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Association of Renin Angiotensin Aldosterone System Inhibitors and Outcomes of Hospitalized Patients With COVID-19

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OBJECTIVES: To determine the association of prior use of renin-angiotensin-aldosterone system inhibitors (RAASIs) with mortality and outcomes in hospitalized patients with COVID-19.

DESIGN: Retrospective observational study.

SETTING: Multicenter, international COVID-19 registry.

SUBJECTS: Adult hospitalized COVID-19 patients on antihypertensive agents (AHAs) prior to admission, admitted from March 31, 2020, to March 10, 2021.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Data were compared between three groups: patients on RAASIs only, other AHAs only, and those on both medications. Multivariable logistic and linear regressions were performed after controlling for prehospitalization characteristics to estimate the effect of RAASIs on mortality and other outcomes during hospitalization. Of 26,652 patients, 7,975 patients were on AHAs prior to hospitalization. Of these, 1,542 patients (19.3%) were on RAASIs only, 3,765 patients (47.2%) were on other AHAs only, and 2,668 (33.5%) patients were on both medications. Compared with those taking other AHAs only, patients on RAASIs only were younger (mean age 63.3 vs 66.9 yr; $p < 0.0001$), more often male (58.2% vs 52.4%; $p = 0.0001$) and more often White (55.1% vs 47.2%; $p < 0.0001$). After adjusting for age, gender, race, location, and comorbidities, patients on combination of RAASIs and other AHAs had higher in-hospital mortality than those on RAASIs only (odds ratio [OR] = 1.28; 95% CI [1.19–1.38]; $p < 0.0001$) and higher mortality than those on other AHAs only (OR = 1.09; 95% CI [1.03–1.15]; $p = 0.0017$). Patients on RAASIs only had lower mortality than those on other AHAs only (OR = 0.87; 95% CI [0.81–0.94]; $p = 0.0003$). Patients on ACEIs only had higher mortality compared with those on ARBs only (OR = 1.37; 95% CI [1.20–1.56]; $p < 0.0001$).

CONCLUSIONS: Among patients hospitalized for COVID-19 who were taking AHAs, prior use of a combination of RAASIs and other AHAs was associated with higher in-hospital mortality than the use of RAASIs alone. When compared with ARBs, ACEIs were associated with significantly higher mortality in hospitalized COVID-19 patients.

KEY WORDS: antihypertensive agents; COVID-19; mortality; outcome; renin-angiotensin-aldosterone system inhibitors

Over the course of the pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), there have been numerous triumphs for the scientific community as well as a surplus of misinformation released to the public with potentially life-threatening implications. In the early stages of the pandemic, research showed that SARS-CoV-2 invades the host cells through the receptor angiotensin-converting enzyme (ACE)–2.

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This well-known enzyme is highly expressed in the vascular endothelium and the lungs, particularly in endothelial and type 2 alveolar epithelial cells (1). Common medications used to treat hypertension, ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) that are collectively known as renin-angiotensin-aldosterone system inhibitors (RAASIs) came into question as experimental studies with animal models showed these medications up-regulate ACE-2 expression leading to increased risk of severe illness (2).

Research suggests that the use of ACEIs and ARBs does not increase the risk of COVID-19, instead, comorbidities such as hypertension, obesity, diabetes mellitus (DM), and cardiovascular disease are risk factors for severe COVID-19 (3, 4). Recent literature does not show increased risk of COVID-19 or hospital outcomes with use of these medications (5, 6). Lopes et al (7) reported that in hospitalized patients with COVID-19, discontinuation of RAASIs did not affect the number of days alive and out of the hospital. Another study showed that discontinuation of RAASIs in patients with COVID-19 may lead to faster and better recovery (8). Additional research has shown that the interaction between SARS-CoV-2 and ACE-2 can lead to dysregulation of RAAS which results in an accumulation of angiotensin II and can have potentially negative effects, such as inflammation, coagulation, and fibrosis (9). Therefore, the use of RAASIs could potentially decrease angiotensin II proinflammatory effects and be beneficial in patients infected with COVID-19. A prospective cohort study by Hippisley-Cox reported reduced risk of COVID-19 in patients receiving RAASIs (10).

With this contrasting evidence, it remains unclear whether use of RAASIs affects the outcomes of hospitalized patients with COVID-19. Society of Critical Care Medicine (SCCM) Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS) COVID-19 Registry is a multicenter, international registry developed by SCCM's Discovery network (11). The aim of this study was to determine the effect of prior use of RAASIs on outcomes of patients hospitalized with laboratory-confirmed SARS-CoV-2 infection included in the VIRUS: COVID-19 Registry database.

MATERIALS AND METHODS

Design, Setting, and Study Population

This is a retrospective observational study of adult patients hospitalized with laboratory-confirmed SARS-CoV-2 infection included in the VIRUS: COVID-19 Registry database (11) from 181 sites in 19 countries between March 31, 2020, and March 10, 2021. A confirmed case of COVID-19 was defined by a positive result on a reverse-transcriptase–polymerase chain reaction assay. For patients with multiple hospital admissions for COVID-19, only the first hospital admission was included in this analysis. Patients under the age of 18 years, those with no recorded discharge status, and those without research authorization to access medical records were excluded. Patients who were not admitted for COVID-19 but were incidentally found to be positive for SARS-CoV-2 were also excluded. Patients on any antihypertensive agents (AHAs) prior to admission were included in the analysis. Patients were followed until hospital discharge or death.

Data Collection

Extensive data were collected by the registry for each patient; however, only a subset was requested for this analysis. Demographic data requested included age, gender, race, and geographical location. Clinical data requested included admission diagnosis, location of initial admission, comorbidities, other prehospitalization medications, smoking status, and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. Outcome data included in-hospital mortality, admission to ICU, hospital and ICU length of stay (LOS), development of complications (e.g., respiratory failure, septic shock, congestive heart failure, etc.), need for organ support therapy such as mechanical ventilation, continuous renal replacement therapy (CRRT), hemodialysis, and extracorporeal membrane oxygenation (ECMO). Patients who were missing data on prehospitalization medications, comorbidities, admission diagnosis, or outcomes were excluded.

The patients were divided into three groups according to the AHAs they were taking prior to admission: 1) patients on RAASIs only, 2) patients on other AHAs only, and 3) patients on both medication classes together. The RAASIs only group included patients on ACEIs and/or ARBs. Other AHAs included non-RAASI medications such as beta blockers, calcium channel blockers, and diuretics. These groups were compared to eliminate many strong sources of bias including prevalent user bias, confounding by hypertension, and age.

Outcome Measures

The primary outcome was in-hospital mortality. Secondary outcomes included hospital and ICU LOS, development of complications, and need for organ support therapy.

Data Management

Study data were recorded and managed using the Mayo Clinic Research Electronic Data Capture (REDCap) system (12). The study was approved by the Mayo Clinic Institutional Review Board (no. 20-002610). The study is registered on ClinicalTrials.gov: NCT04323787. Each study site obtained approval from their local review board with a waiver of informed consent and signed a data use agreement before being granted permission to enter deidentified data from their medical records into the registry.

Statistical Analysis

Group statistics are expressed as mean ± SD for continuous measures (e.g., age, LOS) or as number (percentage) for categorical measures (e.g., race, prevalence of comorbidities). Group characteristics were compared using chi-square test for categorical variables and *t* test or Wilcoxon rank test for continuous variables depending on normality of sample distributions. Appropriateness of assumption of normal distributions for the continuous measures was confirmed by D'Agostino-Pearson omnibus normality test. Multivariable logistic and linear regressions were performed to evaluate the association of RAASIs with mortality and other outcomes during hospitalization after adjusting for other factors: age, gender, race, location (United States vs non-United States), and comorbidities (chronic kidney disease [CKD], chronic pulmonary disease [CPD], congestive heart failure [CHF], DM, hypertension, asthma, coronary artery disease, and cardiac arrhythmia). Cox proportional hazard regression was used to compare the survival curves between the three groups with right censoring of time to event at discharge from hospital. A secondary comparison was made between patients on ACEIs only versus ARBs only. Statistical analysis was performed using R statistical software (R Version 4.0.3 [2020; R Core Team, Vienna, Austria] using packages tidyverse 1.3.1 and survival 3.2-7). A p value of less than 0.05 was considered statistically significant for comparing demographics and primary outcome. For the secondary outcomes ($n = 15$), $p < 0.0033$ was considered statistically significant after using Bonferroni correction ($p = 0.05/15 = 0.0033$).

RESULTS

A total of 29,631 patients were entered into the registry. Two thousand nine hundred seventy-nine patients were excluded from the study as shown in **Figure 1**. Of 26,652 patients, 7,975 patients were on AHAs. Of these, 1,542 patients (19.3%) were on RAASIs only and 3,765 patients (47.2%) were on other AHAs only prior to hospitalization, whereas the remainder were on both of these medications (Fig. 1). For both 26,652 and 7,975 patients, less than 1% of data were missing for age, gender, race, mortality, and hospital LOS. For most of the remaining variables, estimating the percentage of missing data cannot be done directly because of how the data were entered into the REDCap.

Demographic and clinical characteristics of patients with SARS-CoV-2 infection at admission are given in **Table 1** (Supplemental Digital Content, http://links.lww.com/CCM/H154), grouped by use of RAASI only, RAASIs and other AHAs, and other AHAs only. Compared with patients on both medications and those on other AHAs only, patients on RAASIs only were younger (mean age 63.3 vs 67.4 yr in combined RAASIs and other AHAs group and 66.9 yr in other AHAs only group; $p < 0.0001$), were more often male (58.2% vs 55.9% in combined RAASIs and other AHAs group and 52.4% in other AHAs only group; $p = 0.0002$), and were more often White (55.1% vs 50.0% in combined RAASIs and other AHAs group and 47.2% in other AHAs only group, $p < 0.0001$). Patients on RAASIs were more likely to be admitted with diagnosis of acute respiratory distress syndrome (ARDS) (10.2% vs 7.5% in combined RAASIs and other AHAs group and 7.9% in other AHAs only group, $p = 0.0043$), whereas patients on both RAASIs and other AHAs were more likely to have admission diagnosis of acute hypoxic respiratory failure (non-ARDS), acute renal failure/injury, bacterial pneumonia, cardiac arrhythmia/failure, or shock. Even though patients in all groups were on one or more AHAs (RAASIs or others), only 85.4% of patients had a diagnosis of hypertension at admission. Hypertension, DM, obesity, and

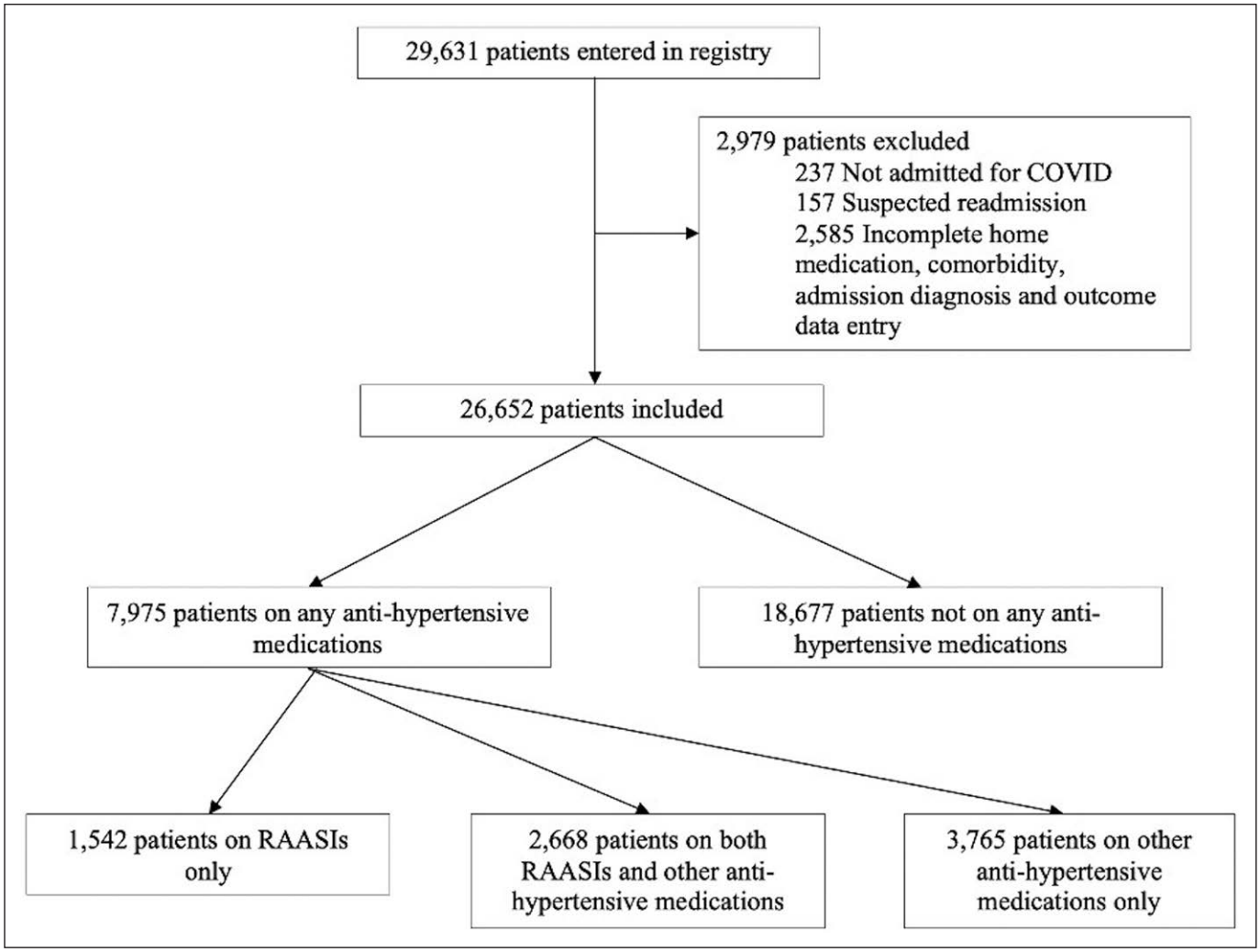

Figure 1. Flow chart of patients in each group after applying exclusion and inclusion criteria.

CHF were more prevalent in patients on combination of RAASIs and other AHAs. Other comorbidities including asthma, CKD, and CPD were significantly higher in the other AHAs only group. There was no difference in the prevalence of smoking between the groups. Mean APACHE II scores were significantly higher in group on both RAASIs and other AHAs (19 vs 16 in RAASIs only group and 18.6 in other AHAs only; $p = 0.010$); however, APACHE II score data were only available for 651 (8.2%) patients.

Group statistics for the outcomes is shown in **Table 1** for all three groups. **Table 2** (Supplemental Digital Content, http://links.lww.com/CCM/H155) shows the comparison of outcomes between these three groups after adjusting for demographics and prehospital comorbidities. Multivariable logistic (for categorical outcomes) or linear (for continuous outcomes) regression models were fit to estimate whether there was a significant effect of RAASIs on outcomes after adjusting for demographics (age, gender, race, and geographical location) and prehospitalization comorbidities (CHF, CPD, CKD, DM, hypertension, asthma, coronary artery disease, and cardiac arrhythmia). Patients on combination of RAASIs and other AHAs had higher in-hospital mortality than those on RAASIs only (odds ratio [OR] = 1.28; 95% CI [1.19–1.38]; $p < 0.0001$) and higher mortality than those on other AHAs only (OR = 1.09; 95% CI [1.03–1.15]; $p = 0.0017$). Patients on RAASIs only had significantly lower mortality than those on other AHAs only (OR = 0.87; 95% CI [0.81–0.94]; $p = 0.0003$). For the secondary outcomes, there was no difference, after adjustment, in the use of CRRT/hemodialysis, admission to ICU, hospital LOS, use of mechanical ventilation or development of complications including respiratory failure, septic shock, CHF, cardiac arrhythmia,

TABLE 1.

Group Statistics for Outcomes of Patients on Renin-Angiotensin-Aldosterone System Inhibitors Only, Renin-Angiotensin-Aldosterone System Inhibitors and Other Antihypertensive Agents and Other Antihypertensive Agents Only

Outcomes	RAASIs Only (*N* = 1,542)	RAASIs and Other AHAs (*N* = 2,668)	Other AHAs Only (*N* = 3,765)	*p*			
				Analysis of Variance	RAASIs Only vs Both Medications	Both Medications vs Other AHAs Only	RAASIs vs Other AHAs Only
In-hospital mortality, *n* (%)	286 (18.5)	640 (24.0)	884 (23.5)	**< 0.0001**	**< 0.0001**	0.66	**< 0.0001**
Use of CRRT/hemodialysis, *n* (%)	66 (4.2)	207 (7.5)	230 (5.9)	**< 0.0001**	**< 0.0001**	0.013	0.012
Time on CRRT (d), mean ± SD	10.0 ± 9.3	9.4 ± 10.1	10.7 ± 11.5	0.42	0.63	0.20	0.60
Use of extracorporeal membrane oxygenation, *n* (%)	19 (1.2)	24 (0.9)	27 (0.7)	0.19	0.38	0.50	0.094
Admitted to ICU, *n* (%)	713 (46.4)	1,241 (47.1)	1,669 (46.9)	0.92	0.71	0.93	0.77
ICU length of stay (d), mean ± SD	14.3 ± 15.3	12.7 ± 12.8	12.0 ± 12.7	**< 0.0001**	**< 0.0001**	**0.0003**	**< 0.0001**
Hospital length of stay (d), mean ± SD	15.9 ± 19.7	15.1 ± 14.3	15.0 ± 16.7	**0.0011**	**0.0027**	0.56	**0.0007**
Use of mechanical ventilation, *n* (%)	424 (27.5)	786 (29.5)	1,004 (26.7)	0.046	0.19	0.015	0.56
Time on ventilator (d), mean ± SD	14.9 ± 14.8	13.1 ± 12.1	13.2 ± 14.9	0.072	0.024	0.87	0.052
Complications during hospitalization, *n* (%)							
Respiratory failure (acute respiratory distress syndrome)	320 (20.8)	576 (21.6)	729 (19.4)	0.085	0.55	0.031	0.26
Mild (P:F 200–300)	21 (8.1)	60 (12.5)	62 (10.5)	0.31	0.10	0.60	0.32
Moderate (P:F 100–199)	73 (28.1)	146 (30.4)	181 (30.7)				
Severe (P:F < 100)	166 (63.8)	275 (57.2)	347 (58.8)				
Septic shock	170 (11.0)	355 (13.3)	435 (11.6)	0.041	0.035	0.038	0.61
Congestive heart failure	24 (1.6)	93 (3.5)	116 (3.1)	**0.0012**	**0.0004**	0.41	**0.0023**
Cardiac arrhythmia	78 (5.1)	202 (7.6)	232 (6.2)	0.0040	**0.0020**	0.030	0.14
Stroke	15 (1.0)	47 (1.8)	39 (1.0)	0.019	0.056	0.017	0.95
Co- or secondary infection	66 (4.3)	139 (5.2)	156 (4.1)	0.11	0.20	0.051	0.88

AHAs = antihypertensive agents, CRRT = continuous renal replacement therapy, P:F = Pao_2:Fio_2 ratio, RAASIs = renin-angiotensin-aldosterone system inhibitors.

Boldface values indicate statistical significance.

stroke, and secondary infections between the groups. ICU LOS was significantly shorter in patients on combination of RAASIs and other AHAs when compared with those on RAASIs only (β = –2.1; 95% CI [–2.9 to –1.3]; $p < 0.0001$). **Table 3** (Supplemental Digital Content, http://links.lww.com/CCM/H156) lists all complications during hospitalization for which the registry gathered data, comparing patients on RAASIs only, RAASIs and other AHAs, and other AHAs only, after adjusting for patient demographics. Patients on combined RAASIs and other AHAs had higher odds of developing acute kidney injury during hospitalization when compared with those on RAASIs only (OR = 1.40; 95% CI [1.19–1.66]; $p < 0.0001$). Even though there were no differences in odds of developing other major complications between the groups,

patients on combined medications had lower odds of not having complications compared with those on RAASIs only (OR = 0.74; 95% CI [0.64–0.86]; $p < 0.0001$).

Cox proportional hazard regression analysis was used to compare the survival curves between the three groups (**Fig. 2**) while adjusting for age, gender, race, and comorbidities: CHF, CPD, CKD, DM, hypertension, asthma, coronary artery disease, and cardiac arrhythmia. When comparing all three groups, we did not find a significant difference in the in-hospital mortality ($p = 0.073$). On pairwise Cox proportional hazard analysis, combined use of RAASIs and other AHAs, compared with use of RAASIs alone, was associated with a significantly higher in-hospital mortality and shorter survival times ($p = 0.023$). When compared with RAASIs only, use of other AHAs only was associated with significantly higher mortality ($p = 0.021$). There was no difference in mortality when comparing use of AHAs only versus combined use of RAASIs and other AHAs ($p = 0.97$).

Secondary analysis was performed to compare group statistics and outcomes for patients on ACEIs only versus ARBs only (**Table 4** [Supplemental Digital Content, http://links.lww.com/CCM/H157], **Table 5** [Supplemental Digital Content, http://links.lww.com/CCM/H158], and **Table 6** [Supplemental Digital Content, http://links.lww.com/CCM/H159], respectively). Of the 1,517 patients on a single RAASI agent, 958 patients (63.2%) were on ACEIs only, whereas 559 patients (36.8%) were on ARBs only. Compared with patients on ARBs only, patients on ACEIs only were significantly younger (mean age 62.6 vs 64.4 yr; $p = 0.012$), more likely to be male (61.3% vs 53.1%; $p = 0.0021$), and more often White (56.4% vs 53.5%; $p = 0.010$). Compared with those on ARBs only, patients on ACEIs only had higher prevalence of DM (56.5% in ACEIs vs 45.3% in ARBs group; $p < 0.0001$) and lower prevalence of hypertension (86.2% in ACEIs vs 92.1% in ARBs group; $p = 0.0007$) and asthma (6.3% in ACEIs vs 10.0% in ARBs group; $p = 0.011$). There were no differences in admission diagnoses or APACHE II scores in both the groups. On comparing the outcomes, patients on ACEIs only had significantly higher in-hospital mortality compared with those on ARBs only (OR = 1.37; 95% CI [1.20–1.56]; $p < 0.0001$). Patients on ACEIs only also had significantly longer hospital

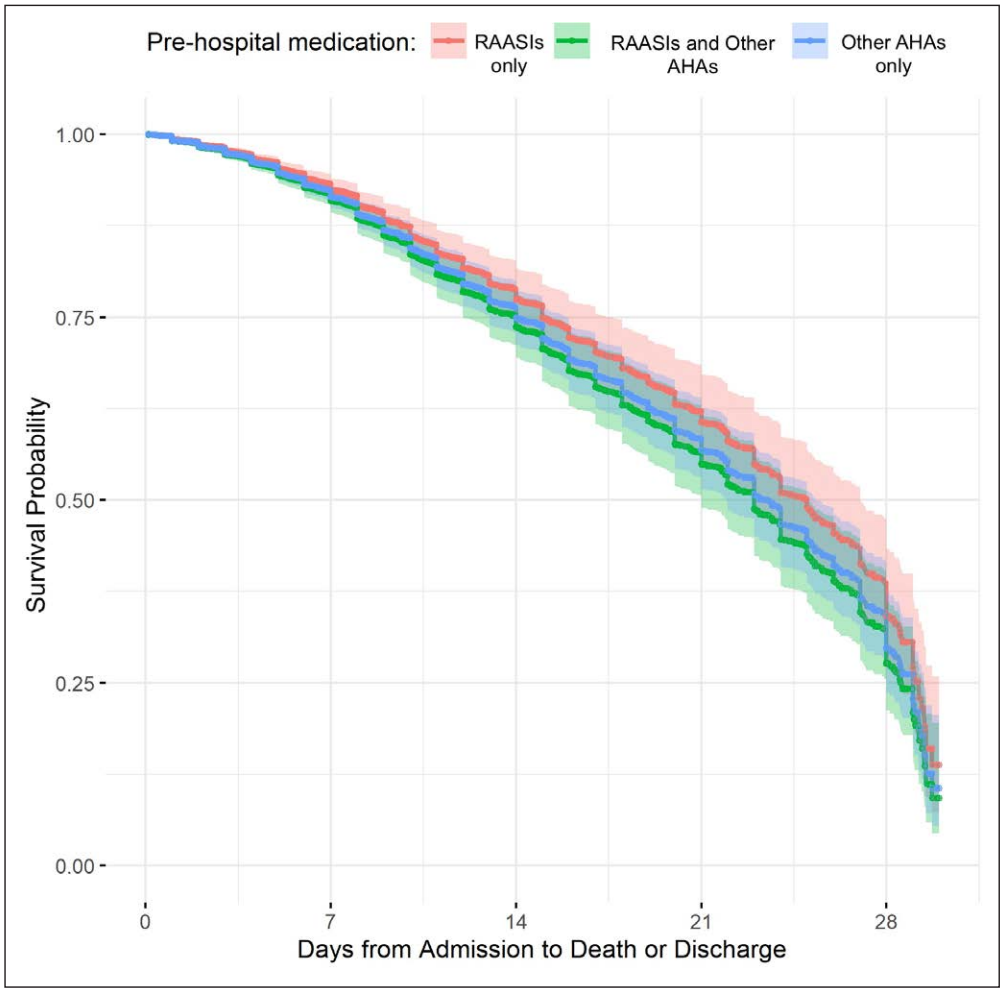

Figure 2. Cox proportional-hazards model comparing survival probability of patients on renin-angiotensin-aldosterone system inhibitors (RAASIs) only, RAASIs and other antihypertensive agents (AHAs) and other AHAs only. Survival time is from hospital admission to death; if the patient did not die, then survival time is right censored at time of discharge from hospital.

LOS compared with ARBs only group (β = 2.9; 95% CI [1.9–3.8]; $p < 0.0001$). For the secondary outcomes, there was no difference, after adjustment, in the use of CRRT/hemodialysis, time on CRRT, admission to ICU, ICU LOS, use of mechanical ventilation, time on ventilator, or development of complications between the two groups. **Table 7** (Supplemental Digital Content, http://links.lww.com/CCM/H160) lists all complications during hospitalization for which the registry gathered data, comparing patients on ACEIs only and ARBs only, after adjusting for patient demographics.

DISCUSSION

Our study suggests that hospitalized patients on RAASIs prior to COVID-19 are at lower risk of mortality during hospitalization when compared with patients who were on other AHAs only prior to admission. Furthermore, mortality risk was also significantly increased for patients on both RAASIs and other AHAs prior to hospitalization compared with those on RAASIs only. To our knowledge, this is the first international study looking at the impact of combined use of RAASIs and other AHAs on mortality in hospitalized COVID-19 patients.

Recently, many studies have shown that RAASIs are not associated with increased risk of having COVID-19 (4, 10). A study by Khera et al (13) showed 40% lower rate of hospitalization in COVID-19 patients using RAASIs. However, for patients who are already hospitalized with COVID-19, there are contradictory data for association of RAASI use prior to hospitalization and mortality. A recent study by Ip et al (14) has shown no association between mortality and use of RAASIs in patients with COVID-19. A systematic review looking at association of mortality with ACEIs use in patients with COVID-19 showed increased mortality in ACEI group in some settings, whereas these findings were not seen in other settings (15). Another study by Bauer et al (8) showed that discontinuation of RAASIs in COVID-19 was associated with faster and better recovery. However, these studies varied with respect to patient ages and mortality and were restricted to one geographical region.

A single-center study conducted in Italy reported lower mortality in patients on RAASIs compared with other AHAs with OR equals to 0.56; however, it did not reach statistical significance, possibly due to their small sample size (16). A meta-analysis by Zhang et al (17) among COVID-19 patients with hypertension also reported a protective effect of the use of RAASIs against mortality, severity/mortality, hospitalization, and rate of transfer to ICU compared with those on non-RAASI AHAs. Some of the other recent systematic reviews and meta-analyses also showed lower mortality in hypertensive patients on RAASIs compared with those on other or no treatment (18–21). However, these studies did not account for whether patients in the RAASI groups were on RAASI only or they were on other AHAs as well. Our study shows lower risk of in-hospital mortality in patients taking only RAASIs prior to admission compared with those who were taking a combination of RAASIs and other AHAs or other AHAs only. Our study results are consistent with another study by Yuan et al (22) that reported that hypertensive COVID-19 patients on RAASIs had a lower risk of mortality, while patients on beta blockers, calcium channel blockers, and diuretics did not show any significant difference when compared with patients with uncontrolled blood pressure. Contradictory to the above studies, we did not notice any association between use of RAASIs and risk of ICU admission in our study. Even though the risk of in-hospital mortality for patients on RAASIs only was lower compared with patients on combination of RAASIs and other AHAs, they had longer ICU LOS. Competing risk of death might have shortened ICU LOS in patients on both RAASIs and other AHAs.

We believe that this higher in-hospital mortality with combined use of RAASIs and other AHAs prior to hospitalization is an interesting and novel finding. As shown in Table 1 (Supplemental Digital Content, http://links.lww.com/CCM/H154), these patients represent a higher comorbid group especially compared with patients on RAASIs only; however, they maintained an independent association with in-hospital mortality even after controlling for these prehospital comorbidities (Table 2, Supplemental Digital Content, http://links.lww.com/CCM/H155). It is possible that patients on both medications may have presented sicker to the hospital. Given that APACHE II scores were only available for about 8.2% patients included in the study, it is difficult to make an interpretation from these data. Another hypothesis is that the combination of different medications with RAASIs like beta blockers, calcium channel blockers, or diuretics may have

inadvertent side effects in patients especially when they are sick. For example, the combination of medications could have hindered heart rate response in COVID-19 or altered pulmonary shunt and thus oxygenation requirements. However, most published literature shows that combination therapy for hypertension is not only more effective in controlling blood pressure but also has fewer side effects due to lower doses of medications required to control blood pressure compared with higher dose monotherapy (23). Besides, the rate of most complications and use of organ support therapy was similar across all the groups which makes this hypothesis less likely. We also noticed that patients on combined RAASIs and other AHAs had significantly higher mortality than those on other AHAs only on logistic regression analysis (Table 2, Supplemental Digital Content, http://links.lww.com/CCM/H155). However, there was no difference in mortality between the two groups on Cox proportional hazard regression analysis. It is possible that other AHAs (even in combination with RAASIs) took away the protective effect of RAASIs.

With respect to RAASIs, ACEIs and ARBs have different mechanisms in the pathogenesis of COVID-19 (24). Therefore, we decided to compare the outcomes of patients on ACEIs versus ARBs prior to hospitalization as our secondary analysis. Most published literature compared patients on ACEIs and/or ARBs with nonusers. However, there are paucity of data on comparison of these two classes of RAASIs and association with mortality. A study by Derington et al (25) evaluated association of mortality among inpatients and outpatients on ARBs versus ACEIs. This study did not find a significant association between ARB or ACEI use and all-cause mortality in inpatients with COVID-19, whereas a significantly lower risk of all-cause hospitalization or mortality was seen among ARB users compared with ACEI users in outpatients. We found a significantly higher mortality in patients on ACEIs compared with those on ARBs in hospitalized COVID-19 patients.

This study has limitations inherent to retrospective registry analyses. A complete case analysis such as ours assumes data are missing completely at random (26). The VIRUS: COVID-19 Registry employs extensive data missingness review and cross-validation process to detect any errors (27). However, there is still a possibility of data entry errors. Patients with incidentally positive SARS-CoV-2 PCR on hospitalization were excluded from the registry. However, the distinction of incidental diagnosis versus an admission for illness due to SARS-CoV-2 was made by the site investigators. Due to the evolving understanding of the varied COVID-19 presentations, this may have resulted in slight over- and/or under-inclusion of patients. Our study included all patients on AHAs prior to hospitalization irrespective of the indication of medication use. However, we have controlled for the most common indications in the multivariable regression model to prevent bias. Since it is a retrospective database study, we could not account for compliance of the patients with these medications and for patients whose home antihypertensive medications were discontinued during hospitalization. It was also unknown how long the patients had been on these medications prior to hospitalization. Lastly, given the observational nature of the analysis and the uncertain mechanisms of causal influence, there is a considerable risk of residual confounding.

CONCLUSIONS

In this multicenter observational study, patients on both RAASIs and other AHAs prior to admission had higher in-hospital mortality than patients on RAASIs only. When compared with ARBs, ACEIs were associated with significantly higher mortality in hospitalized COVID-19 patients. These findings may help in early identification of patients who are at higher risk of morbidity and mortality from COVID-19.

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