Original Article

Differential Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on COVID-19

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Abstract

Background: The effect of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) on the coronavirus disease 2019 (COVID-19) remains controversial from clinic evidence. **Objectives:** The objectives of this study were to report the major characteristics and clinical outcomes of COVID-19 patients treated with ACEIs and ARBs and compare the different effects of the two drugs for outcomes of COVID-19 patients. **Methods:** This is a retrospective, two-center case series of 198 consecutive COVID-19 patients with a history of hypertension. **Results:** Among 198 patients, 58 (29.3%) and 16 (8.1%) were on ARB and ACEI, respectively. Patients who were on ARB or ACEI/ARB had a significantly lower rate of severe illness and acute respiratory distress syndrome (ARDS) when compared with patients treated with ACEI alone or not receiving RAAS blocker ($P < 0.05$). The Kaplan–Meier survival curve showed that patients with ARB in their antihypertensive regimen had a trend toward a higher survival rate when compared with individuals without ARB (adjusted hazard ratio, 0.27; 95% confidence interval [CI], 0.07–1.02; $P = 0.054$). The occurrence rates of severe illness, ARDS, and death were similar in the two groups regardless of receiving ACEI. The Cox regression analyses showed a better survival in the ARB group than the ACEI group (adjusted hazard ratio, 0.03; 95% CI, 0.00–0.58; $P = 0.02$). **Conclusions:** Our data may provide that some evidence of using ARB, but not ACEI, was associated with a reduced rate of severe illness and ARDS, indicating their potential protective impact in COVID-19. Further large sample sizes and multiethnic populations are warranted to confirm our findings.

Keywords: *Acute respiratory distress syndrome, angiotensin-converting enzyme inhibitors, COVID-19, hypertension*

Introduction

The novel coronavirus SARS-CoV-2, which has caused a pandemic of coronavirus disease 2019 (COVID-19), has become a serious threat to human health globally. This disease particularly poses a tremendous hazard to individuals with coexisting comorbidities, including old age and chronic diseases such as hypertension, diabetes mellitus, and chronic lung diseases.[1,2] Similar to SARS-CoV, SARS-CoV-2 utilizes angiotensin-converting enzyme-2 (ACE2) protein on the cell membrane as its host receptor.[3] ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are commonly used in

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hypertensive in COVID-19 patients with hypertension. Thus, there is an increasing interest in the potential effects of these drugs on the outcomes of patients with COVID-19.[4] Recently, in a Chinese retrospective study, Zhang *et al.* reported ACEI/ARB to exhibit a remarkable association with reduced mortality of COVID-19 patients with hypertension.[5] A similar study by Li *et al.* showed ACEI/ARB not affecting the outcome of COVID-19 patients. However, there may be some differences between the use of ACEI versus ARB on the outcomes. On the other hand, a previous study showed that the ACEI and ARB differed in the expression of ACE2 in an animal experiment,[6] suggesting the possibility of differential effects on COVID-19 patients. Of note, it has been reported that East Asian patients have higher incidence of ACEI-induced cough.[7] Therefore, ARB is the predominant drug used in China to block the renin–angiotensin–aldosterone system (RAAS). As the effect of ACEI/ARB on the outcomes of COVID-19 patients is still controversial, we aimed to assess the characteristics and clinical outcomes of patients with a history of hypertension treated with ACEI versus ARB who developed COVID-19.

Methods

Study design and participants

In this retrospective cohort study, we included 198 consecutive COVID-19 patients with a history of hypertension who were admitted between December 26, 2019, and March 6, 2020, at Zhongnan Hospital of Wuhan University and Wuhan Fourth Hospital in Wuhan city, China. We excluded patients who needed to discontinue antihypertensive medications due to hypotension, not being able to take oral medicines or nasal feeding, and patients lost to follow-up [Figure 1]. The diagnosis of COVID-19 was according to the Diagnosis and Clinical Management of 2019 novel coronavirus infected pneumonia (trial version 5, revised version).[8] Reverse transcription–polymerase chain reaction assay was performed to confirm the COVID-19 diagnosis when necessary, based on the WHO established protocol. The local institutional review boards approved this study, and informed consent was obtained from patients or their legal representatives.

Data collection

Demographics, laboratory values, treatment strategies, complications, and clinical outcomes of patients were abstracted from the medical records using a standardized report form designed for this study. The clinical symptoms and laboratory findings at hospital admission and complications and clinical outcomes throughout the hospitalization were collected. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin

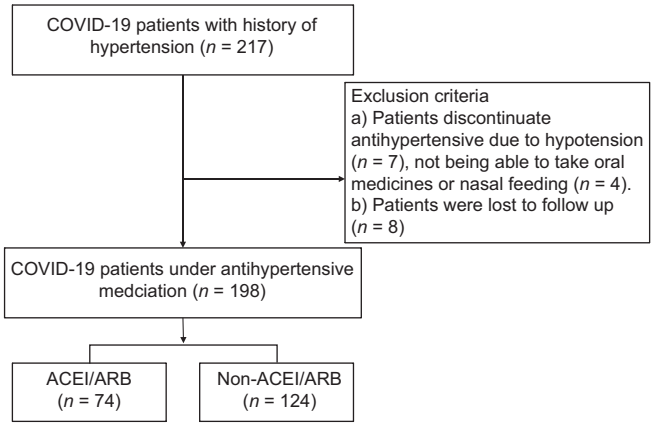

Figure 1: Flowchart of patient enrollment

definition.[9] The severe condition of COVID-19 was determined using the guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV)-infected pneumonia (standard version).[10] Acute kidney injury was defined based on the Kidney Disease: Improving Global Outcomes criteria.[11] Acute liver injury was defined according to the EASL Clinical Practice Guidelines.[12] The primary outcome of this study was survival. The secondary outcomes included the severity of illness, ARDS, acute liver injury, and acute kidney injury. Patients' follow-up times were defined as the time interval from hospitalization to the most recent contact or the time of patient death, whichever came earlier. The latest follow-up date was March 15, 2020.

Statistical analysis

The continuous variables were summarized as medians and interquartile ranges (IQRs) and compared by the Mann–Whitney–Wilcoxon test. The categorical data were summarized using frequencies and percentages and examined by the Chi-square test or the Fisher's exact test, as appropriate. The logistic regression model was used to assess the odds ratio of treatment with ACEI versus ARB on the severity of illness and ARDS. The survival curves of COVID-19 patients were assessed by Kaplan–Meier plots using the log-rank test. The Cox proportional hazards regression model was used to determine the hazard ratios of ACEI versus ARB use on death. All tests were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were conducted by Stata/SE version 12 (StataCorp) and GraphPad Prism version 8 (GraphPad Software, Texas, United State [San Diego, California, United State]).

Results

Participants

A total of 198 COVID-19 patients with hypertension were enrolled. Among these patients, 103 (52%) were women. The median (IQR) age of patients was 65 (56, 73)

years, with a length of hospital stay of 14 (9, 21) days and an overall follow-up of 38 (29, 53) days. There were 74 (37.4%) patients who were on ACEI (16 [8%]) or ARB (58 [29.3%]) treatment. Of these patients, 87 (43.9%) were severely ill, 69 (34.8%) patients developed ARDS, and 22 (11.1%) died. The characteristics of patients are summarized in Table 1.

Primary outcomes

Using the Kaplan–Meier survival curve and the Cox regression analyses, we did not find any significant differences in mortality in the ACEI/ARB group and the non-ACEI/ARB group [P = 0.27; Table 1 and Figure 2a]. The Kaplan–Meier survival curve showed a trend of improved survival among patients treated with ARB when compared with the group not treated with ARB [Figure 2b]. A similar trend was observed by the multivariate regression analysis [adjusted hazard ratio, 0.27; 95% confidence interval (CI), 0.07–1.02; P = 0.054; Table 2]. Using the Kaplan–Meier survival curve and the Cox regression analyses, we did not find any significant differences in mortality in the ACEI group and the non-ACEI group [Figure 2b and Table 2]. The Kaplan–Meier survival curve and the Cox regression analyses showed a better survival in the ARB group than the ACEI group (adjusted hazard ratio, 0.03; 95% CI, 0.00–0.58; P = 0.02; Figure 2c and Tables 2, 3], although there was no significant difference of the mortality rate between the ACEI and ARB groups [P = 0.059; Tables 2 and 3].

Secondary outcomes

The severe disease incidence was lower in the ACEI/ARB-treated group than that in the non-ACEI/ARB group [29.7% vs. 52.4%; P = 0.002; Figure 2d] with an odds ratio (OR) of 0.29 (95% CI, 0.14–0.60) after adjusting for other potential risk factors (P = 0.001). Furthermore, the incidence of severe illness was lower in the ARB-treated group versus the group not treated with ARBs [25.9% (15 of 58) vs. 51.4% (72 of 140), respectively; P = 0.001; Figure 2d], which remained significant after adjusting for confounders. The occurrence rate of severe illness did not change based on the use of ACEI. Compared with ACEIs and ARBs, there was no significant difference in the occurrence rates of severe illness (P = 0.166).

The occurrence of ARDS was lower in the ACEI/ARB group than in the non-ACEI/ARB group [21.6% vs. 42.7%, P = 0.003; Figure 2d] with OR (95% CI) of 0.27 (0.13–0.58) after adjusting confounders (P = 0.001).

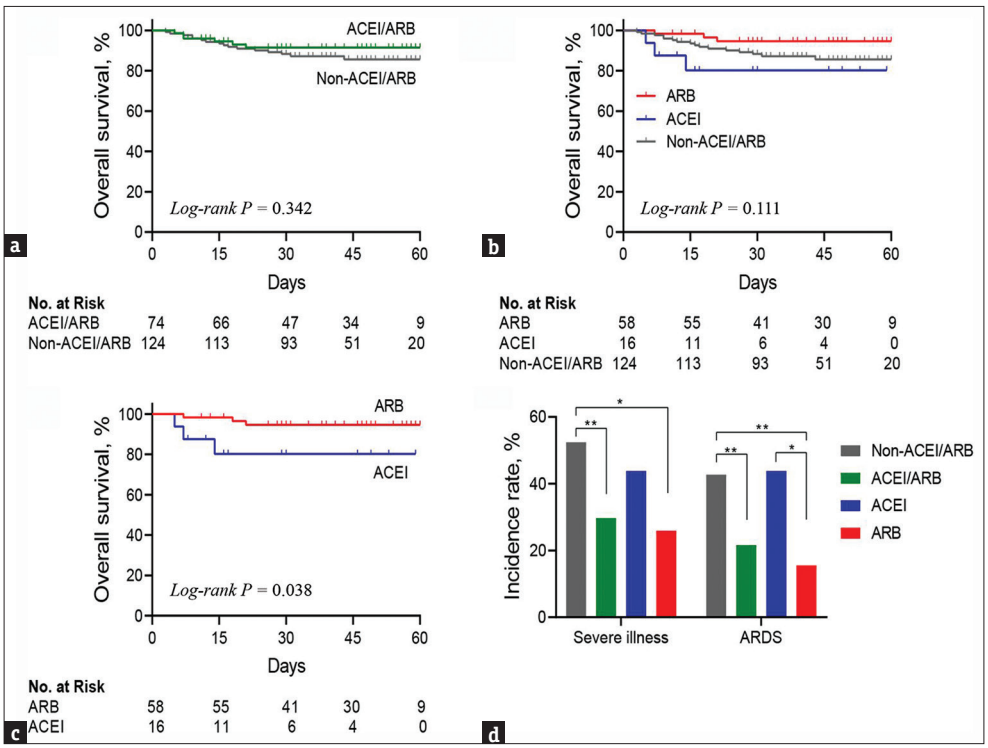

Figure 2: Effects of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors on severe illness, ARDS, and survival in COVID-19 patients. (a) Kaplan–Meier survival curves of the effects of treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker on overall survival in patients with COVID-19. (b) Kaplan–Meier survival curves of the effects of treatment with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker alone on overall survival in patients with COVID-19. (c) Kaplan–Meier survival curves of the effects of treatment with angiotensin-converting enzyme inhibitor compared to angiotensin receptor blocker on overall survival in patients with COVID-19. (d) The incidence rates of severe illness and ARDS by treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, angiotensin-converting enzyme inhibitor alone, and angiotensin receptor blocker alone

Table 1: Patient characteristics based on history of treatment with ACEI/ARB

Characteristic	Total (*n*=198)	ACEI/ARB (*n*=74)	Non-ACEI/ARB (*n*=124)	*P*
Age, median (IQR) - yr	65 (56-73)	66 (56-73)	65 (57-72)	0.755
Female sex - no. (%)	103 (52.0)	28 (37.8)	75 (60.5)	0.002
Comorbidities - no. (%)				
Diabetes	54 (27.3)	23 (31.1)	31 (25.0)	0.353
Cardiovascular disease	49 (24.7)	22 (29.7)	27 (21.8)	0.209
Cerebrovascular disease	20 (10.1)	9 (12.2)	11 (8.9)	0.457
Malignancy	17 (8.6)	7 (9.5)	10 (8.1)	0.735
Chronic kidney disease	11 (5.6)	2 (2.7)	9 (7.3)	0.215
Chronic obstructive pulmonary diseases	5 (2.5)	1 (1.4)	4 (3.2)	0.652
Chronic liver disease	2 (1.0)	1 (1.4)	1 (0.8)	1.000
Fever - no. (%)	173 (87.4)	62 (83.8)	111 (89.5)	0.240
Respiratory rate, median (IQR)	20 (19-22)	20 (19-22)	20 (19-22)	0.513
Pulse, median (IQR)	85 (78-96)	84 (78-91)	87 (79-100)	0.121
Systolic blood pressure	133 (123-145)	134 (130-146)	130 (120-145)	0.091
Diastolic blood pressure	80 (74-87)	80 (74-86)	80 (74-88)	0.412
Laboratory data, median (IQR)				
White blood cell count $\times 10^9$/L	5.6 (4.2-7.3)	5.2 (4.2-6.8)	5.8 (4.2-7.7)	0.323
Lymphocyte count $\times 10^9$/L	1.0 (0.6-1.4)	1.0 (0.7-1.5)	0.9 (0.6-1.3)	0.280
Neutrophil count $\times 10^9$/L	3.9 (2.8-5.6)	3.3 (2.7-5.0)	4.1 (2.8-6.1)	0.088
Platelet count $\times 10^9$/L	201 (139-250)	197 (143-246)	205 (139-265)	0.743
Alanine aminotransferase U/L	28 (17-42)	27 (19-42)	29 (16-43)	0.879
Aspartate aminotransferase U/L	29 (20-47)	29 (20-41)	30 (20-50)	0.549
Creatinine μmol/L	69.0 (57.7-86.8)	73.0 (62.7-89.5)	65.8 (53.7-83.8)	0.023
Urea mmol/L	5.0 (4.0-7.2)	5.3 (4.1-7.3)	4.9 (3.9-7.1)	0.376
Antihypertensive drugs - no. (%)				
CCBs	149 (75.3)	35 (47.3)	114 (91.9)	<0.001
beta-blockers	52 (26.3)	25 (33.8)	27 (21.8)	0.063
Diuretic	15 (7.6)	11 (14.9)	4 (3.2)	0.004
ACEIs	16 (8.1)	16 (21.6)	0	<0.001
ARBs	58 (29.3)	58 (78.4)	0	<0.001
Hospital stay, median (IQR) - days	14 (9-21)	13 (9-19)	14 (10-23)	0.218
Follow-up time, median (IQR) - days	38 (29-53)	39 (29-50)	38 (30-54)	0.511
Adverse event - no. (%)				
Severe illness	87 (43.9)	22 (29.7)	65 (52.4)	0.002
ARDS	69 (34.8)	16 (21.6)	53 (42.7)	0.003
Acute liver injury	37 (18.7)	16 (21.6)	21 (16.9)	0.413
Acute kidney injury	37 (18.7)	11 (14.9)	26 (21.0)	0.287
Death - no. (%)	22 (11.1)	6 (8.1)	16 (12.9)	0.299

CCBs, Calcium channel blockers

The ARB-treated patient group had a significantly lower rate of ARDS than the group not treated with ARB [15.5% vs. 42.9%, $P < 0.001$; Figure 2d], with OR (95% CI) of 0.18 (0.07–0.43) after adjusting for potential risk factors. There was no significant difference in the occurrence of ARDS between those treated with or without ACEI. In a comparison between ACEI and ARB, the incidence of ARDS was lower in the ARB group than in the ACEI group [15.5% vs. 43.8%, $P = 0.020$; Figure 2d], with OR (95% CI) of 0.21 (0.05–0.83) after adjusting confounders ($P = 0.026$).

There were no significant differences between the ACEI/ARB- or ARB-treated group and the group not treated in other major adverse events [Tables 1 and 3].

Discussion

We investigated the differential effects of using ACEI and ARB among COVID-19 patients. The results showed a strong association between ARB treatment and reduced rate of severe illness and ARDS. These findings potentially indicate a protective role for the use of ARB in COVID-19. These observations were not replicated when the use of ACEI was the independent variable.

In our study, more than one-third of patients were on treatment with ACEI/ARB. Due to the high incidence of ACEI-induced cough in Asian population, ARB was not surprisingly used in the majority (78.4%).[7] While we showed a potential benefit from

Table 2: Characteristics of Patients with COVID-19 of treatment with ACEI compared to ARB

Characteristic	ARB (*n*=58)	ACEI (*n*=16)	*P*
Age, median (IQR) - yr	65 (56-73)	67 (54-73)	0.916
Female sex - no. (%)	23 (39.7)	5 (31.2)	0.772
Comorbidities - no. (%)			
Diabetes	17 (29.3)	6 (37.5)	0.531
Cardiovascular disease	18 (31.0)	4 (25.0)	0.764
Cerebrovascular disease	6 (10.3)	3 (18.8)	0.396
Malignancy	5 (8.6)	2 (12.5)	0.640
Chronic kidney disease	2 (3.4)	0	1.000
Chronic obstructive pulmonary diseases	1 (1.7)	0	1.000
Chronic liver disease	1 (1.7)	0	1.000
Fever - no. (%)	49 (84.5)	13 (81.3)	0.715
Respiratory rate, median (IQR)	20 (18-21)	20 (19-22)	0.306
Pulse, median (IQR)	84 (80-90)	88 (77-95)	0.743
Systolic blood pressure	134 (130-145)	135 (121-148)	0.741
Diastolic blood pressure	78 (74-86)	80 (72-90)	0.880
Laboratory data, median (IQR)			
White blood cell count $\times 10^9$/L	5.3 (4.4-6.6)	4.9 (3.9-8.4)	0.790
Lymphocyte count $\times 10^9$/L	1.1 (0.7-1.5)	0.9 (0.5-1.3)	0.208
Neutrophil count $\times 10^9$/L	3.3 (2.8-4.8)	2.9 (2.4-6.0)	0.764
Platelet count $\times 10^9$/L	210 (137-250)	186 (149-214)	0.337
Alanine aminotransferase U/L	27 (19-42)	27 (18-33)	0.729
Aspartate aminotransferase U/L	30 (23-41)	24 (18-39)	0.249
Creatinine μmol/L	71.4 (60.2-89.3)	78.8 (67.8-107.0)	0.274
Urea mmol/L	5.1 (4.0-6.4)	6.5 (4.8-10.6)	0.054
Antihypertensive drugs - no. (%)			
CCBs	27 (46.6)	8 (50.0)	0.807
beta-blockers	19 (32.8)	6 (37.5)	0.723
Diuretic	10 (17.2)	1 (6.3)	0.437
ACEIs	0	16 (100.0)	<0.001
ARBs	58 (100.0)	0	<0.001
Hospital stay, median (IQR) - days	14 (10-19)	11 (7-16)	0.130
Follow-up time, median (IQR) - days	46 (29-54)	23 (13-38)	0.003
Adverse event - no. (%)			
Severe illness	15 (25.9)	7 (43.8)	0.166
ARDS	9 (15.5)	7 (43.8)	0.015
Acute liver injury	11 (19.0)	5 (31.3)	0.291
Acute kidney injury	7 (12.1)	4 (25.0)	0.238
Death - no. (%)	3 (5.2)	3 (18.8)	0.111

CCBs, Calcium channel blockers

the use of ACEI/ARB on the rate of severe illness and ARDS, the advantage was solely limited to the use of ARB among COVID-19 patients.

Recently, Zhang *et al.* reported that ACEI/ARB utilization could be associated with reduced mortality of COVID-19 patients who had a history of hypertension.[5] As the majority of patients in Zhang *et al.*'s study predominantly received ARB, the observed survival benefit could be due to ARB rather than ACEI.[5] Li *et al.* found the use of ACEI/ARB not to be associated with illness severity or mortality,[14] suggesting the uncertainties related to the effects of the use of ACEI and ARB on the outcome of COVID-19 patients.

SARS-CoV-2 uses the ACE2 receptor for entry into target cells.[15] ACE2 is predominantly expressed by epithelial cells of the lung, intestine, kidney, heart, and blood vessels.[16] Animal studies have shown that expression of ACE2 is increased by ACEI/ARB.[17] Thus, they may facilitate infection with COVID-19. Treating COVID-19 patients with ACEI and ARB leads to increased ACE2 receptors in the lung. However, enhanced ACE2 activity as a result of the treatment with RAAS inhibitors showed an essential effect in response to acute injury in animal models.[18] In preclinical models of other viral infections, the restoration of ACE2 by the administration of recombinant ACE2 appeared to reverse

Table 3: Risks of severe illness, ARDS and death by treatment with ARBs or ACE inhibitors

	Unadjusted	Adjusted[1]	Adjusted[2]
ACEI/ARB vs. non-ACEI/ARB			
Severe illness	0.38 (0.21-0.71)	0.34 (0.18-0.66)	0.29 (0.14-0.60)
ARDS	0.37 (0.19-0.71)	0.31 (0.15-0.63)	0.27 (0.13-0.58)
Death	0.64 (0.25-1.63)	0.63 (0.24-1.63)	0.55 (0.20-1.57)
ARB vs. non-ARB			
Severe illness	0.33 (0.17-0.65)	0.29 (0.14-0.59)	0.25 (0.11-0.54)
ARDS	0.24 (0.11-0.54)	0.20 (0.09-0.46)	0.18 (0.07-0.43)
Death	0.35 (0.10-1.20)	0.33 (0.10-1.12)	0.27 (0.07-1.02)
ACEI vs. non-ACEI			
Severe illness	0.99 (0.35-2.78)	1.06 (0.36-3.11)	1.01 (0.32-3.16)
ARDS	1.51 (0.53-4.23)	1.52 (0.53-4.41)	1.52 (0.50-4.61)
Death	2.39 (0.70-8.11)	3.04 (0.87-10.60)	2.81 (0.76-10.30)
ARB vs. ACEI			
Severe illness	0.45 (0.14-1.42)	0.42 (0.13-1.37)	0.38 (0.10-1.53)
ARDS	0.24 (0.07-0.80)	0.22 (0.06-0.78)	0.21 (0.05-0.83)
Death	0.21 (0.04-1.06)	0.06 (0.01-0.53)	0.03 (0.00-0.58)

The risks of Critical illness and ARDS were assessed by logistic regression; the Cox-regression model evaluated the risk of death. [1]Adjusted for age and sex. [2]Adjusted for age, sex, and all the comorbidities of COVID-19 listed in Table 1.

devastating lung injury processes.[19] In experimental animal models, the effects of ACEI and ARB on the ACE2 levels have been reported variably.[6,20,21] Our study indicated a different effect of the use of ACEIs or ARBs to COVID-19 patients, but we could not know the ACE2 true levels in patients induced by ACEI or ARB.

ARDS is a leading cause of death in COVID-19 patients.[2] In the present study, we showed that treatment with ARB, but not ACEI, was associated with reduced risk of severe illness and ARDS. A previous study showed that the use of ACEIs and ARBs was associated with considerable discrepancies in ACE2 expression in animal experiments.[6] Wang *et al.* recently showed that the use of ARB was associated with an increased ACE2 protein by approximately two-fold folds in the heart of aorta-constricted mice.[22] Furthermore, Lely *et al.* found no effect of ACEI treatment on ACE2 protein expression in renal biopsy samples of patients.[23] Contrary to Li *et al.*'s study,[14] our results showed that the use of ACEI/ARB was associated with the severity or mortality of COVID-19 patients with a history of hypertension. Further analysis indicated that the use of ACEI versus ARB was associated with a significantly different incidence of ARDS and mortality [Figure 1a and d].

Our findings warrant confirmation in prospective studies with engagement of larger sample sizes and multiethnic populations. As ACE2 polymorphism is correlated with the extent of ACE2 expression, patients from different races and ethnicities may show the variable protective effect of these medications among patients with COVID-19 and history of hypertension.[24,25] This hypothesis itself warrants further investigations. Furthermore, future mechanistic studies in humans are required to understand the unique interplay between SARS-CoV-2 infection and the RAAS network leading to modifications in ACE2 levels.

Conclusions

The use of ARB, but not ACEI, was associated with a reduced rate of severe illness and ARDS, indicating their potential protective impact in COVID-19. Further large sample sizes and multiethnic populations are warranted to confirm our findings.

Ethics approval and consent to participate

The local institutional review boards approved this study (2020020 to Zhongnan Hospital of Wuhan University and 2020-020-01 to Wuhan Fourth Hospital), and informed consent was obtained from patients or their legal representatives.

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Conflicts of interest

Zhiyong Peng is the Executive Editor-in-Chief of the journal, Kianoush B. Kashani is an Editorial member

grant No. The article was subject to the journal's standard procedures, with peer review handled independently of these members and their research groups.

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