


# BMJ Open What is the association of renin-angiotensin-aldosterone system inhibitors with COVID-19 outcomes: retrospective study of racially diverse patients?

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## ABSTRACT

**Objective** To describe the clinical outcomes of COVID-19 in a racially diverse sample from the US Southeast and examine the association of renin-angiotensin-aldosterone system (RAAS) inhibitor use with COVID-19 outcome.

**Design, Setting, Participants** This study is a retrospective cohort of 1024 patients with reverse-transcriptase PCR-confirmed COVID-19 infection, admitted to a 1242-bed teaching hospital in Alabama. Data on RAAS inhibitors use, demographics and comorbidities were extracted from hospital medical records.

**Primary outcomes** In-hospital mortality, a need of intensive care unit, respiratory failure, defined as invasive mechanical ventilation (iMV) and 90-day same-hospital readmissions.

**Results** Among 1024 patients (mean (SD) age, 57 (18.8) years), 532 (52.0%) were African Americans, 514 (50.2%) male, 493 (48.1%) had hypertension, 365 (36%) were taking RAAS inhibitors. During index hospitalisation (median length of stay of 7 (IQR 4–15) days) 137 (13.4%) patients died; 170 (19.2%) of survivors were readmitted. RAAS inhibitor use was associated with lower in-hospital mortality (adjusted HR, 95% CI (0.56, (0.36 to 0.88),  $p=0.01$ ) and no effect modification by race was observed ( $p$  for interaction=0.81). Among patients with hypertension, baseline RAAS use was associated with reduced risk of iMV, adjusted OR, 95% CI (aOR 0.58, 95% CI 0.36 to 0.95,  $p=0.03$ ). Patients with heart failure were twice as likely to die from COVID-19, compared with patients without heart failure.

**Conclusions** In a retrospective study of racially diverse patients, hospitalised with COVID-19, prehospitalisation use of RAAS inhibitors was associated with 40% reduction in mortality irrespective of race.

## INTRODUCTION

The USA has experienced an unprecedented public health crisis with the COVID-19 pandemic.<sup>1</sup> Persons with cardiovascular and metabolic disease are at increased risk for mortality and morbidity from COVID-19.<sup>2–5</sup>

## Strengths and limitations of this study

- This study background was based on multiple questions regarding the safety of RAAS inhibitors raised by the community of the primary care physicians and patients in the beginning of the COVID-19 pandemic.
- Other strengths of the study include a large racially diverse sample of patients with COVID-19 from the US Southeast and a robust approach to extraction of data from electronic health records.
- Observational retrospective nature of this study does not allow drawing causal inferences.
- Residual unmeasured confounding, such as socioeconomic status, may influence study results.
- The study included patients from a limited geographical area and a single hospital site.
- The data on out-of-hospital mortality and same-hospital readmissions may be incomplete as some COVID-19 patients may have been readmitted to other area hospitals.

Cardiovascular disease and diabetes mellitus are highly prevalent among US adults, with 45% of adults having HTN, 13%—diabetes mellitus, 6.7%—coronary artery disease and 2.4%—heart failure.<sup>6</sup> These chronic conditions disproportionately affect adults in the Southeast compared with other parts of the USA.<sup>6</sup> Patients with hypertension, heart failure, diabetes and chronic kidney disease are often prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors, that is, ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs). In animal studies, performed prior to the emergence of COVID-19, ACEi were found to increase the expression of ACE2 receptors.<sup>7</sup> The SARS-CoV-2 binds to ACE2 receptors in lungs,<sup>8</sup> leading to concerns about potential risks of using RAAS

inhibitors in the setting of COVID-19. While subsequent studies have demonstrated the safety of RAAS inhibitor use among persons with COVID-19 and indication for RAAS use,<sup>9–11</sup> the association of RAAS inhibitor use with hospital readmission after the index COVID-19 admission is not well described.

Most of reports<sup>12</sup> describing the associations of pre-existing use of RAAS inhibitors with COVID-19 outcomes were obtained in White or Asian, not African American populations. Compared with Whites, African Americans have a high incidence of adverse effects of RAAS inhibitors.<sup>13</sup> Disproportionally affected by multiple health disparities, African Americans have also been shown to have an increased risk of severe COVID-19, requiring hospitalisation.<sup>14</sup> Persons of African descent were also at higher risk of contracting COVID-19 in the largest to date cohort study of the COVID-19 susceptibility in England.<sup>15</sup>

To better understand the association of baseline RAAS inhibitor use with outcomes of COVID-19 hospitalisation, we assembled an observational retrospective cohort of racially diverse hospitalised patients with laboratory-confirmed COVID-19 in Alabama. We examined whether baseline RAAS inhibitor use was associated with COVID-19 health outcomes, including (1) in-hospital mortality, (2) need for intensive care unit (ICU) admission (3) acute respiratory failure requiring invasive mechanical ventilation (iMV) and (4) same-hospital readmission for any cause among survivors of the COVID-19 index hospitalisation. We also assessed whether the association between RAAS inhibitor use and mortality differed by race.

## METHODS

### Study participants and procedures

This observational retrospective cohort study included 1024 adult (age 18 and above) patients hospitalised with confirmed COVID-19 between 1 March 2016 and 16 September 2020 at the University of Alabama at Birmingham (UAB) teaching hospital in Birmingham, Alabama. The first cases of the COVID-19 were detected in Birmingham beginning on 1 March 2020. The cases increased very slowly over the spring of 2020, with a sharp surge 10–14 days after 4 July 2020. After the initial surge, COVID-19 cases declined slightly in August 2020, but then started to rise, achieving an spike in December–January 2021 (data not included in this report). The UAB ICU neared but did not exceed capacity. During the first surge of COVID-19 cases in July 2020, UAB Hospital implemented a delayed intubation strategy, favouring treating COVID-19 respiratory failure with supplemental oxygen, delivered via high flow nasal cannula. Therefore, all analyses of respiratory failure were adjusted for the time of the index admission for COVID-19 (before vs after 15 July 2020).

COVID-19 cases were confirmed by reverse-transcriptase PCR (rt-PCR). We extracted patient data electronically from our institution's Electronic Health Record (EHR; Cerner) data warehouse (i2B2) supplemented by manual

chart review. Data were prepared for analyses by the COVID-19 Core data Extraction/Transformation team using Oracle SQL developer (V.11.2). For each of the patients with laboratory-confirmed COVID-19, encounter data for the index admission were obtained, including admission date, date of the earliest positive rt-PCR for COVID-19 and death or discharge date. The admission/discharge dates for all subsequent outpatient and inpatient encounters and dates of death after the index hospitalisation were also electronically extracted. For each of the hospital readmissions (n=172) a manual chart review was conducted to confirm admission/discharge dates. For each of the deaths (n=16) that occurred after index hospitalisation we conducted manual chart review for confirmation. From the initial sample of 1029 patients, we excluded 5 patients with missing index admission dates or missing dates of birth.

### Patient and public involvement

No patients involved.

### Outcomes and main exposure

Study outcomes included in-hospital COVID-19-related mortality, need for the ICU admission, respiratory failure defined by a need for iMV, and same-hospital readmission for any cause after the index hospitalisation. Data on RAAS inhibitors included use of ACEis and ARBs prior to the index COVID-19 hospitalisation, and were derived from the index admission medication reconciliation data in the EHR. If patients were taking a combination medicine that included an ACEi or ARB as one of the components, they were classified as having been prescribed ACEi/ARB in the analysis.

### Covariates

Covariates were selected on the basis of the risk factors for severe COVID-19 infection identified by the Centers for Disease Control and Prevention and previous reports on COVID-19 morbidity and mortality.<sup>16–19</sup> Patient socio-demographic characteristics included age at the index admission (calculated, using birth and admission dates) and self-reported race, sex, marital status and cigarette smoking status. We created age categories as follows: 18–40, 41–64, 65–74 and 75 years and older. Body mass index (BMI) was calculated using height and weight obtained most recently prior to the index COVID-19 admission. BMI categories included: 'underweight' is less than 18.5 kg/m<sup>2</sup>, 'normal weight' 18.5–24.9 kg/m<sup>2</sup>, 'overweight' 25–29.9 kg/m<sup>2</sup> and 'obese' 30 kg/m<sup>2</sup>, and above. We obtained data on comorbidities, including hypertension, coronary artery disease, diabetes, chronic obstructive pulmonary disease, heart failure, chronic kidney disease, HIV, sickle cell disease and history of solid organ transplant using corresponding, International Classification of Diseases, The Tenth Revision (ICD-10) codes.

### Statistical analysis

Patients with COVID-19 who were prescribed RAAS inhibitors at baseline were compared with those who were not

prescribed RAAS inhibitors using two-sided t-tests for continuous variables and  $\chi^2$  tests for categorical variables. We examined the association of RAAS inhibitor use with study outcomes in three different samples: (1) overall sample, (2) patients with any indication for RAAS inhibitor use, such as hypertension, diabetes, chronic kidney disease, coronary artery disease or heart failure and (3) patients with hypertension. Outcomes were assessed with unadjusted and multivariable models. To examine the association of in-hospital mortality from COVID-19 with baseline RAAS inhibitor use we constructed Cox proportional hazards regression models adjusted for age, sex, race, marital status, smoking, BMI and medical conditions. We created an interaction term between RAAS use and race to test for effect modification by race in the fully adjusted models of COVID-19 in-hospital mortality. The need for ICU and the presence of respiratory failure were examined separately in logistic regression models, with adjustment for the same patient characteristics and for the time of admission (before vs after 15 July 2020).

We examined the charts of the survivors of the index COVID-19 admission postdischarge for a same-hospital readmission for any cause using medical records. The EHR data were abstracted for any subsequent in-hospital and outpatient encounter after the index hospitalisation and UAB hospital readmission dates were extracted. The time to readmission was calculated using index discharge data and readmission date. To examine the association between baseline RAAS use and readmissions, we used the Fine and Gray model to account for competing risk of death in the post-discharge period that was adjusted for the same patient characteristics. The proportionality assumption was tested and satisfied in the Cox proportion hazards models. All statistical analyses were performed in SAS software (SAS Institute) V.9.4,

## RESULTS

Among 1024 patients, admitted to UAB hospital with COVID-19 (mean (SD) age, 57 (18.8) years), 532 (52%) were African American, 514 (50 %) were male, 493 (48 %) had hypertension, 323 (32 %) had heart failure, 487 (48 %) were obese, 210 (20.5%) had diabetes and 98 (11 %) were current smokers (table 1). There were 365 (36%) patients taking RAAS inhibitors at baseline. Patients with baseline RAAS use were older, more likely to be African American, and had more comorbidities.

The median length of stay (LOS) for the index COVID-19 hospitalisation was 7 days, (IQR 4–15 days). Maximum LOS was 175 days. Sixty per cent of included COVID-19 cases were admitted after the initial surge in Birmingham, between 15 July 2020 and 16 September 2020. During the index hospitalisation, 137 (13.4%) patients died. Additionally, 16 (1.8%) patients died from any cause postdischarge, either during a hospital readmission or out of the hospital. Cumulative all-cause mortality included 153 (14.9%) deaths. At the time of the cohort assembly on 16 September 2020, 23 patients

remained in the hospital. During the index hospitalisation 466 (45.5%) patients required ICU care, and 276 (27%) persons required iMV. The proportion of patients who were intubated was higher in the early period, before 15 July, compared with the period of after 15 July 2020, when placing the patient with respiratory failure on high flow nasal canula became a preferred treatment strategy: 201 (32.4%) vs 75 (18.6),  $p<0.001$ .

### In-hospital COVID-19 mortality and RAAS use

The median time to death was 13 days (IQR 6–20 days). In the overall study sample, baseline RAAS inhibitor use was associated with significantly reduced risk of in-hospital mortality (adjusted HR (aHR) 0.56, 95% CI 0.36 to 0.88),  $p=0.01$ , after adjustment for all covariates) (figure 1). A similar protective effect of RAAS inhibitor use on mortality was observed among patients with any indication for RAAS inhibitor use (aHR (95% CI) for RAAS inhibitor use 0.59, 95% CI 0.37 to 0.94,  $p=0.03$ ) and among patients with hypertension (aHR for RAAS use 0.54, 95% CI 0.33 to 0.90,  $p=0.02$ ). We did not observe effect modification by race in the overall sample. The RAAS inhibitor use\*race interaction term had associated  $p=0.81$ . Compared with Whites, African American race was not associated with in-hospital mortality from COVID-19 in the adjusted model (aHR 0.88, 95% CI 0.60 to 1.29,  $p$  for trend 0.55) (table 2). Other factors associated with increased cumulative mortality in our sample included age 65–74 years (aHR 3.67 (95% CI 1.85 to 7.31)), age 75 years and older (aHR 4.89 (95% CI 2.36 to 10.14)), obesity (aHR 2.10 (95% CI 1.34 to 3.29)) and pre-existing heart failure (aHR 1.88 (95% CI 1.20 to 2.94)) (table 2).

### COVID-19 in-hospital events and RAAS inhibitor use

RAAS inhibitor use was not associated with the need for ICU in all analyses (figure 2.) In the overall patient sample, RAAS use was not associated with iMV, aOR 0.71 (95% CI 0.48 to 1.06) (figure 3). In contrast, among patients with hypertension, baseline RAAS inhibitor use was significantly associated with reduced odds of iMV after adjustment for covariates (aOR 0.58 (95% CI 0.36 to 0.95),  $p=0.03$ ). African Americans admitted with COVID-19 were more likely to have respiratory failure, requiring iMV: aOR 1.58 (95% CI 1.01 to 2.31),  $p=0.02$ . Other factors associated with the increased risk of iMV for the COVID-19-related respiratory failure included current cigarette smoking (aOR 1.80 (95% CI 1.08 to 3.02),  $p=0.03$ ), pre-existing heart failure (aOR 2.32 (95% CI 1.45 to 3.71),  $p<0.001$ ) and being admitted to UAB before 15 July 2020 (aOR 1.97 (95% CI 1.39 to 2.79),  $p<0.0010$ ).

### Same-hospital 90-day readmissions among COVID-19 survivors

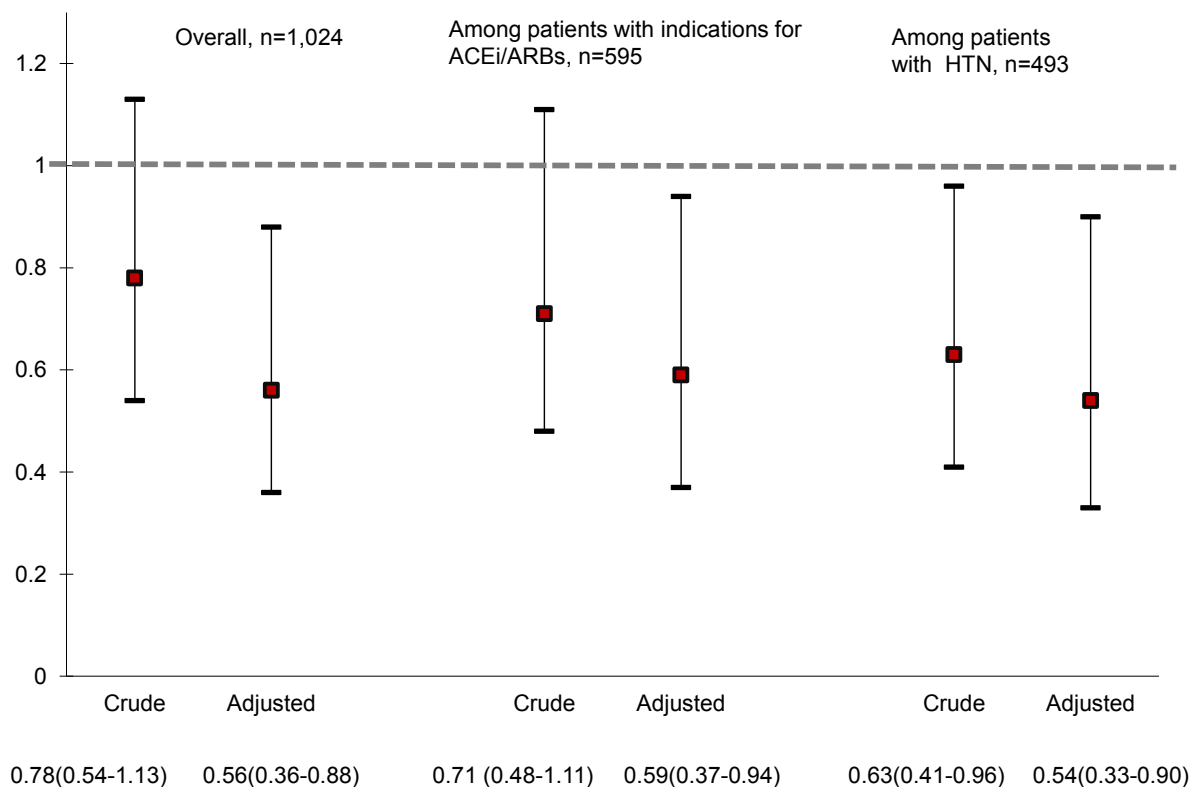
Over a median follow-up of 51 (IQR 28–82) days, 170 (19.2%) of 887 discharged patients were readmitted to the same hospital for any cause (table 1). Among those who were rehospitalised, the median time to readmission


**Table 1** Characteristics of patients, admitted to UAB hospital with COVID-19, between 1 March 2020 and 16 September 2020

	Overall sample, n=1024	No ACEi/ARB Use, n=659	ACEi/ARB use, n=365	P value
	n, (%)	n, (%)	n, (%)	
<b>Sociodemographics</b>				
Age, mean, SD, years	57.0 (18.8)	53.3 (19.7)	63.7 (14.9)	<0.001
Age, categories, years				<0.001
18–40	241 (23.5)	211 (32.0)	30 (8.2)	
41–64	395 (38.6)	234 (35.5)	161 (44.1)	
65–74	202 (19.7)	110 (16.7)	92 (25.2)	
75 and older	186 (18.2)	104 (15.8)	82 (22.5)	
Race				<0.001
White	384 (37.5)	254 (38.5)	130 (35.6)	
African American	532 (52.0)	318 (48.3)	214 (58.6)	
Hispanic or Latino	63 (6.2)	57 (8.6)	6 (1.6)	
Other	20 (2.0)	12 (1.8)	8 (2.2)	
Declined to report	25 (2.4)	18 (2.7)	7 (1.9)	
Male	514 (50.2)	319 (48.4)	195 (53.4)	0.12
Married	414 (40.4)	270 (41.0)	144 (39.5)	0.64
Smoking status				0.09
Never	533 (59.6)	344 (62.3)	189 (55.1)	
Current	98 (10.9)	58 (10.5)	40 (11.7)	
Former	264 (29.5)	150 (27.2)	114 (33.2)	
<b>Comorbidities</b>				
Body mass index (BMI), kg/m <sup>2</sup>				0.24
Underweight, BMI <18.5	27 (2.7)	16 (2.5)	11 (3.1)	
Normal Weight, BMI=18.5–24	227 (22.5)	159 (24.5)	68 (18.9)	
Overweight, BMI=25–30	268 (26.6)	168 (25.8)	100 (27.9)	
Obese, BMI=30 and above	487 (48.3)	307 (47.2)	180 (50.1)	
Hypertension	493 (48.1)	204 (31.0)	289 (79.2)	<0.001
Coronary artery disease	340 (33.2)	149 (22.6)	191 (52.3)	<0.001
Diabetes	210 (20.5)	71 (10.8)	139 (38.1)	<0.001
COPD	138 (13.5)	52 (7.9)	86 (23.6)	<0.001
Heart failure	323 (31.5)	131 (19.9)	192 (52.6)	<0.001
Chronic kidney disease	325 (31.7)	139 (21.1)	186 (51.0)	<0.001
HIV positive status	75 (7.3)	24 (3.6)	51 (14.0)	<0.001
Sickle cell disease	10 (1.0)	7 (1.1)	3 (0.8)	0.71
Recipient of solid-organ transplant	40 (3.9)	16 (2.4)	24 (6.6)	0.001
<b>In-hospital events</b>				
Admission after 15 July 2020	621 (60.6)	398 (60.4)	223 (61.1)	0.83
Required intensive care unit	466 (45.5)	287 (43.6)	179 (49.0)	0.09
Invasive mechanical ventilation	276 (27.0)	179 (27.2)	97 (26.6)	0.84
In-hospital death	137 (13.4)	96 (14.6)	41 (11.2)	0.13
<b>Postdischarge events among the survivors of the index admission</b>				
All-cause same-hospital readmission (during 1 March 2020–16 September 2020)	n=877	n=563	n=324	
All-cause same-hospital readmission (during 1 March 2020–16 September 2020)	170 (19.2)	97 (16.7)	76 (23.5)	0.01
Death from any cause after index admission	16 (1.8)	9 (1.0)	7 (2.2)	0.54
Cumulative mortality (death during 1 March 2020–16 September 2020)	153 (14.9)	105 (15.9)	48 (13.2)	0.23

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; UAB, University of Alabama at Birmingham.





**Figure 1** COVID-19 in-hospital mortality, HR, 95% CIs for ACE inhibitors/angiotensin receptor blocker (ACEi/ARB) use. Figure 1 presents crude and adjusted HRs and 95% CIs for in-hospital COVID-19 mortality. Indications for ACEi/ARB use included HTN, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories and medical conditions: HTN, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HIV, COPD, history of solid organ transplant. Among those with HTN, model adjusts for age, race, sex, marital status, smoking, BMI categories and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. **Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HTN, hypertension, RAAS, renin-angiotensin-aldosterone system.**

following the index discharge was 10 days (IQR 4–29 days). The proportion of persons with same-hospital readmission among those with baseline RAAS inhibitor use was 23.5%, compared with 16.7% among those who were not prescribed RAAS inhibitors ( $p=0.01$ ) (table 1). In the fully adjusted Cox proportional models, accounting for death as a competing risk, baseline RAAS agent use was not associated with readmissions (table 3). Compared with white patients, patients of the Hispanic/Latino/Asian or other race/ethnicity were less likely to be readmitted (aHR 0.42, 95% CI 0.20 to 0.90). African American race was not statistically significantly associated with hospital readmission (aHR 1.11, 95% CI 0.78 to 1.60). Among the chronic medical conditions only diabetes was significantly associated with higher risk for same-hospital

readmission after the index COVID-19 admission (aHR 1.56, 95% CI 1.02 to 2.94).

## DISCUSSION

This study presents data from 1024 patients with COVID-19 admitted to a teaching hospital in Alabama. Results of this study support the safety of maintaining patients with chronic conditions on ACEis and ARBs during the COVID-19 pandemic and expands previous reports by demonstrating the protective effect of the ACEis/ARBs from mortality in a racially diverse sample of patients with COVID-19. Among patients with hypertension, the use of ACEis/ARsB prior to contracting COVID-19 was associated with a reduction in the likelihood of endotracheal

**Table 2** Factors, associated with in-hospital mortality among patients with COVID-19, admitted to UAB Hospital, between 1 March 2020 and 16 September 2020

	aHR	95% CI	P value
ACEi/ARB use	0.56	0.36 0.88	0.01
Age, years			<0.001
18–40	ref	– –	–
40–64	1.69	0.82 3.52	
65–74	4.07	2.10 9.24	
75 and older	5.53	2.52 12.14	
Race:			0.55
African American	0.88	0.60 1.29	
Hispanic/Latino/Asian/other	0.68	0.32 1.45	
White	ref		
Male	1.43	0.97 2.10	0.07
Married	0.91	0.63 1.34	0.64
Current smoker	1.04	0.51 2.14	0.91
Body mass index, kg/m <sup>2</sup> :			0.001
<18.5	1.91	0.63 5.79	
18.5–24	ref		
25–29	1.39	0.81 2.37	
30 and above	2.50	1.54 4.06	
Hypertension	0.91	0.52 1.57	0.73
Coronary artery disease	0.78	0.57 1.20	0.26
Chronic kidney disease	0.87	0.54 1.38	0.54
Heart failure	1.96	1.21 3.15	0.006
Diabetes	1.07	0.62 1.84	0.98
COPD	1.07	0.58 1.95	0.84
HIV	1.51	0.76 3.03	0.23
Solid-organ transplant recipient	1.56	0.61 3.96	0.35

Multivariable-adjusted Cox proportional hazards regression model. ACEi, ACE inhibitor; aHR, adjusted HR; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease.

intubation by nearly 40%. Further, ACEi/ARB use was not associated with greater need for ICU-level care or with an increase in the same-hospital readmissions.

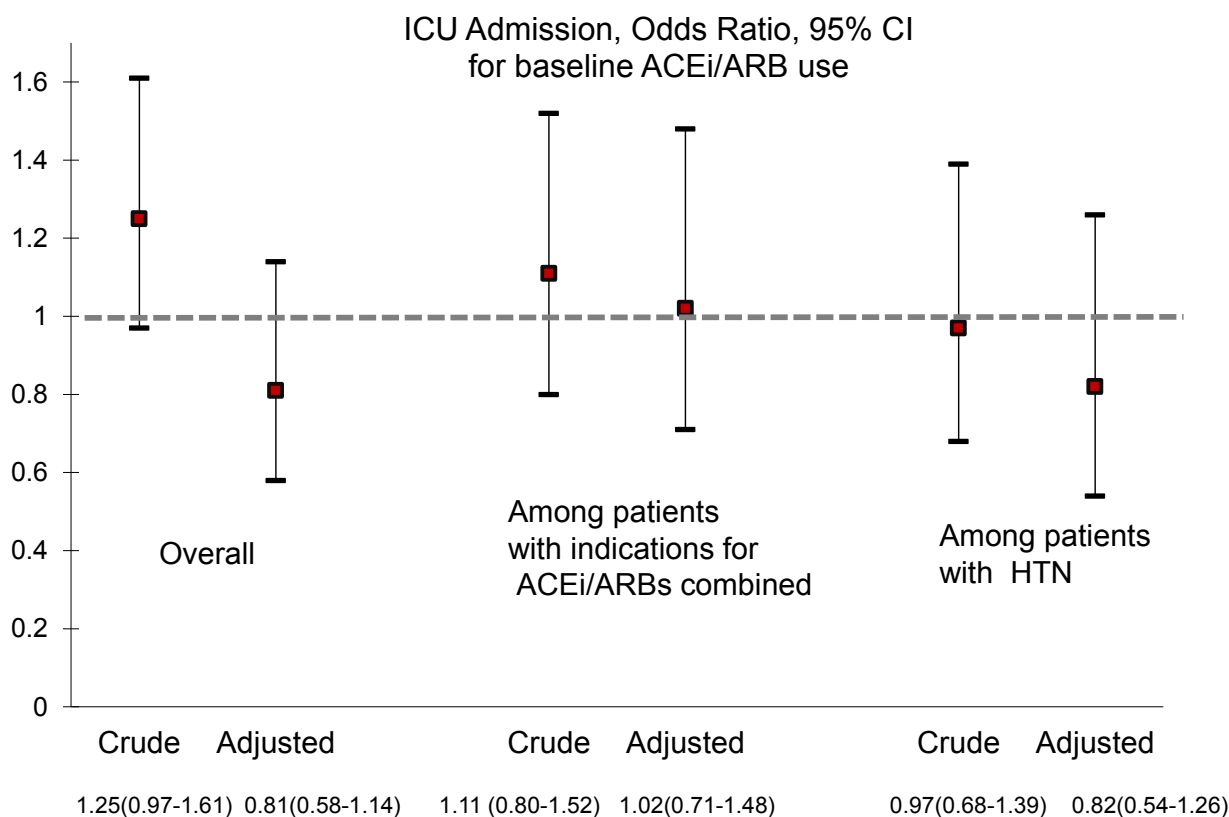
Baseline use of ACEi/ARB was associated with 40% lower in-hospital mortality in patients with COVID-19, after controlling for potential confounders such as age, sex, race, obesity, smoking and chronic medical conditions. These results were similar in the sample of patients who had any indication for RAAS inhibitors, and in patients with hypertension. Previous research has shown no association between the use of RAAS inhibitors and

susceptibility to COVID-19,<sup>20</sup> and has demonstrated the safety of continuing these medications during the pandemic.<sup>10 11 21</sup> Similarly to our results, in 1.4 million patients with hypertension, heart failure, diabetes, kidney disease or ischaemic heart disease registered in the Swedish National Patient Registry, ACEi/ARB use was associated with a reduced mortality in COVID-19 cases (aHR 0.89, 95% CI (0.82 to 0.96)).<sup>22</sup> Our study expands on previous findings by demonstrating both safety and reduction in COVID-19-related mortality associated with RAAS inhibitor use in a racially diverse sample where 50% of patients were African American. Potential mechanisms of protective effects of ACEi/ARB in COVID-19 are not well understood. One of the potential explanations of the decreased mortality among patients on ACEi/ARB medications prior to COVID-19 is that patients' chronic conditions were better controlled before the infection, which, in turn, reduced complications of COVID-19. Another body of research suggests that prolonged RAAS use may, in fact, downregulate ACE2 receptor expression, limit inflammation and reduce lung injury in COVID-19.<sup>23–25</sup> Unfortunately, the design of our study does not allow us to prove or disprove this hypothesis.

Half of the patients hospitalised with the COVID-19 infection in our sample were African American, whereas the proportion of African Americans in Alabama is only 26.7%. This finding highlights the racial disparity in the COVID-19 pandemic, in which a higher proportion of African Americans developed severe COVID-19 infection, requiring hospitalisation,<sup>26</sup> compared with Whites. African Americans were also more likely to require iMV in our study. However, similar to other studies of COVID-19 outcomes in the US,<sup>27</sup> race was not an independent predictor of death or hospital readmission in our study.

Our findings confirm previous observations that advanced age, obesity, and comorbidities are associated with death from COVID-19.<sup>16 28</sup> Importantly, more than 30% of our patient sample admitted with severe COVID-19 had pre-existing heart failure, a rate almost 10 times higher than the prevalence of heart failure in the general population. Heart failure was the only chronic condition, in addition to age and obesity in our sample, that was independently associated with increased in-hospital mortality from complications related to COVID-19. Patients with heart failure were also at increased risk of developing respiratory failure, requiring iMV. These represent a particularly vulnerable group requiring special attention from healthcare to reduce mortality and morbidity from the COVID-19.<sup>29 30</sup>

The rate of same-hospital readmissions among COVID-19 survivors was 19%, similar to that in a recent study of the patients with COVID-19, treated in the Veterans Affairs hospital system<sup>31</sup> but higher, than in other reports estimating that only 3%–10% of patients were rehospitalised after the index COVID-19 admission.<sup>32 33</sup> The high rates of hospital readmission in our study sample may be explained by the high level of chronic disease prevalence and worse general health in



**Figure 2** Intensive care use, OR, 95% CI for ACE inhibitor/angiotensin receptor blocker (ACEi/ARB) use. Figure 2 presents crude and adjusted ORs and 95% CIs for in-hospital COVID-19 mortality. Indications for ACEi/ARB use included HTN, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HTN, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant. Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories and medical conditions: HIV, COPD, history of solid organ transplant. Among those with HTN, model adjusts for age, race, sex, marital status, smoking, BMI categories and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid-organ transplant. BMI, body mass index; COPD, chronic obstructive pulmonary disease;

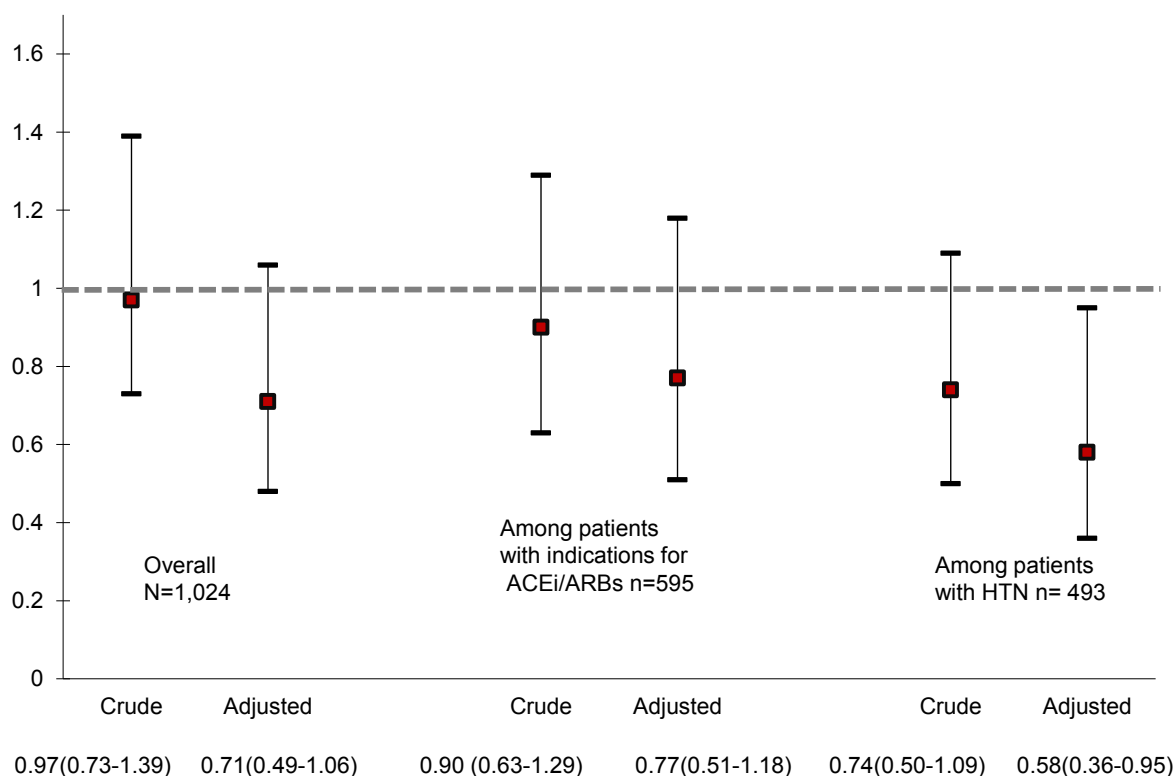
**Abbreviations: ICU, intensive care unit; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HTN, hypertension, RAAS, renin-angiotensin-aldosterone system.**

the general population of Alabama. Importantly, diabetes was significantly associated with increased re-admission risk among COVID-19 survivors. Alabama has the third highest prevalence of diabetes among adults (14%) in the USA, according to the National Diabetes Statistics Report-2020 by the Centers of Disease Control. Our findings are likely to extend to states with a similar high prevalence of diabetes mellitus and underscore the importance of close outpatient follow-up of this at-risk population.

Study limitations include limited geographical area and single hospital site. The data on out-of-hospital mortality and same-hospital readmissions may be incomplete, as some COVID-19 patients may have been readmitted to other area hospitals. On average 30% of patients

originally admitted to the UAB hospital are readmitted to other hospitals. The observational retrospective nature of this study does not allow drawing causal inferences. Additionally, residual unmeasured confounding, such as socioeconomic status, may influence study results. EHR data regarding pre-existing medical conditions and smoking may be incomplete. Strengths of the study include a large racially diverse sample from the US Southeast, a region disproportionately affected by COVID-19 and high prevalence of multiple comorbidities. Further, we were able to develop a robust approach to extraction of data from EHR and assemble a cohort of the patients with COVID-19.

In conclusion, in this retrospective study, the use of RAAS inhibitors was associated with decreased in-hospital



**Figure 3** Respiratory failure, requiring invasive mechanical ventilation, OR, 95% CIs, for ACE inhibitor/angiotensin receptor blocker (ACEi/ARB) use. Indications for ACEi/ARB use include HTN, chronic kidney disease, coronary artery disease, diabetes and heart failure. Overall model adjusts for age, race, sex, marital status, smoking, BMI categories, and medical conditions: HTN, chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs after 15 July 2020). Among those with indication for RAAS inhibitor, model adjusts for age, race, sex, marital status, smoking, BMI categories and medical conditions: HIV, COPD, history of solid-organ transplant, time of admission (before vs after 15 July 2020). Among those with HTN, model adjusts for age, race, sex, marital status, smoking, BMI categories and medical conditions: chronic kidney disease, coronary artery disease, diabetes, heart failure, HIV, COPD, history of solid organ transplant, time of admission (before vs after 15 July 2020).

**Abbreviations:** BMI, body mass index; COPD, chronic obstructive pulmonary disease; HTN, hypertension; RAAS, renin-angiotensin-aldosterone system.

mortality from COVID-19 in a racially diverse sample. RAAS inhibitor use was not associated with ICU-level care or hospital readmissions in the cohort of patients with COVID-19, while patients with diabetes were at a high risk for same-hospital readmission. Among patients with hypertension, baseline RAAS inhibitor use was associated with a reduced risk of iMV. This retrospective study may support the continuation of RAAS inhibitors during the COVID-19 pandemic unless there are contraindications for these pharmacological agents.

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**Table 3** Factors associated with same-hospital readmission among patients with COVID-19, between 1 March 2020 and 16 September 2020

	aSHR	95% CI	P value
Use of ACEi/ARB	1.19	0.82 1.72	0.37
Age, years			0.23
18–40	ref	– –	–
40–64	0.90	0.59 1.37	
65–74	0.75	0.44 1.27	
75 and older	0.54	0.29 1.01	
Race:			0.04
African American	1.11	0.78 1.60	
Hispanic/Latino /Asian/Other	<b>0.42</b>	<b>0.20 0.90</b>	
White	ref		
Male	1.01	0.71 1.43	0.95
Married	1.32	0.94 1.86	0.11
Current smoker	0.70	0.40 1.20	0.19
Body mass index, kg/m <sup>2</sup> :			0.05
<18.5	1.20	0.53 2.71	
18.5–24	ref		
25–29	0.69	0.44 1.07	
30 and above	<b>0.59</b>	<b>0.39 0.90</b>	
Hypertension	0.84	0.51 1.38	0.48
Coronary artery disease	0.87	0.58 1.29	0.47
Chronic kidney disease	1.19	0.76 1.86	0.46
Heart failure	1.41	0.92 2.16	0.11
Diabetes	<b>1.56</b>	<b>1.02 2.39</b>	<b>0.04</b>
COPD	1.28	0.76 2.14	0.36
HIV	0.92	0.50 1.70	0.79
Solid-organ transplant recipient	0.84	0.39 1.81	0.66

Bold p<0.05.

Multivariable-adjusted Cox proportional hazards regression model. Death after index admission is accounted as a completing risk. ACEi, ACE inhibitor; aSHR, adjusted sub-HR ; COPD, chronic obstructive pulmonary disease.

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#### REFERENCES

- Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. *N Engl J Med* 2020;382:1268–9.
- Li B, Yang J, Zhao F, *et al*. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020;109:531–8.
- Porcheddu R, Serra C, Kelvin D, *et al*. Similarity in case fatality rates (cfr) of COVID-19/SARS-COV-2 in Italy and China. *J Infect Dev Ctries* 2020;14:125–8.
- Yang J, Zheng Y, Gou X. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis* 2020.
- Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.
- Virani SS, Alonso A, Benjamin EJ, *et al*. Heart disease and stroke Statistics-2020 update: a report from the American heart association. *Circulation* 2020;141:e139–596.
- Vuille-dit-Bille RN, Camargo SM, Emmenegger L, *et al*. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. *Amino Acids* 2015;47:693–705.
- Wan Y, Shang J, Graham R, *et al*. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol* 2020;94. doi:10.1128/JVI.00127-20. [Epub ahead of print: 17 03 2020].
- Mackey K, King VJ, Gurley S, *et al*. Risks and impact of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers on SARS-CoV-2 infection in adults: a living systematic review. *Ann Intern Med* 2020;173:195–203.
- Cohen JB, Hanff TC, William P, *et al*. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med* 2021;9:275–84.
- Fosbøl EL, Butt JH, Østergaard L, *et al*. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA* 2020;324:168–77.
- Shah P, Owens J, Franklin J, *et al*. Baseline use of angiotensin-converting enzyme inhibitor/AT1 blocker and outcomes in hospitalized coronavirus disease 2019 African-American patients. *J Hypertens* 2020;38:2537–41.
- Miller DR, Oliveria SA, Berlowitz DR, *et al*. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension* 2008;51:1624–30.



- 14 Gu T, Mack JA, Salvatore M, *et al.* Characteristics associated with racial/ethnic disparities in COVID-19 outcomes in an academic health care system. *JAMA Netw Open* 2020;3:e2025197.
- 15 Hippisley-Cox J, Young D, Coupland C, *et al.* Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart* 2020;106:1503–11.
- 16 Richardson S, Hirsch JS, Narasimhan M, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the new York City area. *JAMA* 2020;323:2052–9.
- 17 Clift AK, Coupland CAC, Keogh RH, *et al.* Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ* 2020;371:m3731.
- 18 Goyal P, Choi JJ, Pinheiro LC, *et al.* Clinical characteristics of Covid-19 in New York City. *N Engl J Med* 2020;382:2372–4.
- 19 Goyal P, Ringel JB, Rajan M, *et al.* Obesity and COVID-19 in New York City: a retrospective cohort study. *Ann Intern Med* 2020;173:855–8.
- 20 Mehta N, Kalra A, Nowacki AS, *et al.* Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1020–6.
- 21 Lopes RD, Macedo AVS, de Barros E Silva PGM, *et al.* Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA* 2021;325:254–64.
- 22 Savarese G, Benson L, Sundström J, *et al.* Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. *Eur J Heart Fail* 2021;23:476–85.
- 23 Baral R, Tsampasian V, Debski M, *et al.* Association between renin-angiotensin-aldosterone system inhibitors and clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *JAMA Netw Open* 2021;4:e213594.
- 24 Reynolds HR, Adhikari S, Pulgarin C, *et al.* Renin-Angiotensin-Aldosterone system inhibitors and risk of Covid-19. *N Engl J Med* 2020;382:2441–8.
- 25 Zhang P, Zhu L, Cai J, *et al.* Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020;126:1671–81.
- 26 Chang MH, Moonesinghe R, Truman BI. COVID-19 hospitalization by race and ethnicity: association with chronic conditions among Medicare beneficiaries, January 1–September 30, 2020. *J Racial Ethn Health Disparities*;2021.
- 27 Price-Haywood EG, Burton J, Fort D, *et al.* Hospitalization and mortality among black patients and white patients with Covid-19. *N Engl J Med* 2020;382:2534–43.
- 28 Levy TJ, Richardson S, Coppa K. Development and validation of a survival calculator for hospitalized patients with COVID-19. *medRxiv* 2020.
- 29 Bhatt AS, Jering KS, Vaduganathan M, *et al.* Clinical outcomes in patients with heart failure hospitalized with COVID-19. *JACC Heart Fail* 2021;9:65–73.
- 30 Gorodeski EZ, Goyal P, Cox ZL, *et al.* Virtual visits for care of patients with heart failure in the era of COVID-19: a statement from the heart failure Society of America. *J Card Fail* 2020;26:448–56.
- 31 Donnelly JP, Wang XQ, Iwashyna TJ, *et al.* Readmission and death after initial hospital discharge among patients with COVID-19 in a large multihospital system. *JAMA* 2021;325:304–6.
- 32 Lavery AM, Preston LE, Ko JY, *et al.* Characteristics of hospitalized COVID-19 patients discharged and experiencing same-hospital readmission - United States, March–August 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1695–9.
- 33 Somani SS, Richter F, Fuster V, *et al.* Characterization of patients who return to hospital following discharge from hospitalization for COVID-19. *J Gen Intern Med* 2020;35:2838–44.