The follow-up study continued until March 24, 2020. Discharged or in-hospital death were also considered end-point of study. The discharge criteria were as follows: (1) Normal body temperature for more than 3 d; (2) Respiratory symptoms significantly improved; (3) Chest imaging remission; and (4) Negative nucleic acid tests of sputum, nasopharyngeal swabs, or other respiratory tract samples for two consecutive times sampled with at least 24-h interval. The deceased patients were recorded as right censored, as no discharge outcome had occurred.

The study was approved by the Institutional Review Board of Peking University Third Hospital (IRB00006761-M2020060), and a waiver of written informed consent was obtained.

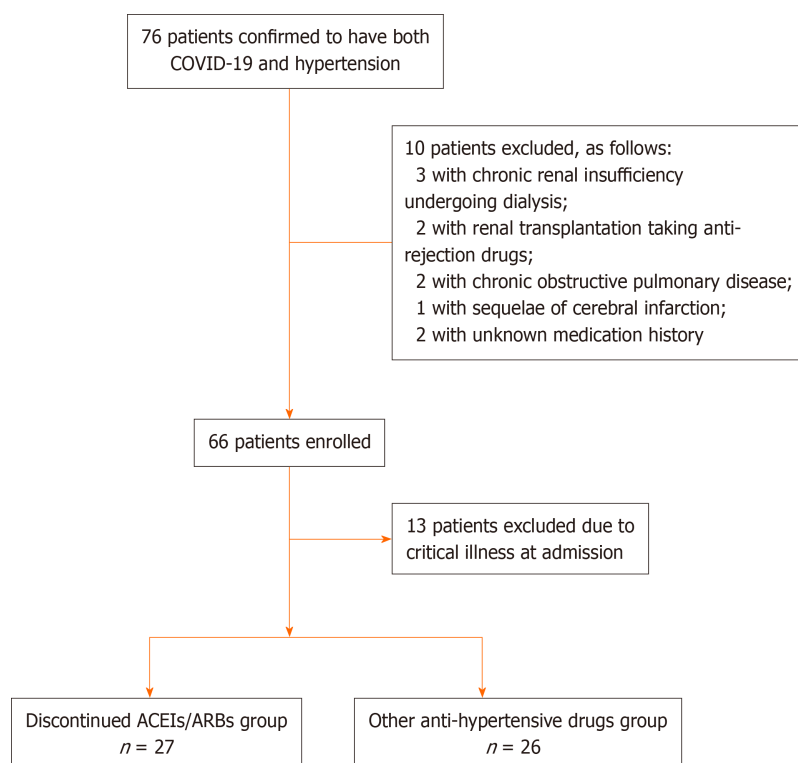


Figure 1 Enrollment and randomization of patients. COVID-19: Coronavirus disease 2019; ACEIs/ARBs: Angiotensin converting enzymes inhibitors or angiotensin receptor blockers.

Statistical analysis

Continuous variables were described by median and quartile, and the Mann-Whitney *U* test was used for comparison between groups. For categorical variables, the chi-square test, continuity-corrected chi-square test, or Fisher's exact test was used. Patients receiving ACEIs/ARBs before hospitalization might have experienced blood pressure fluctuations after medication switching. We used repeated-measures analysis of variance (repeated-measures ANOVA) to compare the changes in blood pressure level after admission, as well as the overall blood pressure level, between the discontinued ACEIs/ARBs group and the other anti-hypertensive drugs group. In the repeated-measures ANOVA, the choice to use ACEIs/ARBs was defined as a between-subject factor, while blood pressure on the day of admission was defined as a covariant (see Figure 2). Cox proportional hazard model was used to estimate the hazard ratio (HR) and its 95% confidence interval (CI) for significant factor screening. Factors with a *P* value < 0.1 were selected as potential confounders in the comparison of baseline characteristics between the discontinued ACEIs/ARBs group and the other anti-hypertensive drugs group, as well as in the univariate Cox proportional hazards model. Cox risk ratio model was used to explore whether the previous use of ACEIs/ARBs, after deducting confounding factors, was related to the prognosis of the disease. The qSOFA score was closely related to COVID-19 disease severity, so it was included in the multi-factor Cox proportional hazard model to indicate severity of disease.

To clarify further the impact of ACEIs/ARBs on prognosis in patients with different severities on admission, multivariate Cox proportional hazard models of moderate and severe patients were established to explore the association between the discontinuous usage of ACEIs/ARBs and disease severity. A two-sided α of less than 0.05 was considered statistically significant. The researchers used the SPSS version 24.0 program for statistical analysis (IBM Corp., Armonk, NY, United States).

RESULTS

Baseline characteristics

A total of 53 patients met the inclusion criteria, of whom 27 (51%) switched from ACEIs/ARBs to CCBs and 26 continued with their usual non-ACEIs/ARBs anti-

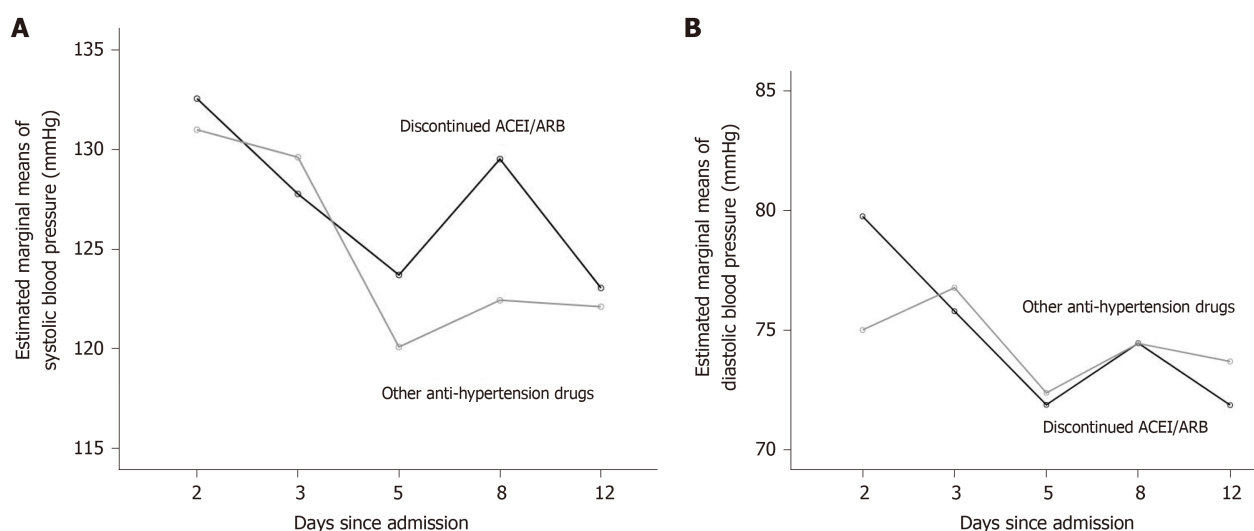


Figure 2 Comparison of blood pressure level after admission between two groups.

hypertensive drugs. The patients' median age was 67 years, and the median time from symptoms onset to hospital admission was 14 d. There were 24 moderate cases (45.3%) and 29 severe cases (54.7%) in the cohort. The initial symptom commonly experienced was fever in 35 cases (66%) and cough in 12 cases (22.6%). Bilateral ground-glass opacity was the most commonly seen chest imaging findings.

As shown in Table 1, age, qSOFA score, and the levels of albumin and interleukin-10 (IL-10) differed significantly between the discontinued ACEIs/ARBs group and the other anti-hypertensive drugs group ($P < 0.05$). There was no significant difference between the two groups in other labs or clinical management strategy (see Supplementary Table 1).

The results of repeated-measures ANOVA showed that the models of both systolic and diastolic blood pressure met the spherical test (systolic pressure: $P = 0.287$, diastolic pressure: $P = 0.653$). There was no significant difference between the groups in terms of the trends in systolic and diastolic blood pressure over time (Mauchly's test of Sphericity; systolic: $P = 0.533$, diastolic: $P = 0.308$). The tests of between-subject effects showed that systolic and diastolic blood pressure were not significantly different between the two groups ($P = 0.355$ and 0.822 , respectively). The blood pressure levels of the two groups after admission were generally similar.

The univariate Cox proportional risk model showed that the hospital stay between those two groups was 23 d [interquartile range (IQR) 16.0-31.0] and 21.5 d (IQR 15.0-27.0), respectively. In subgroup analysis, the median time of hospital stay in moderate patients was 21 d (IQR 17.0-25.5) and 16.5 d (IQR 12.0-19.5), respectively. In severe patients, it was 23 d (IQR 15.0-32.0) and 24.5 d (IQR 23.0-31.0), respectively. Among patients who had not been discharged, those who had discontinued ACEIs/ARBs were 42.4% less likely to be discharged (HR = 0.424, 95% CI is 0.187-0.962, $P = 0.040$) compared to those who had been using other anti-hypertensive drugs. The results are shown in Table 2 and Figure 3A.

After control for other potential confounding factors, the multivariate Cox proportional risk model showed that patients who discontinued ACEIs/ARBs underwent longer hospital stay; the difference was statistically significant ($P < 0.05$).

The effect of discontinue using ACEIs/ARBs was stronger in patients with moderate disease than among all patients [HR = 0.224 (0.005, 0.998); $P = 0.0497$]. The results are shown in Table 3 and Figure 3B.

In patients with severe disease, no association between discontinue using ACEIs/ARBs and disease prognosis was found [HR = 0.793 (0.215, 2.926); $P = 0.728$]. The results are shown in Table 3 and Figure 3C.

DISCUSSION

In the present study, we analyzed the clinical characteristics of 53 COVID-19 patients with hypertension and found that the median time of hospital stay was longer in the discontinued ACEIs/ARBs group than the other anti-hypertensive drugs. Moreover,

Table 1 Patients' characteristics and differences between discontinued angiotensin converting enzymes inhibitors or angiotensin receptor blockers group and other anti-hypertensive drugs group

Characteristic	Patients with both COVID-19 and hypertension			χ^2/z	P value
	Total (n = 53)	Discontinued ACEIs/ARBs (n = 27)	Other anti-hypertensive drugs (n = 26)		
Male sex, n (%)	26 (49.1)	15 (57.7)	11 (42.3)	0.930	0.335
Age, median yr (IQR)	67 (59, 73)	64 (55, 72)	70 (66, 73)	-2.369	0.018
Initial symptom, n (%)					
Fever (temperature ≥ 37.3 °C)	35 (66)	19 (54.3)	16 (45.7)	6.895	0.186 ¹
Cough	12 (22.6)	4 (33.3)	8 (66.7)		
Dyspnea	1 (1.9)	0 (0)	1 (100)		
Chest tension	1 (1.9)	0 (0)	1 (100)		
Exhausted	1 (1.9)	1 (100)	0 (0)		
Anorexia	1 (1.9)	1 (100)	0 (0)		
Diarrhea	2 (3.8)	2 (100)	0 (0)		
Severity of illness, n (%)					
Moderate	24 (45.3)	12 (50)	12 (50)	0.016	0.901
Severe	29 (54.7)	15 (51.7)	14 (48.3)		
qSOFA score, n (%)					
0	26 (49.1)	17 (65.4)	9 (34.6)	4.259	0.039
≥ 1	27 (50.9)	10 (37)	17 (63)		
CURB-65 score, n (%)					
0	17 (32.1)	12 (70.6)	5 (29.4)	3.874	0.145 ¹
1	28 (52.8)	12 (42.9)	16 (57.1)		
≥ 2	8 (15.1)	3 (37.5)	5 (62.5)		
Comorbidities, n (%)					
Diabetes	21 (39.6)	10 (47.6)	11 (52.4)	0.154	0.695
Coronary heart disease-	13 (24.5)	8 (61.5)	5 (38.5)	0.774	0.379
Duration of hypertension, median-yr (IQR)	10 (5, 16)	10 (6, 20)	10 (5, 10)	1.811	0.707
Chest CT results, n (%)					
Bilateral lesions	48 (90.6)	24 (50)	24 (50)	0	1
Ground glass	32 (60.4)	15 (46.9)	17 (53.1)	0.535	0.465
Consolidation	6 (11.3)	4 (66.7)	2 (33.3)	0.148	0.701
Hydrothorax	5 (9.4)	2 (40)	3 (60)	0.002	0.965
Patch shadow	37 (69.8)	19 (51.4)	18 (48.6)	0.008	0.928
Laboratory tests, median (IQR)					
White blood cell count, $\times 10^9$ /L	5.23 (4.56, 6.46)	5.22 (4.28, 6.99)	5.41 (4.76, 6.01)	-0.285	0.776
Lymphocyte count, $\times 10^9$ /L	0.99 (0.68, 1.49)	0.81 (0.61, 1.5)	1.05 (0.78, 1.49)	-1.228	0.219
Platelet count, $\times 10^9$ /L	247 (209, 285)	250 (202, 319)	247 (217, 280)	1.087	0.852
Hemoglobin, g/L	122 (115, 130)	122 (115, 129)	122 (115, 132)	-0.142	0.887
Alanine transaminase, U/L	21 (15, 31)	21 (14, 31)	20 (15, 30)	-0.027	0.979

Albumin, g/L	34.9 (31.3, 38.3)	33.4 (30.1, 35.9)	36.4 (31.7, 39)	-2.127	0.033
Total bilirubin, μ mol/L	9.5 (7, 13.4)	9.1 (6.4, 13.4)	10.2 (7.4, 14.1)	-0.881	0.378
LDH, μ mol/L	265 (228, 313)	290 (228, 367)	262 (224, 300)	1.174	0.240
BUN, mmol/L	4.6 (3.4, 5.9)	4.6 (3.9, 6)	4.5 (3.2, 5.7)	0.854	0.393
Creatinine, μ mol/L	71 (58, 90)	68 (59, 90)	71.5 (58, 90)	0.089	0.929
Prothrombin time, s	13.9 (13.2, 14.4)	13.8 (13.2, 14.3)	14 (13.2, 14.6)	-0.633	0.527
APTT, s	40.2 (35.6, 43.7)	40.8 (36.8, 44.6)	37.7 (35.3, 43.5)	1.148	0.251
Fibrous protein, g/L	4.81 (4, 6.18)	4.73 (4, 6.98)	4.85 (3.72, 6)	0.534	0.593
D-dimer, μ g/L	0.93 (0.48, 1.77)	0.75 (0.47, 1.69)	1.11 (0.48, 1.81)	-0.409	0.682
hs-CRP, mg/L	21.2 (1.2, 81.4)	27.2 (5, 97.5)	16.6 (0.8, 57.9)	1.130	0.258
Procalcitonin, ng/mL	0.04 (0.02, 0.08)	0.04 (0.02, 0.06)	0.04 (0.02, 0.09)	0.290	0.772
Serum ferritin, μ g/L	486 (328.35, 1023.85)	601.15 (387, 1173.3)	438.35 (321.4, 767.2)	1.244	0.213
IL-2R, U/mL	669 (445.5, 1013.5)	684.5 (488, 1172)	669 (407, 1010)	0.522	0.602
IL-6, pg/mL	8.76 (3.08, 37.12)	10.23 (3.91, 40.54)	7.66 (3.08, 34.24)	0.439	0.660
IL-8, pg/mL	13.35 (5.75, 23.2)	17.55 (7.4, 27.2)	10.4 (5.3, 18.9)	1.395	0.163
IL-10, pg/mL	5 (5, 5.45)	5 (5, 7.6)	5 (5, 5)	2.463	0.014 ²
hs-TnI, pg/mL	3.6 (2.9, 5.3)	4.5 (2.3, 7.6)	3.6 (3.6, 3.6)	1.090	0.267
Myoglobin, ng/mL	51.6 (37.8, 90)	50.7 (40, 134.6)	55.5 (31.8, 86.3)	0.365	0.715
CKMB, ng/mL	1.1 (0.5, 1.7)	1.2 (0.5, 1.9)	0.8 (0.5, 1.5)	0.508	0.611
NT-ProBNP, pg/mL	142.0 (71.0, 308.0)	113.0 (57.0, 311.0)	179.5 (75.0, 290.0)	-1.005	0.315
Time from onset to admission, median day (IQR)	14 (10, 18)	15 (10, 18)	12 (9, 18)	0.919	0.358

Only one patient's organ failure assessment (QSOFA) was 2, QSOFA for all other patients was 0 or 1. Therefore, QSOFA was involved as a binary variable (0, ≥ 1) in univariate and multivariate Cox proportional hazard model. ¹Chi-square test for continuity correction. ²Mean rank in the discontinued angiotensin converting enzymes inhibitors or angiotensin receptor blockers (ACEIs/ARBs) group = 30.73—slightly higher than that in the other anti-hypertensive drugs group (22.27). COVID-19: Coronavirus disease 2019; ACEIs/ARBs: Angiotensin converting enzymes inhibitors or angiotensin receptor blockers; qSOFA: Quick sequential organ failure assessment; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; APTT: Activated partial thromboplastin time; hs-CRP: High-sensitive C-reactive protein; IL-2R: Interleukin-2 receptor; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; hs-TnI: High sensitive cardiac troponin I; CKMB: Creatine phosphokinase isoenzyme; NT-ProBNP: N-terminal pro-brain natriuretic peptide; IQR: Interquartile range; CT: Computed tomography.

this phenomenon was more significant in moderate cases, which revealed the significant impact of ACEIs/ARBs in COVID-19 patients with confirmed hypertension.

Concerns raised about using ACEIs/ARBs in hypertensive patients with COVID-19 because SARS-CoV-2 enters and infects human through ACE2. ACE and ACE2 are key regulatory enzymes in RAAS network. ACEIs/ARBs are RAAS blockers that control blood pressure by antagonizing ACE and angiotensin receptors^[21-23]. ACE2 is a counterregulatory enzyme that degrades Ang II to angiotensin 1-7 (Ang1-7) and reverses the vasoconstrictive effect of ACE to maintain the balance of RAAS system. Additionally, studies have shown that ACEIs/ARBs might increase ACE2 expression, which might facilitate infection by SARS-CoV-2 and aggravate the disease, thus leading to potential longer hospital stay^[16]. But solid evidence is still lacking for confirming the effects of ACEIs and ARBs on lung-specific expression of ACE2 in animal models and humans, especially in COVID-19 patients.

On the other hand, several studies have shown that ACEIs/ARBs may also have a protective effect. It was reported^[24-26] that long-term ACEIs/ARBs treatment was associated with shorter length of hospital stay, lower rate of intubation/mechanical ventilation, and reduced 30-d mortality in patients with pneumonia. Further studies found that serum Ang II levels increased significantly in patients with acute lung injury, promoting the progress of acute lung injury through AT1R, which causes vasoconstriction, inflammation, fibrosis, and oxidation^[27,28]. A study in COVID-19 patients published by Liu *et al*^[29] confirmed that plasma Ang II level increased significantly in these patients and that it was linearly correlated with virus titer and

Table 2 Univariate Cox proportional risk model associated with each indicator and prognosis

	B	HR (95%CI)	Significance
ACEIs/ ARBs	-0.289	0.749 (0.426, 1.319)	0.317
Gender	-0.516	0.597 (0.333, 1.070)	0.083
Age	-0.007	0.993 (0.961, 1.025)	0.650
Initial symptom			0.280
Fever (temperature ≥ 37.3 °C)	-0.225	0.799 (0.393, 1.623)	0.534
Cough	1.464	4.324 (0.547, 34.167)	0.165
Dyspnea	0.012	1.012 (0.137, 7.496)	0.991
Chest tension	1.811	6.115 (0.75, 49.843)	0.091
Exhaustion	1.811	6.115 (0.75, 49.843)	0.091
Anorexia	0.782	2.185 (0.286, 16.699)	0.451
Severity of illness	-0.541	0.582 (0.328, 1.032)	0.064
qSOFA score	-0.719	0.487 (0.272, 0.871)	0.015
CURB-65 score			0.178
CURB-65 (1)	-0.552	0.576 (0.305, 1.086)	0.088
CURB-65 (2)	-0.65	0.522 (0.211, 1.288)	0.158
Diabetes	-0.093	0.911 (0.512, 1.622)	0.752
Coronary heart disease	0.62	1.860 (0.953, 3.630)	0.069
Chest CT results (single and bilateral)	0.658	1.930 (0.681, 5.466)	0.216
Chest CT results (ground glass opacity)	-0.135	0.874 (0.487, 1.569)	0.652
Chest CT results (consolidation)	0.127	1.136 (0.481, 2.681)	0.772
Chest CT results (pleural effusion)	-0.976	0.377 (0.134, 1.060)	0.064
Chest CT results (patch shadow)	0.199	1.220 (0.651, 2.287)	0.534
Urine protein	-0.151	0.860 (0.466, 1.587)	0.630
Influenza antibody			0.607
Influenza A antibody	-0.305	0.737 (0.405, 1.341)	0.318
Influenza B antibody	-0.117	0.889 (0.305, 2.596)	0.830
Duration of hypertension	-0.008	0.992 (0.953, 1.032)	0.678
White blood cell count	-0.112	0.894 (0.749, 1.067)	0.216
Lymphocyte count	0.322	1.380 (0.774, 2.461)	0.275
Platelet	0.001	1.001 (0.997, 1.005)	0.651
Hemoglobin	-0.007	0.993 (0.969, 1.018)	0.576
Alanine transaminase	-0.015	0.985 (0.965, 1.005)	0.131
Albumin	0.138	1.148 (1.058, 1.246)	0.001
Total bilirubin	-0.031	0.969 (0.918, 1.024)	0.263
LDH	-0.004	0.996 (0.992, 0.999)	0.013
BUN	-0.088	0.916 (0.806, 1.041)	0.177
Creatinine	-0.01	0.990 (0.979, 1.002)	0.099
Prothrombin time	0.027	1.027 (0.895, 1.178)	0.701
APTT	-0.022	0.978 (0.944, 1.013)	0.217
Fibrous protein	-0.039	0.962 (0.794, 1.165)	0.689
BD-dimer	-0.056	0.945 (0.89, 1.004)	0.065

Bhs-CRP	-0.006	0.994 (0.989, 0.999)	0.017
B procalcitonin	-0.703	0.495 (0.069, 3.562)	0.485
B Serum ferritin	-0.001	0.999 (0.999, 1.000)	0.027
IL-1 β	0.098	1.103 (0.927, 1.311)	0.268
IL-2R	-0.001	0.999 (0.998, 1.000)	0.007
IL-6	-0.002	0.998 (0.993, 1.003)	0.370
IL-10	-0.093	0.911 (0.813, 1.021)	0.108
hs-TnI	-0.016	0.984 (0.924, 1.048)	0.619
Myoglobin	-0.004	0.996 (0.993, 1.000)	0.051
CKMB	-0.037	0.964 (0.879, 1.058)	0.440
NT-ProBNP	0	1.000 (1.000, 1.000)	0.938

ACEIs/ARBs: Angiotensin converting enzymes inhibitors or angiotensin receptor blockers; qSOFA: Quick sequential organ failure assessment; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; APTT: Activated partial thromboplastin time; hs-CRP: High-sensitive C-reactive protein; IL-1 β : Interleukin-1 β ; IL-2R: Interleukin-2 receptor; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; hs-TnI: High sensitive cardiac troponin I; CKMB: Creatine phosphokinase isoenzyme; NT-ProBNP: N-terminal pro-brain natriuretic peptide; IQR: Interquartile range; CT: Computed tomography; HR: Hazard ratio; CI: Confidence interval.

Table 3 Multivariate Cox proportional risk model to investigate the association between discontinuation of angiotensin converting enzymes inhibitors or angiotensin receptor blockers and prognosis

	All the objects		Stratified by admission severity			
	HR (95%CI)	P value	Moderate		Severe	
			HR (95%CI)	P value	HR (95%CI)	P value
ACEIs/ ARBs	0.424 (0.187, 0.962)	0.040	0.224 (0.050, 0.998)	0.0497	0.793 (0.215, 2.926)	0.728
qSOFA score	0.455 (0.201, 1.026)	0.058	0.685 (0.112, 4.199)	0.682	0.576 (0.161, 2.053)	0.395
Gender	1.116 (0.527, 2.363)	0.774	0.733 (0.100, 5.368)	0.760	0.850 (0.267, 2.698)	0.782
Coronary heart disease	3.497 (1.475, 8.291)	0.004	2.207 (0.569, 8.562)	0.252	3.695 (0.933, 14.64)	0.063
Chest CT results pleural effusion	0.577 (0.187, 1.778)	0.338	0.348 (0.042, 2.871)	0.327	0.294 (0.037, 2.303)	0.244
Albumin	1.087 (0.969, 1.219)	0.153	1.110 (0.860, 1.433)	0.423	1.163 (0.970, 1.394)	0.104
LDH	0.997 (0.992, 1.002)	0.239	1.000 (0.988, 1.012)	0.982	0.995 (0.988, 1.001)	0.128
Creatinine	0.978 (0.959, 0.997)	0.026	0.958 (0.920, 0.997)	0.036	0.993 (0.964, 1.023)	0.660
D-dimer	0.972 (0.907, 1.043)	0.431	0.489 (0.147, 1.624)	0.243	0.963 (0.889, 1.042)	0.349
hs-CRP	0.999 (0.988, 1.009)	0.793	0.993 (0.963, 1.025)	0.670	1.000 (0.985, 1.016)	0.953
Serum ferritin	1.000 (0.999, 1.001)	0.998	1.001 (0.997, 1.006)	0.600	1.001 (1.000, 1.002)	0.172
IL2R	1.000 (0.999, 1.002)	0.485	1.000 (0.998, 1.003)	0.814	1.000 (0.999, 1.002)	0.722
Myoglobin	1.002 (0.995, 1.010)	0.489	1.014 (1.002, 1.026)	0.026	0.993 (0.983, 1.003)	0.153

ACEIs/ARBs: Angiotensin converting enzymes inhibitors or angiotensin receptor blockers; qSOFA: Quick sequential organ failure assessment; LDH: Lactate dehydrogenase; hs-CRP: High-sensitive C-reactive protein; IL-2R: Interleukin-2 receptor; HR: Hazard ratio; CI: Confidence interval.

severity of lung injury. A small-sample clinical study in patients with acute respiratory distress syndrome by Khan *et al*^[30] showed that the level of Ang II decreased and the level of Ang 1-7 increased after an injection of human recombinant ACE2.

Evidence showing the effects of ACEIs and ARBs on lung-specific expression of ACE2 in humans and animal models are still controversial^[31-35]. However, in animal models of acute lung injury, ACE activity and Ang II expression increased, but ACE2 activity and Ang-1-7 level decreased in animal models of acute lung injury, suggesting that ACE, Ang II, and AT1R are important factors in promoting acute lung injury,

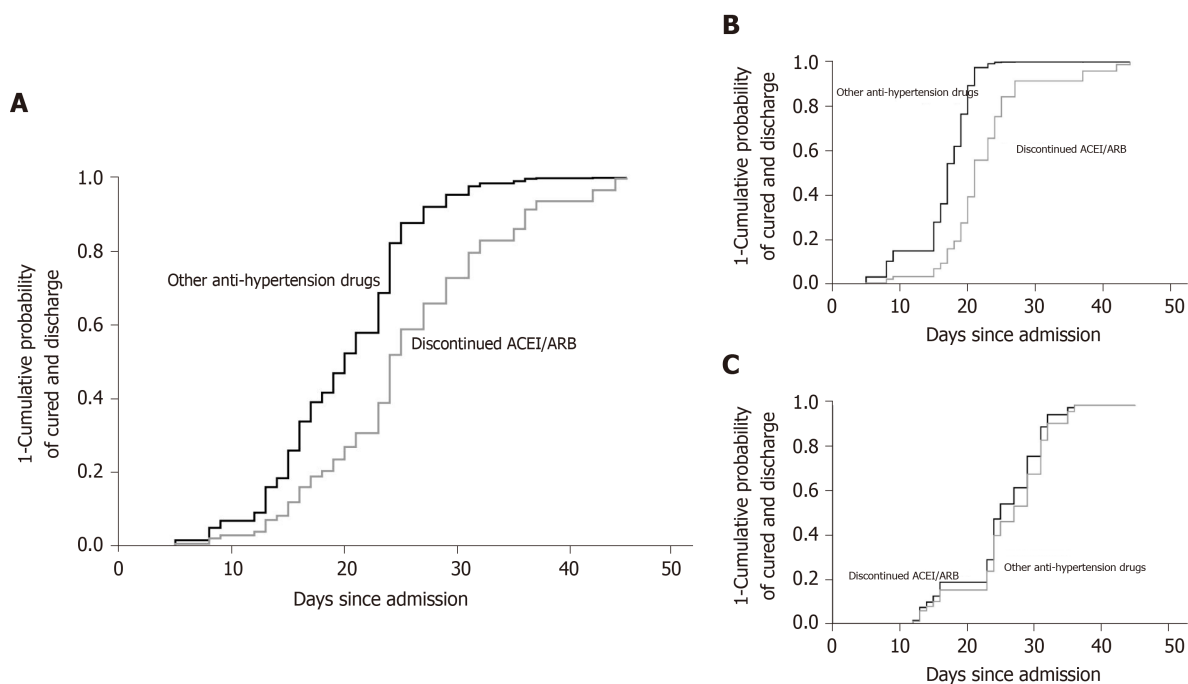


Figure 3 The cumulative probability of discharge in patients. A: The cumulative probability of discharge (all patients); B: The cumulative probability of discharge (moderate cases); C: The cumulative probability of discharge (severe cases).

while the ACE2, Ang 1-7, and Mas receptor pathway might play protective roles. A study published by Imai *et al*^[36] showed that ACE2 knock-out mice had significantly higher levels of Ang II than normal wild-type control mice and that pulmonary vascular permeability and lung injury were significantly higher in the knock-out mice. In the same study, recombinant human ACE2 and AT1R inhibitors improved the symptoms of acute lung injury in the ACE2 knock-out mice. In a mouse model of acute lung injury induced using the Spike-Fc protein of SARS-CoV, the level of Ang II also increased significantly, while the expression of ACE2 was down-regulated, and applying ARBs effectively attenuated pulmonary edema^[11]. These studies indicated that ACE2 converts Ang II to Ang1-7, which finally binds to Mas receptor and mediates many beneficial actions, including vasodilation and anti-inflammatory, antioxidant, and anti-apoptotic effects^[37-39]. Therefore, potential explanation for longer hospital stays in our patients who discontinued ACEIs/ARBs might be down-regulation of ACE2 and subsequent deteriorated lung injury^[40,41].

Furthermore, according to a recent study by Huang *et al*^[42] in hypertensive COVID-19 patients, there was no significant difference in length of hospital stay and clinical outcome between patients with both COVID-19 and hypertension who continued to take RAAS blockers and those who took non-RAAS blockers. Another study conducted by Zhang *et al*^[43] showed that it was unlikely that inpatient ACEIs/ARBs would be associated with an increased risk of mortality.

As we all know, COVID-19 is particularly severe in patients with underlying cardiovascular diseases. There is no extra benefit to withdraw RAAS inhibitors in patients in otherwise stable condition. RAAS inhibitors show renal and myocardial protective effects, and discontinuation may cause damage in high-risk patients who show decompensation^[44]. Monteil *et al*^[45] show that SARS-CoV-2 can directly infect engineered human blood vessel organoids and human kidney organoids, which can be inhibited by ACE2. Combining the current study with other medical evidence^[5,6,46], we would rather recommend not to change patients' medication. However, the mechanism of drug interaction is complex, and the impact of drugs on patients may depend on the final equilibrium state. The effects of ACEIs/ARBs for COVID-19 patients complicated with hypertension requires further study.

There were several limitations of our study. First, our study was carried out in a single center, and sample size was limited by patient volume and strict recruitment criteria. Interpretation of our findings might be underestimated. However, our study was the first clinical study to explore the effect of ACEIs/ARBs withdrawal in COVID-19 patients. Second, we could not manage to enroll a third arm of patients who continued using ACEIs/ARBs after admission. Therefore, we could not objectively compare the differences among the patients who were using ACEIs/ARBs

continuously, patients adjusted drugs after admission, and patients using non-ACEI/ARBs continuously.

CONCLUSION

Discontinuing ACEIs/ARBs in confirmed COVID-19 patients with hypertension resulted in a prolonged hospital stay. This phenomenon was more significant in moderate cases. Nonetheless, we believe that ACEIs/ARBs should be continued in patients with both COVID-19 and hypertension unless further evidence demonstrates adverse outcomes.

ARTICLE HIGHLIGHTS

Research background

During the coronavirus disease 2019 (COVID-19) pandemic, several studies have revealed that sustained ingestion of angiotensin converting enzymes inhibitors or angiotensin receptor blockers (ACEIs/ARBs) had no harmful effects on COVID-19 patients complicated with hypertension.

Research motivation

The role of angiotensin converting enzyme-2 (ACE2) receptor in COVID-19 pathophysiological process remains unclear. We expect to provide more important evidence for ACEIs/ARBs usage in clinical application.

Research objectives

To explore the impact of ACEIs/ARBs discontinued usage on COVID-19 patients complicated with hypertension.

Research methods

This study was based on a COVID-19 cohort from a patient registry of all COVID-19 patients admitted to an isolated unit in a tertiary hospital. All COVID-19 patients complicated with hypertension were recruited in our study and divided into discontinued ACEIs/ARBs group or other anti-hypertensive drugs group. We compared characteristics and clinical outcomes between those two different groups of patients.

Research results

A total of 53 patients were enrolled, 27 patients switched from ACEIs/ARBs to CCBs while 26 patients continued with non-ACEIs/ARBs. After controlling potential confounding factors using the Cox proportional hazards model, hospital stay was longer in patients who discontinued ACEIs/ARBs, with a hazard ratio (HR) of 0.424 [95% confidence interval (CI): 0.187-0.962; $P = 0.040$], than in patients using other anti-hypertensive drugs. A sub-group analysis showed that the effect of discontinuing ACEIs/ARBs was stronger in moderate cases [HR = 0.224 (95%CI: 0.005-0.998; $P = 0.0497$)].

Research conclusions

Our data revealed that discontinuing ACEIs/ARBs treatment after COVID-19 diagnosis results in a prolonged hospital stay. This phenomenon was more significant in hospitalized patients with moderate COVID-19. Our research suggested that ACEIs/ARBs should be continued in patients with both COVID-19 and hypertension unless further evidence demonstrates adverse outcomes.

Research perspectives

The mechanism of ACE2 in COVID-19 patients complicated with hypertension remains unclear and may be more complex, requiring further research to explore this area in the future.

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