Adverse impact of renin-angiotensin system blockade on the clinical course in hospitalized patients with severe COVID-19: a retrospective cohort study

Jeong-Hoon Lim
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Jang-Hee Cho
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Yena Jeon
Department of Statistics, Kyungpook National University
Ji Hye Kim
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Ga Young Lee
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Soojee Jeon
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Hee Won Noh
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Yong-Hoon Lee
Division of Pulmonology, Department of Internal Medicine, Kyungpook National University School of Medicine
Jaehee Lee
Division of Pulmonology, Department of Internal Medicine, Kyungpook National University School of Medicine
Hyun-Ha Chang
Division of Infectious Disease, Department of Internal Medicine, Kyungpook National University School of Medicine
Hee-Yeon Jung
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Ji-Young Choi
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Sun-Hee Park
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Chan-Duck Kim
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Yong-Lim Kim
Division of Nephrology, Department of Internal Medicine, Kyungpook National University School of Medicine
Shin-Woo Kim (ksw2kms@knu.ac.kr)

Division of Infectious Disease, Department of Internal Medicine, Kyungpook National University School of Medicine

Research Article

Keywords: Renin-Angiotensin System, Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Type 1 Receptor Blocker, COVID-19, Mortality.

Posted Date: September 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-74553/v1

Abstract

We investigated the association between angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) and the risk of mortality in hospitalized severe COVID-19 patients. A retrospective cohort study was performed on all hospitalized COVID-19 patients in tertiary hospitals in Daegu, Korea. Patients were classified based on whether they received ACE-I or ARB before COVID-19 diagnosis. The Cox proportional hazards regression model was used for the analysis of survival. Of 130 COVID-19 patients, 30 (23.1%) who received ACE-I or ARB showed an increased the risk of in-hospital mortality (adjusted HR, 2.15; 95% CI, 1.04 to 4.44; *P* = 0.038). ACE-I or ARB were also associated with acute respiratory distress syndrome or mechanical ventilation (adjusted OR, 3.38; 95% CI, 1.18 to 9.69; *P* = 0.024), and acute kidney injury or shock (adjusted OR, 2.81; 95% CI, 1.04 to 7.56; *P* = 0.042). Among the patients with ACE-I or ARB, 14 (46.7%) discontinued the therapy and the cessation was associated with a higher mortality rate. ACE-I or ARB therapy in severe COVID-19 patients was associated with occurrence of severe complications and increased in-hospital mortality. Discontinuation of ACE-I or ARB in patients with more severe COVID-19 was not associated with improvement of mortality.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) spread worldwide from Wuhan, China, initiating the second pandemic of the 21st century [1-3]. The pathogen of COVID-19 was identified as a novel betacoronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4-6]. As of July 19, SARS-CoV-2 had infected more than 14 million individuals and caused 598,000 deaths worldwide [7].

The spike protein of SARS-CoV-2 binds to the cellular receptor for intracellular entry. The host protein for entry is known as angiotensin-converting enzyme 2 (ACE2) in the lungs [8]. Binding of the spike protein to ACE2 results in ACE2 downregulation, prohibiting the main function of ACE2 to degrade angiotensin (Ang) II to Ang 1-7. This contributes to lung injury because the increased Ang stimulates angiotensin receptor 1 to enhance pulmonary vascular permeability [9,10].

Renin-angiotensin system (RAS) blockades, such as ACE inhibitor (ACE-I) or angiotensin II receptor blocker (ARB), increase expression of ACE2 and could enhance entry of SARS-CoV-2 into target cells [11,12]. On the other hand, ACE-I and ARB may block the excessive Ang-mediated angiotensin receptor 1 activation caused by SARS-CoV-2 and protect the infected patients against acute lung injury [13]. However, the role of RAS blockade in the treatment of COVID-19 remains controversial. In this study, we report the association between RAS blockade therapy and the risk of mortality in patients with severe COVID-19 and compare the outcomes between patients who continued and discontinued RAS blockade.

Results

Baseline characteristics and clinical course

Of the 130 patients hospitalized with severe or critical COVID-19, 30 patients (23.1%) received ACE-I (1.5%) or ARB (21.5%) therapy before hospitalization (Figure 1). The baseline characteristics are shown in Table 1. The median age was 67.0 years and 53.8% were men. Initial vital signs, such as blood pressure, heart rate,

respiratory rate, and body temperature at admission, and National Early Warning Score (NEWS) were not different between the patients treated with and without ACE-Is or ARBs. The duration from symptom onset to COVID-19 diagnosis were also not different between the 2 groups. Patients with ACE-I or ARB medication had a higher rate of comorbid hypertension than nonmedication patients (63.3% vs 33.0%; $P = 0.005$). The rates of other comorbid diseases, including diabetes, tumor, heart diseases, and chronic kidney disease, were not different between the 2 groups (all, $P > 0.05$), and the Charlson Comorbidity Index (CCI) score was higher in ACE-I- or ARB-treated patients, with borderline significance (4.1 ± 1.7 vs 3.3 ± 2.4; $P = 0.049$). Among the laboratory indices on admission, white blood cell count and creatinine were higher among ACE-I and ARB medication patients, and estimated glomerular filtration rate (eGFR) was lower in ACE-I and ARB medication patients compared with nonmedication patients (all, $P < 0.05$). Other laboratory data, including lymphocyte count, high-sensitivity C-reactive protein, albumin, procalcitonin, lactate dehydrogenase, creatine phosphokinase, and ferritin did not differ between the 2 groups (all, $P > 0.05$).

During hospitalization, serious complications such as Acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) have occurred more frequently in patients with ACE-I or ARB medication than in nonmedication patients (ARDS: 46.7% vs 20.0%; $P = 0.004$; AKI: 36.7% vs 14.0%; $P = 0.006$) (Table 2). Medication used to treat COVID-19 was similar between the 2 groups, and critical care rates, such as invasive mechanical ventilation (MV), extracorporeal membrane oxygenation, and continuous renal replacement therapy (CRRT), were also not different. The mean duration of hospital stay was 23.8 days, and 36 deaths (27.7%) occurred during hospitalization. Patients who survived all recovered from COVID-19. The in-hospital death rate was significantly higher in the ACE-I and ARB medication patients than those in the nonmedication group (46.7% vs 22.0%; $P = 0.008$).

Association between ACE-I and ARB medication and in-hospital death

Figure 2 shows the 28-day mortality according to the ACE-I and ARB therapy at the time of admission. The mortality rate was significantly higher in the ACE-I and ARB medication patients than the nonmedication patients ($P = 0.012$). To clearly identify the association, we performed the multivariate Cox regression analysis to reduce confounding effects of variables. ACE-I and ARB therapy had significant associations with in-hospital death after adjusting for age, sex, and NEWS (model 1: adjusted hazard ratio [aHR], 2.30; 95% confidence interval [CI], 1.15 to 4.60; $P = 0.019$). The higher mortality rate in the ACE-I and ARB therapy group remained significant after additional adjustments for hypertension and CCI (model 2: aHR, 2.14; 95% CI, 1.05 to 4.35; $P = 0.036$) and further adjustments for laboratory data (model 3: aHR, 2.15; 95% CI, 1.04 to 4.44; $P = 0.038$) (Table 3).

Association between ACE-I and ARB medication and serious outcomes

In addition to in-hospital death, the associations between ACE-I and ARB therapy and the occurrence of serious in-hospital complications, such as ARDS, use of MV, AKI, and shock, were also evaluated. Table 4 shows the result of multivariate logistic regression analysis for serious complications. After adjusting for possible confounding factors, ACE-I and ARB therapy were found to have a significant association with ARDS or MV treatment (adjusted odds ratio [aOR], 3.38; 95% CI, 1.18 to 9.69; $P = 0.024$) and with AKI or shock (aOR, 2.81; 95% CI, 1.04 to 7.56; $P = 0.042$).

Outcomes of patients who discontinued ACE-I and ARB medication

Subgroup analyses for serious outcomes were conducted among patients with ACE-I and ARB medication at the time of admission (n = 30). Patients with ACE-I or ARB therapy were divided according to the maintenance of ACE-I or ARB during hospitalization. Sixteen patients (54.3%) continued ACE-I or ARB medication, and 14 patients discontinued medication because of hypotension, hyperkalemia, AKI, and sedation status for MV. The incidence of in-hospital death, ARDS, use of MV, and use of CRRT were significantly higher in the group of patients who discontinued ACE-I and ARB treatment than those who continued with the treatment (all, $P < 0.05$) (Table 5). Figure 3 shows the 28-day mortality according to ACE-I and ARB maintenance. Patients who discontinued ACE-I and ARB use showed a lower rate of survival than other patient groups, but patients who continued ACE-I and ARB showed a survival rate similar to the group of ACE-I and ARB nonmedication patients.

Discussion

We investigated the effect of ACE-I or ARB therapy in hospitalized patients with severe COVID-19. Our cohort showed comparable comorbidities between patients with and without ACE-I or ARB, except hypertension. ACE-I or ARB treatment was associated with in-hospital complications and mortality in severe COVID-19 patients. However, withdrawal of ACE-I or ARB, which was determined by clinical course, did not improve patients' survival. This suggests that COVID-19 patients on ACE-I or ARB therapy require more careful monitoring and intensive treatment.

Several large studies have been published to demonstrate the effect of ACE-I and ARB on the mortality of patients with COVID-19 [14-16]. They reported that the use of ACE-I or ARB was not associated with mortality in COVID-19 patients. However, the conclusion regarding the use of RAS blockade in COVID-19 is still inconsistent, even among several meta-analyses. Most meta-analyses have reported that ACE-I and ARB use was not associated with mortality [17-19], but one showed a relationship between ACE-Is and ARBs and lower mortality among hypertensive COVID-19 patients [17]. Another meta-analysis reported an overall protective effect of RAS blockade with death and critical disease [20]. The heterogeneous conclusions might be related to the fact that some population-based studies could not assess confounding factors such as obesity, severity of diabetes, and control of hypertension. Adjustment of several crucial confounding variables for outcome of COVID-19 might result in a different conclusion.

We reported a negative impact of ACE-I and ARB use among hospitalized Korean patients. Liabeuf et al described the association of RAS blockade use with a higher risk of severe COVID-19 in 268 hospitalized patients, which is consistent with our results [21]. The difference of these studies compared with the previous reports is that all confounding factors such as body mass index, blood pressure, and various laboratory data were identified in severe hospitalized patients with COVID-19. Availability of definite treatment outcomes in hospitalized patients could also make the effect of RAS blockade different. Some research was biased toward including more patients who died early in their hospital course [22]. In such cases, comparisons of long-term prognosis might yield different results. Taken together, our study suggests that the effect of RAS blockade might differ in more severe hospitalized COVID-19 patients when all variables and treatment outcomes are considered.

The present results are similar to those reported in a nationwide population study in Korea [23]. Mortality of hospitalized cases was higher among RAS blockade users than nonusers, although the use of RAS blockade was not an independent risk factor in multivariate analysis. In addition, RAS blockade was independently associated with severe disease, such as need for high-flow nasal cannula among 1954 hospitalized patients. The conflicting effect of RAS blockade compared with other studies might also be attributable to racial differences in ACE2 expression. Considering that the East Asian population expresses higher ACE2 in tissue than other populations [24], upregulation of ACE2 induced by RAS blockade might be more prominent in influencing the prognosis of Asian patients with COVID-19. This hypothesis should be confirmed by further prospective cohort studies or randomized controlled trials.

Severe COVID-19 was associated with multiple organ injuries such as ARDS [25-27] and AKI [28-30], which were identified as independent risk factors for mortality in patients with COVID-19. However, the association of ACE-I or ARB use with AKI or ARDS is still not fully understood. Some studies did not find any relationship between the use of ACE-I or ARB and the development of AKI [31,32]. Contrary to these results, Oussalah et al reported a harmful effect of long-term ACE-I or ARB use on the renal function and further interaction with the occurrence of AKI and ARDS in 149 hospitalized COVID-19 patients [33]. Our study highlighted the possible association between ACE-I or ARB use and a significant increase in both ARDS and AKI. Considering that ACE2 is abundantly expressed in the proximal tubules of the kidney as well as type II alveolar epithelium of lung [34], induction of ACE2 expression by RAS blockade might affect the binding of SARS-CoV-2 to kidney tissue, deteriorating renal function.

Little is known about the effect of discontinued RAS blockade in COVID-19. Richardson et al showed an increasing trend in mortality in ACE-I and ARB users compared with nonusers, with approximately 50% of the patients discontinuing the drug in the course of hospitalization [22]. Lam et al compared COVID-19 patients who continued and discontinued ACE-I or ARB after excluding cases of hypotension and AKI [35]. Patients who could continue ACE-I or ARB demonstrated lower mortality and intensive care unit admission rates. This suggests that the ability to continue ACE-I or ARB therapy was associated with better clinical outcomes of COVID-19. These results support the hypothesis that the discontinuation of ACE-I or ARB adversely affects outcomes of COVID-19. Our study also showed worse outcomes in patients who discontinued ACE-I or ARB, suggesting a deteriorating effect of the discontinuation. However, the present study design is not suitable for evaluating the withdrawal effect of ACE-I or ARB. Cessation of ACE-I or ARB was determined by the patient's condition, ie, AKI or shock. Thus, patients with more severe COVID-19 discontinued RAS blockade. If ACE-I or ARB adversely affects the prognosis of COVID-19, it could be hypothesized that discontinuation of the drug might improve the outcomes, even in severe patients. However, our study could not find such effect of ACE-I or ARB, but could only confirm the association between poor outcome and drug discontinuation during the treatment of COVID-19. A conclusion for the cessation effects ACE-Is and ARBs can be drawn only through well-designed prospective studies.

The present study has several limitations that should be considered in the interpretation of our results. Although our study was conducted in 2 independent hospitals, it had a retrospective design and a limited number of patients. Our results should be investigated in larger studies with long-term follow-up to prove the causal relationship. Nevertheless, the advantage of our study is that the detailed course of treatment as well as laboratory findings and patients' characteristics were evaluated to confirm the association between ACE-I or

ARB and prognosis. Because most of the patients were discharged and there were no critically ill patients at the end of the survey, it can be said that the investigation of outcomes was clearly evaluated in our cohort. Another limitation is that the conflicting impact of ACE-I and ARB could not be easily explained. ACE-I and ARB adversely affected both patients who have taken the drugs and discontinued them after hospitalization. A biphasic role of ACE-I and ARB depending on the phase of the disease might be suggested to explain our results: ACE-I or ARB use could initially lead to an increased risk of SARS-CoV-2 entry into the lung and kidney by overexpression of ACE2. However, withdrawal of the drug after COVID-19 infection might be associated with loss of its effect to maintain ACE2 activity, which is beneficial to lung injury [36]. This presumptive effect could be demonstrated through further analysis or research considering known confounders to the course of COVID-19 such as hypertension, cardiovascular disease, hypotension, and AKI.

In conclusion, ACE-I or ARB therapy in patients with severe COVID-19 was associated with the occurrence of severe complications and increased in-hospital mortality. Discontinuation of ACE-I or ARB in patients with more severe COVID-19 was not associated with improvement of mortality. Our findings provide data for a harmful effect of RAS blockade on COVID-19. Further prospective trials are warranted on this class of drugs in the management of patients with COVID-19.

Methods

Patients and data

This study was conducted as a retrospective cohort study that analyzed all patients with COVID-19 who were admitted to 2 university-based tertiary hospitals in Daegu, South Korea (Kyungpook National University Hospital and Kyungpook National University Chilgok Hospital). COVID-19 was confirmed based on nasopharyngeal and oropharyngeal swab samples using real-time reverse transcriptase polymerase chain reaction (rRT-PCR) for SARS-CoV-2 [28]. At the time of initial diagnosis, COVID-19 patients were classified into 4 categories (mild, moderate, severe, and critical) using the Telephone Severity Scoring System according to age, symptoms, underlying diseases, and social factors [37]. Briefly, severe patients were suspected to have severe pneumonia with cough and fever of 38°C or higher. Critical patients were suspected to have critical pneumonia if they experienced shortness of breath for more than 1 day and had a respiratory rate of 30 or more per minute. Only severe and critical patients were admitted to tertiary hospitals in Daegu, South Korea because of the acute hospital bed shortage. Patient data were collected from February 17 to May 31, 2020. Among the 169 COVID-19 patients who were admitted to the 2 hospitals, 130 patients were able to identify previous medication. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [38]. We surveyed the data for patient demographics, medication history, clinical symptoms, comorbid diseases, clinical course, and laboratory findings from the electronic medical records. Oral medication history, including ACE-Is and ARBs, was recorded at the time of hospital admission. We also investigated whether patients took medication or not during their hospitalization. The laboratory findings contained complete blood count, liver function test, renal function test, and inflammatory markers. The study protocol was reviewed and approved by the Institutional Review Boards (IRBs) of Kyungpook National University Hospital (2020-03-044) and Kyungpook National University Chilgok hospital (2020-04-013). Both IRBs approved waiver of informed consent because the study did not infringe on patient's privacy or health. This study was performed in accordance with the declaration of Helsinki.

Definition

Shock was defined as systolic blood pressure of less than 90 mmHg for more than 30 minutes or requiring the use of vasopressors to maintain a systolic blood pressure higher than 90 mmHg [39]. Acute kidney injury was defined according to the Kidney Disease Improving Global Guidelines, namely (1) an increase in serum creatinine of 0.3 mg/dL or more within 48 hours, (2) an increase in serum creatinine of 1.5 or more times the baseline, or (3) urine volume less than 0.5 mL/kg per hour for 6 hours [40]. ARDS was defined according to the Berlin Definition [41]. The NEWS, an early warning score facilitating the early recognition and response to patient deterioration [42], consists of 7 parameters: respiratory rate, peripheral oxygen saturation, use of supplemental oxygen, body temperature, systolic blood pressure, heart rate, and neurological status. Each parameter is assigned a score of 0 to 3. The CCI score was developed as a prognostic classification and weighting method that predicts mortality based on patient age and comorbid diseases [43]. Patients with ACE-I or ARB medication were defined as those using ACE-I or ARB at the time of admission regardless of medication during hospitalization.

Clinical management

All patients received symptomatic care with antipyretic and antitussive agents. Hospitalized COVID-19 patients were treated with lopinavir and ritonavir or darunavir and cobicistat with or without hydroxychloroquine. Critical COVID-19 patients were also treated with corticosteroid or intravenous immunoglobulin, according to the physicians' decision.

Statistical analysis

The Kolmogorov-Smirnov test was applied to analyze the normal distribution of variables. Data are expressed as the mean ± standard deviation or median (interquartile range) based on distribution of the variables for continuous variables, and numbers (percentage) for categorical variables. The Student's *t* test and Mann–Whitney *U* test were used for continuous variables and the Pearson chi-square test or Fisher's exact test were used for categorical variables, as appropriate. Kaplan–Meier analysis with log-rank test was used to compare the 28-day survival rate between the groups. Univariate and multivariate Cox proportional hazard regression analyses were performed to evaluate the association between ACE-I or ARB therapy and patient survival. Variables that were potentially associated with mortality or had a difference in baseline characteristics were entered into the multivariate analysis. To determine the effects of ACE-I or ARB therapy on serious complications, multivariate logistic regression analyses were performed after adjusting possible confounding factors. The statistical analyses were performed with SPSS version 22.0 (IBM Corp., Armonk, NY). A *P* value of less than 0.05 was considered statistically significant.

Declarations

Acknowledgments

We thank all medical staff for their effort in COVID-19 patient care. This work was supported by a research grant from Daegu Medical Association COVID19 scientific committee; and the Research Program funded by the Korea Centers for Disease Control and Prevention (fund code 2020-03-044).

Author Contributions

Research idea and study design: JHC; data acquisition: JHL, JHK, GYL, SJJ, HWN, HYJ, JYC, SHP, CDK, YLK, YHL, JL, HHC, and SWK; data analysis/interpretation: YJ, JHC and JHL; writing of the paper: JHC and JHL; supervision or mentorship: SWK. All authors contributed to and reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional Information

Data Availability Statement

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

References

1 Huang, C. *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**, 497-506, doi:10.1016/s0140-6736(20)30183-5 (2020).

2 Wang, D. *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* **323**, 1061-1069, doi:10.1001/jama.2020.1585 (2020).

3 Guan, W.-j. *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine* **382**, 1708-1720, doi:10.1056/NEJMoa2002032 (2020).

4 Lu, R. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* **395**, 565-574, doi:10.1016/S0140-6736(20)30251-8 (2020).

5 Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* **382**, 727-733, doi:10.1056/NEJMoa2001017 (2020).

6 Kim, J.-M. *et al.* Identification of Coronavirus Isolated from a Patient in Korea with COVID-19. *Osong public health and research perspectives* **11**, 3-7, doi:10.24171/j.phrp.2020.11.1.02 (2020).

7 Wuhan Coronavirus (2019-nCoV) Global Cases (by Johns Hopkins CSSE). *Case Dashboard* (2020).

https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 [Assessed 15 19 July 2020].

8 Hoffmann, M. *et al.* SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **181**, 271-280.e278, doi:10.1016/j.cell.2020.02.052 (2020).

9 Imai, Y. *et al.* Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* **436**, 112-116, doi:10.1038/nature03712 (2005).

10 Kuba, K. *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* **11**, 875-879, doi:10.1038/nm1267 (2005).

11 Ishiyama, Y. *et al.* Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension* **43**, 970-976, doi:10.1161/01.HYP.0000124667.34652.1a (2004).

12 Klimas, J. *et al.* Perinatally administered losartan augments renal ACE2 expression but not cardiac or renal Mas receptor in spontaneously hypertensive rats. *J Cell Mol Med* **19**, 1965-1974, doi:10.1111/jcmm.12573 (2015).

13 Gurwitz, D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res*, doi:10.1002/ddr.21656 (2020).

14 Mancia, G., Rea, F., Ludergnani, M., Apolone, G. & Corrao, G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med* **382**, 2431-2440, doi:10.1056/NEJMoa2006923 (2020).

15 Reynolds, H. R. *et al.* Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med* **382**, 2441-2448, doi:10.1056/NEJMoa2008975 (2020).

16 Li, J., Wang, X., Chen, J., Zhang, H. & Deng, A. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. *JAMA Cardiol* **5**, 1-6, doi:10.1001/jamacardio.2020.1624 (2020).

17 Guo, X., Zhu, Y. & Hong, Y. Decreased Mortality of COVID-19 With Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients With Hypertension: A Meta-Analysis. *Hypertension* **76**, e13-e14, doi:10.1161/hypertensionaha.120.15572 (2020).

18 Pranata, R. *et al.* The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *Diabetes Metab Syndr* **14**, 983-990, doi:10.1016/j.dsx.2020.06.047 (2020).

19 Greco, A. *et al.* Outcomes of renin-angiotensin-aldosterone system blockers in patients with COVID-19: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother*, doi:10.1093/ehjcvp/pvaa074 (2020).

20 Pirola, C. J. & Sookoian, S. Estimation of Renin-Angiotensin-Aldosterone-System (RAAS)-Inhibitor effect on COVID-19 outcome: A Meta-analysis. *J Infect* **81**, 276-281, doi:10.1016/j.jinf.2020.05.052 (2020).

21 Liabeuf, S. *et al.* Association between renin-angiotensin system inhibitors and COVID-19 complications. *Eur Heart J Cardiovasc Pharmacother*, doi:10.1093/ehjcvp/pvaa062 (2020).

22 Richardson, S. *et al.* Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* **323**, 2052-2059, doi:10.1001/jama.2020.6775 (2020).

23 Jung, S. Y., Choi, J. C., You, S. H. & Kim, W. Y. Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based cohort study. *Clin Infect Dis*, doi:10.1093/cid/ciaa624 (2020).

24 Cao, Y. *et al.* Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov* **6**, 11, doi:10.1038/s41421-020-0147-1 (2020).

25 Yang, X. *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* **8**, 475-481, doi:10.1016/s2213-2600(20)30079-5 (2020).

26 Wu, C. *et al.* Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* **180**, 1-11, doi:10.1001/jamainternmed.2020.0994 (2020).

27 Zhou, F. *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* **395**, 1054-1062, doi:10.1016/s0140-6736(20)30566-3 (2020).

28 Lim, J. H. *et al.* Fatal Outcomes of COVID-19 in Patients with Severe Acute Kidney Injury. *J Clin Med* **9**, doi:10.3390/jcm9061718 (2020).

29 Fisher, M. *et al.* AKI in Hospitalized Patients with and without COVID-19: A Comparison Study. *J Am Soc Nephrol*, doi:10.1681/asn.2020040509 (2020).

30 Fominskiy, E. V. *et al.* Prevalence, Characteristics, Risk Factors, and Outcomes of Invasively Ventilated COVID-19 Patients with Acute Kidney Injury and Renal Replacement Therapy. *Blood Purif*, 1-8, doi:10.1159/000508657 (2020).

31 Hirsch, J. S. *et al.* Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* **98**, 209-218, doi:10.1016/j.kint.2020.05.006 (2020).

32 Chung, S. M. *et al.* The Risk of Diabetes on Clinical Outcomes in Patients with Coronavirus Disease 2019: A Retrospective Cohort Study. *Diabetes Metab J* **44**, 405-413, doi:10.4093/dmj.2020.0105 (2020).

33 Oussalah, A. *et al.* Long-Term ACE Inhibitor/ARB Use Is Associated with Severe Renal Dysfunction and Acute Kidney Injury in Patients with severe COVID-19: Results from a Referral Center Cohort in the North East of France. *Clin Infect Dis*, doi:10.1093/cid/ciaa677 (2020).

34 Mizuiri, S. & Ohashi, Y. ACE and ACE2 in kidney disease. *World J Nephrol* **4**, 74-82, doi:10.5527/wjn.v4.i1.74 (2015).

35 Lam, K. W. *et al.* Continued in-hospital ACE inhibitor and ARB Use in hypertensive COVID-19 patients is associated with positive clinical outcomes. *J Infect Dis*, doi:10.1093/infdis/jiaa447 (2020).

36 Sommerstein, R., Kochen, M. M., Messerli, F. H. & Gräni, C. Coronavirus Disease 2019 (COVID-19): Do Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers Have a Biphasic Effect? *J Am Heart Assoc* **9**, e016509, doi:10.1161/jaha.120.016509 (2020).

37 Kim, S.-W., Lee, K. S., Kim, K., Lee, J. J. & Kim, J.-y. A Brief Telephone Severity Scoring System and Therapeutic Living Centers Solved Acute Hospital-Bed Shortage during the COVID-19 Outbreak in Daegu, Korea. *J Korean Med Sci* **35** (2020).

38 Levey, A. S. *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* **150**, 604-612, doi:10.7326/0003-4819-150-9-200905050-00006 (2009).

39 Wilson, R. F. & Walt, A. J. *Management of Trauma: Pitfalls and Practice*. (Williams & Wilkins, 1996).

40 Khwaja, A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* **120**, c179-184, doi:10.1159/000339789 (2012).

41 Ranieri, V. M. *et al.* Acute respiratory distress syndrome: the Berlin Definition. *JAMA* **307**, 2526-2533, doi:10.1001/jama.2012.5669 (2012).

42 Smith, G. B., Prytherch, D. R., Meredith, P., Schmidt, P. E. & Featherstone, P. I. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation* **84**, 465-470, doi:https://doi.org/10.1016/j.resuscitation.2012.12.016 (2013).

43 Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* **40**, 373-383, doi:10.1016/0021-9681(87)90171-8 (1987).

Tables

Table 1. Baseline characteristics

	All (n = 130)	ACE-I/ARB (n = 30)	No ACE-I/ARB (n = 100)	*P* value
Age, y	67.0 (57.0–78.0)	72.0 (63.0–78.0)	66.0 (55.0–77.0)	0.102
Sex, male n, %	70 (53.8)	21 (70.0)	49 (49.0)	0.060
Body mass index, kg/m^2	23.8 ± 3.4	24.6 ± 3.8	23.5 ± 3.3	0.225
Systolic BP, mmHg	135.3 ± 24.7	142.6 ± 26.5	132.8 ± 24.0	0.060
Diastolic BP, mmHg	78.4 ± 16.0	78.1 ± 20.4	78.4 ± 14.5	0.918
Heart rate, beats per min	88.7 ± 16.8	94.0 ± 16.3	87.8 ± 17.0	0.078
Respiratory rate, breath per min	23.2 ± 12.3	26.2 ± 23.5	22.3 ± 5.8	0.380
Body temperature, ℃	37.1 ± 0.7	37.1 ± 0.6	37.1 ± 0.8	0.817
NEWS	3.9 ± 3.2	4.2 ± 3.5	3.8 ± 3.1	0.612
Days from symptom onset to diagnosis	7.8 ± 8.0	8.2 ± 7.0	7.7 ± 8.4	0.777
Comorbid diseases, n (%)				
Diabetes	33 (25.4)	11 (36.7)	22 (22.0)	0.150
Hypertension	52 (40.0)	19 (63.3)	33 (33.0)	0.005
Chronic lung disease	8 (6.2)	4 (13.3)	4 (4.0)	0.062
Tumor	12 (9.2)	2 (6.7)	10 (10.0)	0.580
Heart failure	3 (2.3)	1 (3.3)	2 (2.0)	0.670
Coronary heart disease	10 (7.7)	3 (10.0)	7 (7.0)	0.696
Chronic kidney disease	12 (9.2)	4 (13.3)	8 (8.0)	0.376
End-stage renal disease	8 (6.2)	3 (10.0)	5 (5.0)	0.318
CCI	3.5 ± 2.3	4.1 ± 1.7	3.3 ± 2.4	0.049
Laboratory findings				
White blood cell count, $\times 10^9/L$	6.4 (4.5–8.4)	7.2 (6.1–10.7)	6.0 (4.1–7.9)	0.003
Lymphocyte count, $\times 10^9/L$	0.9 (0.6-1.2)	0.9 (0.6–1.5)	0.9 (0.6–1.2)	0.721
hs-CRP, mg/dL	6.4 (2.0-12.5)	6.7 (2.7–16.0)	6.1 (1.7–11.3)	0.192
Albumin, g/dL	3.5 ± 0.5	3.4 ± 0.6	3.5 ± 0.5	0.451
Procalcitonin, ng/mL (n=82)	0.10 (0.05–0.25)	0.08 (0.03–0.57)	0.10 (0.05–0.22)	0.495
LDH, U/L (n=111)	338.0 (233.0–494.0)	388.5 (242.0–542.5)	317.0 (232.0–469.0)	0.211
CPK, U/L (n=85)	73.0 (49.0–177.5)	73.0 (53.0–135.0)	73.5 (45.0–211.0)	0.870
Ferritin, ng/mL (n=91)	418.1 (243.9–843.0)	531.0 (239.0–982.0)	388.0 (245.9–781.3)	0.488
Creatinine, mg/dL	0.8 (0.7–1.3)	1.1 (0.7–1.7)	0.8 (0.6–1.2)	0.010
eGFR, mL/min/1.73 m^2	87.0 (54.0–98.0)	62.5 (41.0–87.5)	88.0 (60.0–100.0)	0.004
Chest radiographic findings, n (%)				

Ground-glass opacity	56 (43.1)	15 (50.0)	41 (41.0)	0.383
Patchy consolidation	72 (55.4)	18 (60.0)	54 (54.0)	0.562

BP, blood pressure; CCI, Charlson Comorbidity Index; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; NEWS, National Early Warning Score.

Table 2. Comparison of complications, treatment, and clinical outcomes

	All (n = 130)	ACE-I/ARB (n = 30)	No ACE-I/ARB (n = 100)	*P* value
Length of hospital stay, d	23.8 ± 16.5	20.3 ± 14.3	24.9 ± 17.1	0.189
Treatment, n (%)				
Antibiotics	99 (76.2)	26 (86.7)	73 (73.0)	0.123
Lopinavir/ritonavir	73 (56.2)	20 (66.7)	53 (53.0)	0.186
Darunavir/cobicistat	33 (25.4)	8 (26.7)	25 (25.0)	0.854
Hydroxychloroquine	91 (70.0)	24 (80.0)	67 (67.0)	0.173
Glucocorticoid	48 (36.9)	13 (44.8)	35 (35.0)	0.374
IVIG	13 (10.0)	2 (6.7)	11 (11.0)	0.731
Oxygen therapy	87 (66.9)	21 (70.0)	66 (66.0)	0.683
Invasive MV	25 (19.2)	7 (23.3)	18.0 (18.0)	0.516
ECMO	4 (3.1)	2 (6.7)	2 (2.0)	0.231
CRRT	9 (6.9)	4 (13.3)	5 (5.0)	0.210
ICU admission	38 (29.2)	10 (33.3)	28 (28.0)	0.595
Complications, n (%)				
ARDS	34 (26.2)	14 (46.7)	20 (20.0)	0.004
Acute kidney injury	25 (19.2)	11 (36.7)	14 (14.0)	0.006
Shock	54 (41.5)	15 (50.0)	39 (39.0)	0.284
Clinical outcomes, n (%)				0.008
In-hospital death	36 (27.7)	14 (46.7)	22 (22.0)	
Recovery	94 (72.3)	16 (53.3)	78 (78.0)	

ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; IVIG, intravenous immunoglobulin; MV, mechanical ventilation.

Table 3. Associated factors of patient survival in the Cox proportional hazard model

Variables	Univariate		Model 1†		Model 2‡		Model 3§	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value	aHR (95% CI)	*P* value	aHR (95% CI)	*P* value
ACE-I/ARB medication	2.40 (1.23–4.71)	0.010	2.30 (1.15–4.60)	0.019	2.14 (1.05–4.35)	0.036	2.15 (1.04–4.44)	0.038
Age	1.77 (1.32–2.37)	<0.001	1.97 (1.39–2.79)	<0.001	1.62 (1.14–2.32)	0.008	1.63 (1.13–2.36)	0.009
Sex (ref: F)	1.10 (0.56–2.14)	0.784	1.14 (0.57–2.29)	0.715	1.08 (0.53–2.23)	0.831	1.07 (0.51–2.24)	0.857
NEWS	1.14 (1.04–1.26)	0.006	1.16 (1.05–1.28)	0.003	1.20 (1.08–1.34)	0.001	1.21 (1.08–1.34)	0.001
Hypertension	1.71 (0.88–3.29)	0.111			0.93 (0.47–1.84)	0.840	0.93 (0.47–1.86)	0.842
CCI	1.28 (1.14–1.44)	<0.001			1.35 (1.12–1.63)	0.002	1.35 (1.12–1.64)	0.002
WBC count	1.08 (1.00–1.18)	0.064					1.00 (0.90–1.10)	0.932
eGFR	0.99 (0.98–1.00)	0.048					1.00 (0.99–1.01)	0.902

aHR, adjusted hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NEWS, National Early Warning Score; WBC, white blood cell.

†Model 1: adjusted for age, sex, and NEWS; ‡Model 2: adjusted for Model 1 plus hypertension and CCI; §Model 3: adjusted for Model 2 plus WBC count and eGFR.

Table 4. Associated factors for serious complications in the multivariate logistic regression analysis

	ARDS or MV		AKI or shock	
Variables	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
ACE-I/ARB medication	3.38 (1.18–9.69)	0.024	2.81 (1.04–7.56)	0.042
Age	1.12 (0.74–1.70)	0.580	0.87 (0.61–1.22)	0.410
Sex (ref: F)	1.53 (0.59–3.96)	0.379	0.99 (0.45–2.18)	0.975
NEWS	1.36 (1.15–1.60)	<0.001	1.30 (1.12–1.50)	<0.001
Hypertension	0.96 (0.35–2.65)	0.942	0.83 (0.34–2.03)	0.686
CCI	1.14 (0.86–1.53)	0.359	1.11 (0.89–1.39)	0.342
WBC count	1.10 (0.96–1.27)	0.173	0.89 (0.78–1.02)	0.096
eGFR	0.99 (0.98–1.01)	0.430	0.99 (0.97–1.00)	0.061

ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; CI, confidence interval; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; MV, mechanical ventilation; NEWS, National Early Warning Score; OR, odds ratio; WBC, white blood cell.

Table 5. Comparisons of serious outcomes according to ACE-I/ARB maintenance in patients with ACE-I/ARB medication

Variables, n (%)	ACE-I/ARB keep (n = 16)	ACE-I/ARB withdrawal (n = 14)	*P* value
In-hospital death	3 (18.8)	11 (78.6)	0.001
ARDS	4 (25.0)	9 (64.3)	0.030
Acute kidney injury	4 (25.0)	7 (50.0)	0.156
Shock	6 (37.5)	9 (64.3)	0.143
Heart failure	2 (12.5)	3 (21.4)	0.642
MV	1 (6.3)	6 (42.9)	0.031
ECMO	0	2 (14.3)	0.209
CRRT	0	4 (28.6)	0.037

ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation.

Figures

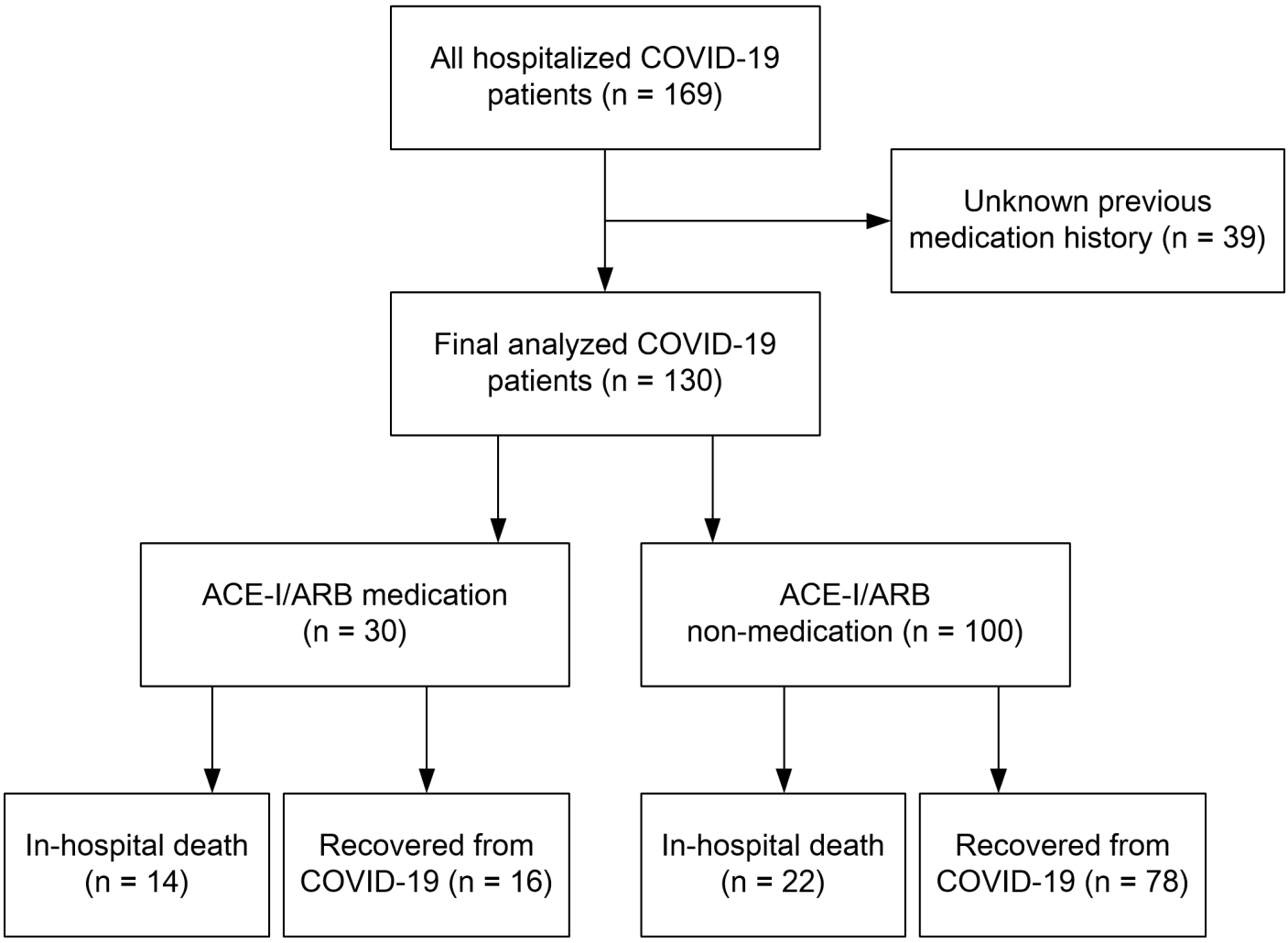

Figure 1

Flow diagram of the study participants.

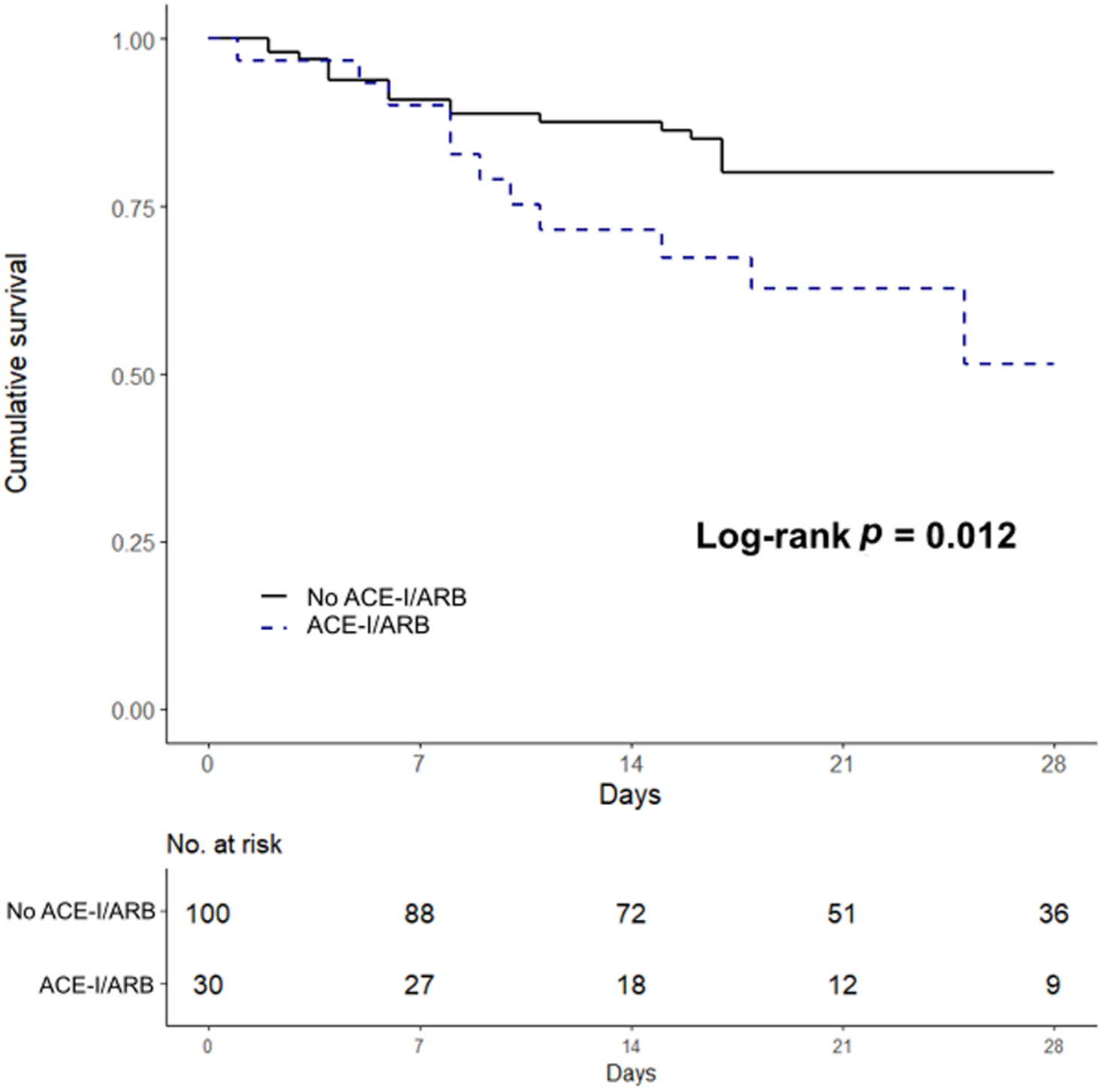

Figure 2

Kaplan–Meier survival curve for 28-day mortality of hospitalized COVID-19 patients according to ACE-I and ARB medication on admission.

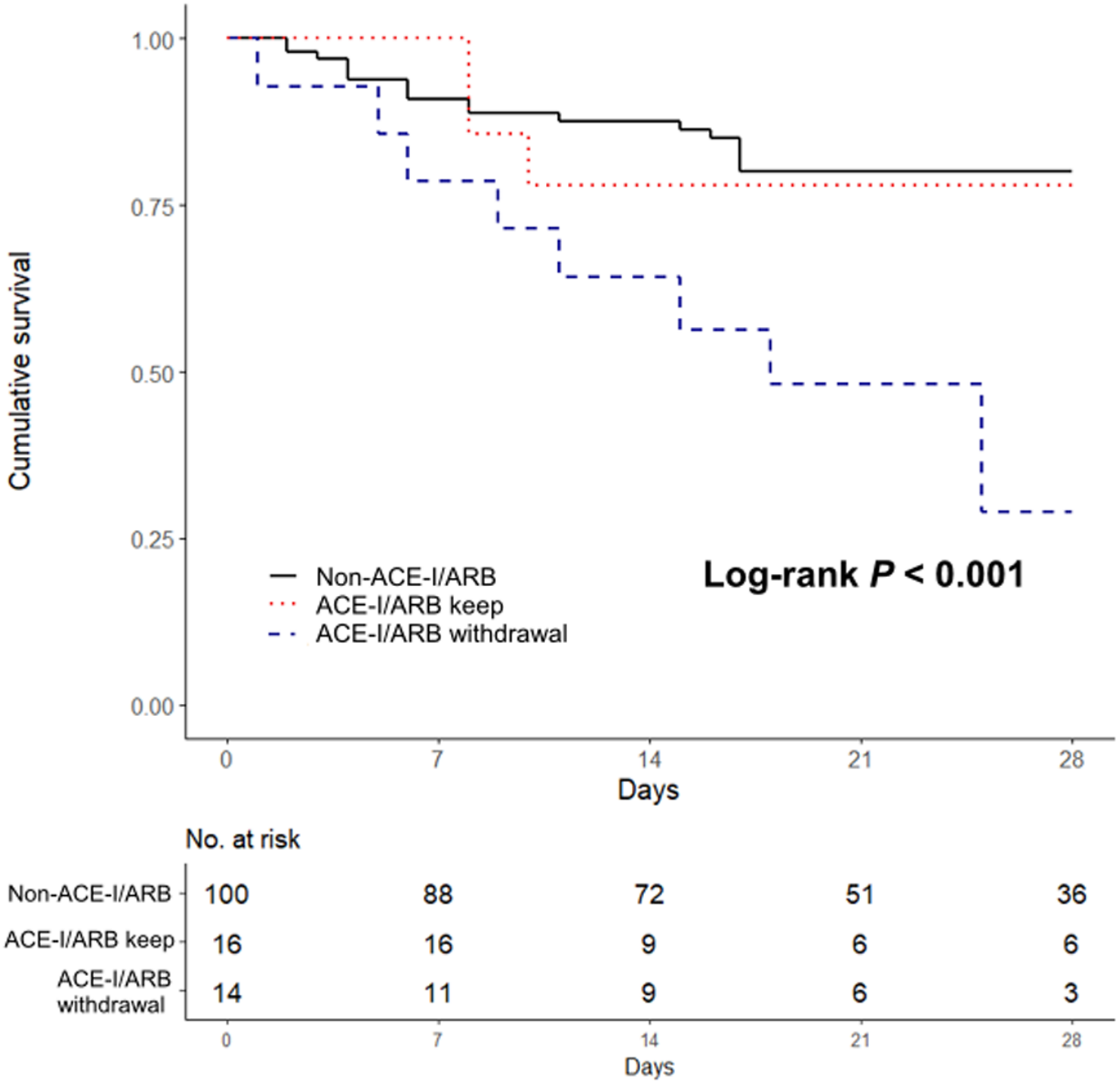

Figure 3

Kaplan–Meier survival curve for 28-day mortality of hospitalized COVID-19 patients according to ACE-I and ARB medication and maintenance during hospitalization.