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

Lianjiu su[1], Jiahao Zhang[1], nanhui jiang[1], Juan Li[2], Jie Yang[2], Li He[1], qin Xie[1], rong huang[1], fang Liu[1], ying feng[1], Kianoush Kashani[3], rengyun liu[4], qiaofa lu[2], and Zhiyong Peng[1]

[1]Wuhan University Zhongnan Hospital
[2]Huazhong University of Science and Technology
[3]Mayo Clinic
[4]Sun Yat-sen University First Affiliated Hospital

May 11, 2020

Abstract

AIMS To report the major characteristics and clinical outcomes of COVID-19 patients treated with ACE inhibitors 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 were on ARB and ACEI, respectively. Patients who were on ARB or ACEI/ARB had a significantly lower rate of severe illness and 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 towards a higher survival rate when compared with individuals without ARB (adjusted hazard ratio, 0.27; 95% 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 analysis to compared ACEI vs. ARB groups showed a significantly lower mortality rate in the ARB group (adjusted hazard ratio, 0.03; 95% CI, 0.00-0.58; P=0.02). CONCLUSIONS Our data may provide 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.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

ARB, but not ACEI, was associated with a reduced rate of severe illness and ARDS, indicating their potential protective impact in COVID-19

WHAT THIS STUDY ADDS

The effect of ACEI and ARB might be different to COVID-19. Further large sample sizes and multiethnic populations are warranted to confirm this findings.

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]. Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB) are commonly used in 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 vs. 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 vs. 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 did not exclude patients who needed to discontinue antihypertensive medications due to hypotension, not being able to take oral medicines, or had an increase in their serum creatinine level. The diagnosis of COVID-19 was according to the World Health Organization (WHO) interim guidance[8]. RT-PCR 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 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 KDIGO (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 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 exact test, as appropriate. The logistic regression model was used to assess the odds ratio of treatment with ACEI vs. 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 vs. ARB use on death. All tests were 2-sided, and P-value >0.05 was considered as statistically significant. All analyses were conducted by Stata/SE version 12 (Stata Crop) and GraphPad Prism version 8 (GraphPad Software Inc).

Results

Participants

A total of 198 COVID-19 patients with hypertension were enrolled. Among these patients, 103 (52%) were women. The median (interquartile range [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 non-ACEI/ARB group (P = 0.27; **Table1; Figure 1A**). Similar results found in the ARB group compared non-ARB group and ACEI group compared to the non-ACEI group. 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 1B**). A similar trend was observed by the multivariate regression analysis (adjusted hazard ratio, 0.27; 95% CI, 0.07-1.02; P=0.054; **Table 3**). 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 1B** ; **Table 3**). The Kaplan-Meier survival curve and the Cox-regression analyses showed a better survival in the ARB groups than the ACEI group (adjusted hazard ratio, 0.03; 95% CI, 0.00-0.58; P=0.02; **Figure 1C** ;**Table 2 and 3**), although there was no significant difference of the mortality rate between ACEI and ARB groups (P = 0.059; **Table 2 and 3**).

Secondary outcomes

The severe disease incidence was lower in ACEI/ARB treated group than in non-ACEI/ARB group (29.7% versus 52.4 %; P = 0.002; **Figure 1D**) with an odds ratio (OR) of 0.29 (95% confidence interval [CI], 0.14-0.60) after adjusting for other potential risk factors (P=0.001). Also, the incidence of severe illness was lower in the ARBs treated group vs. the group not treated with ARBs [25.9% (15 of 58) vs. 51.4% (72 of 140), respectively; P=0.001; **Figure 1D**], which remained significant after adjusting for confounders. The occurrence rate of severe illness did not change based on the use of ACEI. Compared with ACEI and ARBs, there was no significant difference in the occurrence rates of severe illness (P = 0.172).

The occurrence of ARDS was lower in ACEI/ARB group than in non-ACEI/ARB group (21.6% versus 42.7%, P = 0.003; **Figure 1D**) with OR (95%CI) of 0.27 (0.13-0.58) after adjusting confounders (P = 0.001). The ARB treated patients group had a significantly lower rate of ARDS than the group not treated with ARB (15.5% versus 42.9%, P<0.001; **Figure 1D**), 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 who treated with or without ACEI. In a comparison between ACEI and ARB, the incidence of ARDS was lower in ARB than in the ACEI group (15.5% versus 43.8%, P =0.020; **Figure 1D**), with OR (95%CI) of 0.21 (0.05-0.83) after adjusting confounders (P =0.026).

There were no significant differences between ACEI/ARB or ARB treated and the group not treated in other major adverse events (**Table 1 and 2**).

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. Not surprisingly, ARB was used in the majority (78.4%), as Chinese patients' compliance decreases with ACEI is used[13] primarily due to the higher incidence of ACEI-induced cough in Asian population[7]. While we showed a potential benefit from 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. 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 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 ACEI or ARBs to COVID-19 patients but we couldn't know the ACE2 true levels in patients induced by ACEI of ARBs.

Acute respiratory distress syndrome (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. The frequency of that while was not statistically different, however, there was an impressive trend towards ARB benefits. A previous study showed that the use of ACEI 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 2-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 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 vs. ARB was associated with a significantly different incidence of ARDS and mortality (Figures 1A and 1D).

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. Also, 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.

Funding:

This work was supported by the National Natural Science Foundation (grants 81772046 and 81971816 to Dr. Peng) and the Special Project for Significant New Drug Research and Development in the Major National Science and Technology Projects of China (2020ZX09201007 to Dr. Peng).

Author Contributions : Drs Z. Peng, Q. Lu, and R. Liu designed the study. L Su, J Zhang, N Jiang, J Li, J Yang, L He, Q Xie, R Huang, F Liu, F Yuan, Y Feng, J Jiang, and R. Liu analyzed the data and performed the statistical analyses. L. Su, R. Liu, J Yang, and J Li drafted the initial manuscript. B, Kashani made a critical revision of the initial manuscript.All authors reviewed the drafted manuscript for critical content and approved the final version.

No competing interests to declare

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Figure legends

Figure 1. Effects of ARBs and ACE inhibitors on the severe illness, ARDS and survival in Covid-19 patients.

(A)Kaplan-Meier survival curves of the effects of treatment with ACEI/ARB on overall survival in patients with Covid-19.

(B) Kaplan-Meier survival curves of the effects of treatment with ACEI or ARB alone on overall survival in patients with Covid-19.

(C) Kaplan-Meier survival curves of the effects of treatment with ACEI compared to ARB on overall survival in patients with Covid-19.

(D)The incidence rates of severe illness and ARDS by treatment with ACEI/ARB, ACEI alone, and ARB alone.

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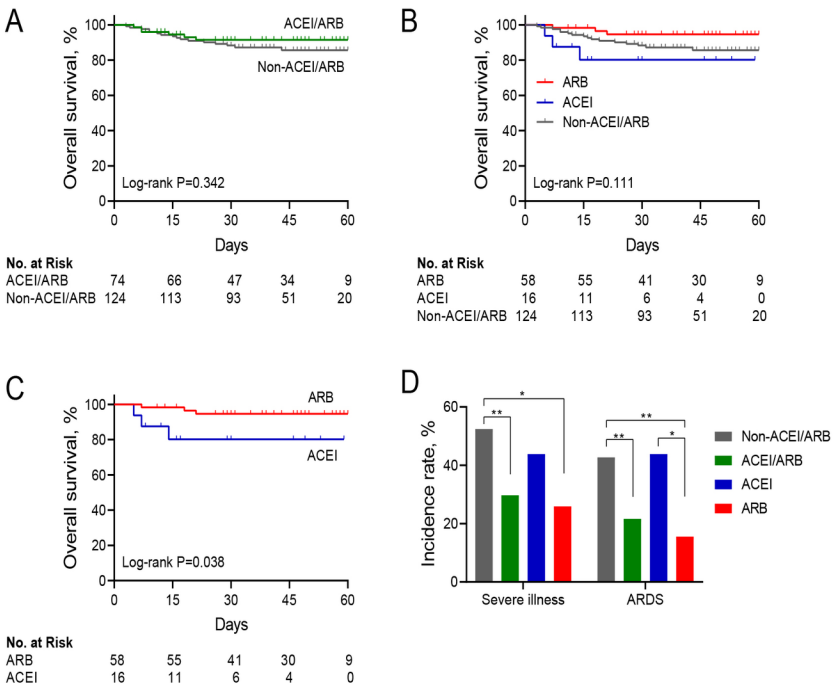

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