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Effect of Renin-Angiotensin-Aldosterone System Blockers on Adverse Outcomes in COVID-19 Patients

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Abstract

Introduction: Angiotensin-converting enzyme 2 (ACE2) of the renin-angiotensin-aldosterone system (RAAS) serves as a functional receptor to gain entry into the cells for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). The interaction between SARS-CoV-2 and ACE2 is a potential virulent factor in infectivity. Our study aimed to ascertain the association of RAAS inhibitors with adverse cardiovascular and other outcomes in hospitalized COVID-19 patients. ***Methods:*** This is a retrospective study of medical records of ≥18-year-old patients hospitalized for COVID-19 from March 2020 to October 2020. Primary outcomes were acute cardiovascular events (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction type 1, acute congestive heart failure, acute stroke) and mortality. Secondary outcomes were respiratory failure, need for and duration of mechanical ventilation, acute deep vein thrombosis or pulmonary embolism (DVT/PE), and readmission rate. ***Results:*** Among 376 hospitalized COVID-19 patients, 149 were on RAAS inhibitors. No statistically significant differences were found between RAAS inhibitor and non-RAAS inhibitor groups with respect to acute cardiovascular events (6% vs. 6.2%, $p = 0.94$), acute DVT/PE (4.7% vs. 4.8%, $p = 0.97$), hypoxia (62.4% vs. 58.6%, $p = 0.46$), need for mechanical ventilation (18.1% vs. 16.7%, $p = 0.72$), mortality (19.5% vs. 22%, $p = 0.56$), and readmission rate (11.4% vs. 14.1%, $p = 0.45$). Some nuances discovered were a higher rate of hospitalizations among Native Americans receiving RAAS inhibitors (30.2% vs. 19.8%) and significantly lower levels of procalcitonin in patients on RAAS inhibitors. ***Conclusions:*** Among hospitalized patients with COVID-19, those on RAAS inhibitors showed no significant differences in acute cardiovascular events, acute DVT/PE, hypoxia, need for mechanical ventilation, readmission, or mortality rate compared to those not on them. However, further large-scale studies are needed to validate these findings.

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was responsible for the pandemic infecting over 766 million people worldwide, resulting in over 6.9 million deaths globally [1, 2]. As reported by the Johns Hopkins University of Medicine, the total confirmed cases in the USA surpassed 103.8 million, including 1.1 million deaths. The disease presentation varies greatly from asymptomatic to life-threatening complications, including respiratory failure needing mechanical ventilation and multi-organ failure resulting in death. The global mortality rate varied by country, ranging from 0.1% to 4.9%, with 1.1% in the USA [3]. Multiple risk factors have been linked to the disease severity and mortality, including cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease (CLD), obesity, cancers and immunosuppression, smoking, and chronic kidney disease (CKD) [4].

The role of renin-angiotensin-aldosterone system (RAAS) inhibitors in the pathophysiology of COVID-19 infectivity and virulence is poorly understood. The RAAS is a multi-hormonal system that plays a significant role in regulating blood pressure, volume status, and plasma electrolytes and is involved in the pathogenesis of hypertension, cardiovascular and kidney diseases [5]. RAAS inhibitors are known to have significant cardio-protective effects and improve cardiovascular outcomes in patients with atherosclerotic cardiovascular disease, and have been frequently used in this patient population [6]. However, using RAAS inhibitors has been shown to increase the expression of angiotensin-converting enzyme 2 (ACE2), which serves as a functional receptor for the SARS-CoV-2 virus to gain entry into target human cells [7, 8]. ACE2 of the RAAS, predominantly located on the surfaces of the epithelial and vascular endothelial cells, especially in the heart and lungs, is responsible for the conversion of angiotensin I and II to angiotensin 1–7 and 1–9, which have vasodilatory and anti-inflammatory functions [5, 7, 8]. The interaction between SARS-CoV-2 and ACE2 is considered a potential virulent factor in SARS-CoV-2 infectivity and remains an area of interest [8]. RAAS inhibitors may promote SARS-CoV-2 infection by increased expression of ACE2; on the contrary, upregulation of ACE2 could also prevent severe lung injury through anti-inflammatory properties of angiotensin 1–7 and 1–9 [7].

To date, only a few studies explored the effect of RAAS inhibitors on the severity of SARS-CoV-2 infection and cardiovascular outcomes. There is no clear evidence to reject or support the use of RAAS inhibitors in COVID-19 patients [9–11]. Consequently, our study aimed to ascertain the association between using RAAS inhibitors and adverse cardiovascular and other clinical outcomes in COVID-19 patients requiring hospitalization.

Methods

This was an observational retrospective study conducted from March 2020 to October 2020. The study was conducted in a small community hospital with a diverse population involving relatively high proportions of Native Americans and African Americans. Study inclusion criteria comprised all patients aged ≥18 years and hospitalized for COVID-19. Data were collected and de-identified by chart review. The variables of interest included patient demographics, comorbid conditions (diabetes mellitus, hypertension, coronary artery disease [CAD], hyperlipidemia, atrial fibrillation, history of deep vein thrombosis [DVT] or pulmonary embolism [PE], congestive heart failure (CHF) [12], CLD, CKD [13]), home medications, inflammatory markers (D-dimer, lactate dehydrogenase, ferritin, procalcitonin), chest X-ray findings, inpatient medications, hypoxia (SpO_2 <94%), use of mechanical ventilation, acute medical problems (ST-elevation myocardial infarction [STEMI], non-STEMI type 1, acute CHF, acute cerebrovascular accidents, acute DVT/PE, acute kidney injury [AKI]), length of hospitalization, readmission, and death.

Primary outcomes were acute cardiovascular events (STEMI, non-STEMI type 1, acute CHF, acute stroke) and death in patients who were on RAAS inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) compared to those who were not on them. Secondary outcomes were hypoxia, defined as SpO_2 <94%, need for and length of mechanical ventilation, acute DVT/PE, and readmission rate. Statistical power analyses were conducted with alpha = 0.05 (penalized for multiple analyses), a two-tailed test was assumed, and conventional Cohen's medium-sized effect size was used. For an expected power of at least 80%, a minimum sample size of 250 (about 15% markup to account for missing observations) was needed for statistical significance. The two-tailed testing assumption for the power calculation implied that the protective effect of the RAAS inhibitors could be either way for the RAAS and non-RAAS inhibitor groups, respectively. All patients were COVID-19 infected – COVID-19 was new, and there had been no accessible conclusive prior studies that theorized or specified a unique direction for the protective effect of RAAS inhibitors for COVID-19 infections. Furthermore, as an observational rather than experimental study, demonstrating inferiority was neither relevant nor a goal.

Frequencies/percentages were generated for categorical variables to estimate the rate/proportions of the variables of interest. For continuous variables, measures of central tendency such as mean (or median, as necessary) and dispersion, namely, standard deviation (or the range, as appropriate), were computed. Group differences between those utilizing RAAS inhibitors versus those not utilizing RAAS inhibitors were explored using χ^2 tests or independent sample t tests depending on the nature of the outcome of interest – categorical or continuous, respectively. Further, multivariable binary logistic regression analyses were conducted to account for any confounding factors in the association between RAAS inhibitor use and the outcomes of interest. All statistical tests were considered significant wherever $p \leq 0.05$.

Table 1. Demographics and other baseline characteristics of COVID-19 patients included in the study

	On RAAS inhibitors/blockers (n = 149)	Not on RAAS inhibitors/blockers (n = 227)
Gender, *n* (%)		
Male	45.6 (68)	41.4 (94)
Female	54.4 (81)	58.6 (133)
Age, mean±SD, years	63.7±14.52	61.2±18.67
Race/ethnicity, *n* (%)		
Non-Hispanic whites	28.9 (43)	31.7 (72)
Non-Hispanic blacks	36.2 (54)	37.5 (85)
Native American	30.2 (45)	19.8 (45)
Others/Hispanic-Latino/Asian	4.7 (7)	11.0 (25)
BMI, mean±SD	32.9±8.29	32.3±10.17
Obesity, *n* (%)		
Overweight (BMI 25.0–29.9)	32.9 (49.0)	23.8 (54.0)
Class I obesity (BMI 30–34.9)	24.8 (37.0)	21.6 (49.0)
Class II obesity (BMI 35–39.9)	14.8 (22.0)	9.7 (22)
Class III obesity (BMI ≥40)	14.1 (21.0)	18.9 (43)
Preexisting/chronic medical problems, *n* (%)		
Diabetes mellitus	58.4 (87)	43.2 (98)
Hypertension	98.0 (146)	67.0 (152)
Hyperlipidemia	69.1 (103)	47.1 (107)
Atrial fibrillation	8.1 (12)	7.0 (16)
History of DVT/PE	4.7 (7)	4.8 (11)
CAD	26.2 (39)	23.3 (53)
CHF	14.8 (22)	11.9 (27)
CLD	19.5 (29)	20.3 (46)
CKD	17.4 (26)	23.8 (54)
On chronic dialysis	3.4 (5)	7.0 (16)
Medication prior to admission		
On antiplatelet therapy, *n* (%)		
Aspirin	34.9 (52)	27.3 (62)
Clopidogrel	6.0 (9)	10.6 (24)
Ticagrelor	0.0 (0)	1.8 (4)
Dual antiplatelet therapy	4.0 (6)	3.5 (8)
On anticoagulation, *n* (%)		
Coumadin	1.3 (2)	1.8 (4)
Apixaban	3.4 (5)	7.0 (16)
Rivaroxaban	3.4 (5)	0.9 (2)
Enoxaparin	0.7 (1)	0.9 (2)

COVID-19, coronavirus disease 2019; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease.

Results

A total of 376 distinct medical records of hospitalized patients with COVID-19 from March 2020 to October 2020 were reviewed and included in the study. Of the 376 patients, 149 (39.6%) were on RAAS inhibitors (Table 1). Most patients were female in the groups of RAAS inhibitors (54.4%) and non-RAAS inhibitors (58.6%). The mean age of patients was 63.7 years in RAAS inhibitor and 61.2 years in non-RAAS inhibitor groups. An observed lower proportion of Native Americans had COVID-19 in the non-RAAS inhibitor group (19.8%) compared to the RAAS inhibitor group (30.2%), p = 0.26, though not statistically significant. There was no significant difference

in BMI between RAAS inhibitor (32.9 ± 8.29) and non-RAAS inhibitor groups (32.3 ± 10.17), $p = 0.55$.

There was no statistically significant difference between RAAS inhibitor and non-RAAS inhibitor groups regarding the proportion of patients who had hypoxia (62.4% vs. 58.6%, $p = 0.46$), oxygen support via nasal cannula (63.1% vs. 57.3%, $p = 0.26$), high flow oxygen support (31.5% vs. 30%, $p = 0.76$), mechanical ventilation (18.1% vs. 16.7%, $p = 0.72$), and length of mechanical ventilation (11.19 ± 10.24 vs. 8.84 ± 6.98, $p = 0.51$) (Table 2). Additionally, except for procalcitonin on presentation ($p = 0.05$), no statistically significant difference was found between RAAS inhibitor and non-RAAS inhibitor groups regarding D-dimer levels on presentation ($p = 0.84$) and at peak ($p = 0.52$), lactate dehydrogenase on presentation ($p = 0.55$) and at peak ($p = 0.90$), and ferritin on presentation ($p = 0.38$) and at peak ($p = 0.82$). Furthermore, there was no statistically significant difference between RAAS inhibitor and non-RAAS inhibitor groups regarding the number of patients who had discernable chest X-ray findings (78.5% vs. 76.2%, $p = 0.60$), who were receiving therapeutic doses of enoxaparin (28.2% vs. 34.4%, $p = 0.21$), those taking antibiotics (83.9% vs. 81.1%, $p = 0.49$), those taking remdesivir (40.9% vs. 39.6%, $p = 0.80$), those taking dexamethasone (61.7% vs. 57.3%, $p = 0.40$), and those who received convalescent plasma (9.4% vs. 6.2%, $p = 0.25$). Additionally, no statistically significant difference was observed between the two groups regarding acute cardiovascular events (6% vs. 6.2%, $p = 0.94$), acute DVT/PE (4.7% vs. 4.8%, $p = 0.97$), AKI (36.9% vs. 33.9%, $p = 0.55$), median length of hospitalization (5 vs. 4 days, $p = 0.40$), readmission rate (11.4% vs. 14.1%, $p = 0.45$), or mortality rate (19.5% vs. 22%, $p = 0.56$).

Multivariable binary logistic regression analysis was performed to determine the effect of gender, age, race, use of RAAS inhibitors, diabetes mellitus, hypertension, CAD, CKD, and CLD on the odds of developing hypoxia, acute DVT/PE, need for mechanical ventilation, mortality, and readmission rate (Tables 3–7). Interestingly, it was found that age <65 years was associated with increased odds of developing hypoxia (OR: 2.01, 95% CI: 1.25 to 3.23, $p = 0.004$) and the presence of hypertension was associated with decreased odds of developing hypoxia (OR: 0.50, 95% CI: 0.27 to 0.95, $p = 0.034$). Furthermore, male gender was associated with decreased odds of requiring mechanical ventilation (OR: 0.56, 95% CI: 0.32 to 0.99, $p = 0.046$), patients with diabetes had increased odds of developing acute DVT/PE (OR: 16.48, 95% CI: 2.00 to 135.37, $p = 0.009$), and CKD patients had decreased odds of readmission for COVID-19 infection. Patients aged <65 years had increased odds of dying from COVID-19 infection (OR: 2.92, 95% CI: 1.63 to 5.22, $p < 0.001$). However, the multivariable binary logistic regression analysis did not show any association of RAAS inhibitor use with hypoxia, acute DVT/PE, need for mechanical ventilation, mortality, or readmission rate.

Discussion

In the present study, no statistically significant associations were found between RAAS blockade, via either the ACE or the angiotensin receptor, and acute cardiovascular events, acute DVT/PE, hypoxia, need for mechanical ventilation, duration of mechanical ventilation, AKI, overall mortality, or readmission rate. It is known already that patients with cardiovascular disease may be more susceptible to coronavirus infections [14]. It has been theorized that blockage of either the ACE or angiotensin II receptor could, potentially, have implications on adverse events associated with COVID-19 via upregulation of the ACE2 receptor, increasing infiltration of implicated cells by the virus, and so increasing mortality in these patients [8, 15–18]. Outside of COVID-19 enhancing systemic ACE2 levels [19], human studies have not demonstrated drug-induced increases in ACE2 levels associated with ACEI/ARB [20, 21]. Haslbauer et al. [22] even went on to measure ACE2 levels in the lung tissue of deceased COVID-19 patients but found widely varying levels depending on cell type and had no statistical significance. In addition, other studies to date have shown that not only is there no increase in mortality among patients with COVID-19 taking RAAS blockers, but also that no significant reason existed to discontinue these agents purely because of COVID-19 infection [15, 23–27], including those with STEMI [28]. Hence, our study results agree with these earlier findings.

Nonetheless, despite these concurring conclusions, small nuances were discovered within our data, indicating at least some relation between RAAS blockade and certain aspects of COVID-19 infection after accounting for confounding variables. For example, hypertensive patients who were taking ACEIs or ARBs were found to have significantly lower odds of hypoxia. This may be due to the anti-inflammatory properties of angiotensin 1–7 and 1–9 produced from the breakdown of angiotensin I and II by increased expression of ACE-2 due to RAAS inhibition from ACEIs or ARBs [5, 7]. Similar results were demonstrated by Mahanaimy et al. [29], who found a lower risk of severe COVID-19 infection in hypertensive patients who were using RAAS blockers compared to those not taking them. Our study also showed a lower likelihood of males requiring mechanical ventilation. This result is consistent with those of other studies that demonstrated possible sex-stratified differences in mortality. Ma et al. [30] found that male

Table 2. Comparative analysis of variables of interest between COVID-19 patients on RAAS inhibitors/blockers and those not on RAAS inhibitors/blockers

	On RAAS inhibitors/blockers (n = 149)	Not on RAAS inhibitors/blockers (n = 227)	p value
Hypoxia (SpO_2 <94%), n (%)	62.4 (93)	58.6 (133)	0.462
O_2 support, n (%)			
On nasal cannula O_2 support	63.1 (94)	57.3 (130)	0.263
On high flow oxygen (≥6 L/min)	31.5 (47)	30.0 (68)	0.758
On mechanical ventilation, n (%)	18.1 (27)	16.7 (38)	0.723
Duration of mechanical ventilation, mean±SD, days	11.19±10.24	8.84±6.98	0.509
Inflammatory markers			
D-dimer			
On presentation (median [IQR])	1.18 [1.45]	0.96 [1.61]	0.835
Peak (median [IQR])	1.53 [1.95]	1.36 [2.50]	0.522
LDH			
On presentation, mean±SD	314.1±270.07	308.1±176.81	0.546
Peak, mean±SD	406.6±452.38	334.0±162.82	0.904
Ferritin			
On presentation (median [IQR])	512.9 [769.8]	632.3 [1,260.95]	0.383
Peak (median [IQR])	726.6 [1,289.12]	784.5 [1,345.5]	0.826
Procalcitonin			
On presentation (median [IQR])	0.65 [0.45]	0.74 [0.65]	0.050
Peak (median [IQR])	0.83 [2.54]	0.90 [1.68]	0.359
Positive chest X-ray findings, n (%)	78.5 (117)	76.2 (173)	0.604
Inpatient medications			
Received therapeutic dose of enoxaparin	28.2 (42)	34.4 (78)	0.208
Received antibiotics	83.9 (125)	81.1 (184)	0.488
Received remdesivir	40.9 (61)	39.6 (90)	0.802
Received dexamethasone	61.7 (92)	57.3 (130)	0.397
Received convalescent plasma	9.4 (14)	6.2 (14)	0.249
Acute medical problems, n (%)			
Cardiovascular events (STEMI, type 1 NSTEMI, CHF, CVA)	6 (9)	6.2 (14)	0.937
DVT/PE	4.7 (7)	4.8 (11)	0.965
AKI	36.9 (55)	33.9 (77)	0.552
Needed dialysis for AKI	5.4 (8)	6.2 (14)	0.747
Length of hospitalization (median [IQR]), days	5.0 [8]	4.0 [6]	0.400
Readmissions, n (%)	11.4 (17)	14.1 (32)	0.447
Death, n (%)	19.5 (29)	22 (50)	0.561

COVID-19, coronavirus disease 2019; RAAS, renin-angiotensin-aldosterone system; SD, standard deviation; IQR, interquartile range; LDH, lactate dehydrogenase; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident; DVT, deep vein thrombosis; PE, pulmonary embolism; AKI, acute kidney injury.

patients who were taking ACEIs had a higher mortality risk, while female patients taking ARBs had a lower mortality risk. Furthermore, odds of acute DVT/PE during hospitalization were higher in diabetic patients who were being treated with RAAS inhibition. In terms of readmission rate, only patients with CKD were shown to have been influenced by RAAS blockade. Interestingly, our study showed patients younger than 65 years old were found to have significantly higher odds of hypoxia and mortality compared with those older than 65 years. This contrasts with

Table 3. Multivariable logistic regression analysis for hypoxia in hospitalized COVID-19 patients

	B	S.E.	Wald	df	Sig. (*p* value)	Exp(B) (OR)	95% CI for Exp(B)	
							lower	upper
Gender (male)	−0.218	0.228	0.914	1	0.339	0.804	0.514	1.258
On RAAS inhibitors	0.145	0.249	0.339	1	0.560	1.156	0.709	1.885
Diabetes mellitus	−0.455	0.234	3.772	1	0.052	0.634	0.401	1.004
Hypertension	−0.685	0.324	4.479	1	0.034	0.504	0.267	0.951
CAD	−0.186	0.291	0.406	1	0.524	0.831	0.469	1.471
CKD	−0.075	0.298	0.063	1	0.802	0.928	0.517	1.664
CLD	−0.296	0.293	1.024	1	0.311	0.744	0.419	1.320
Recategorized race			3.235	3	0.357			
Non-Hispanic whites	0.791	0.447	3.127	1	0.077	2.206	0.918	5.300
Non-Hispanic blacks	0.587	0.447	1.725	1	0.189	1.798	0.749	4.317
Native Americans	0.695	0.472	2.168	1	0.141	2.003	0.794	5.050
Dichotomized age (<65 years)	0.698	0.242	8.323	1	0.004	2.010	1.251	3.229
Constant	−0.495	0.469	1.117	1	0.290	0.609		

Table 4. Multivariable logistic regression analysis for mechanical ventilation in COVID-19 patients

	B	S.E.	Wald	df	Sig. (*p* value)	Exp(B) (OR)	95% CI for Exp(B)	
							lower	upper
Gender (male)	−0.572	0.287	3.981	1	0.046	0.564	0.322	0.990
On RAAS inhibitors	0.048	0.307	0.024	1	0.877	1.049	0.575	1.913
Diabetes mellitus	−0.226	0.291	0.601	1	0.438	0.798	0.451	1.412
Hypertension	−0.398	0.456	0.763	1	0.382	0.672	0.275	1.640
CAD	0.493	0.355	1.928	1	0.165	1.637	0.816	3.284
CKD	−0.382	0.345	1.232	1	0.267	0.682	0.347	1.340
CLD	−0.023	0.354	0.004	1	0.948	0.977	0.488	1.957
Recategorized race			0.298	3	0.960			
Non-Hispanic whites	0.193	0.582	0.110	1	0.740	1.213	0.387	3.798
Non-Hispanic blacks	0.029	0.570	0.003	1	0.959	1.029	0.337	3.145
Native Americans	0.161	0.602	0.071	1	0.789	1.175	0.361	3.820
Dichotomized age (<65 years)	0.538	0.304	3.128	1	0.077	1.712	0.943	3.107
Constant	1.878	0.626	8.997	1	0.003	6.540		

several other studies that demonstrated reductions in mortality of COVID-19 patients who were treated with ACEI/ARB [6, 26, 31–36]. Alhaddad et al. [16] examined the effects of RAAS blockade on COVID-19 severity and arrived at similar conclusions, except in a more generalized sense; ACEI/ARB use was associated with not only a significant reduction in the numbers of AKI but also intensive care unit admissions, need for mechanical ventilation, and death. Interestingly, in a large international, prospective, observational cohort study performed by Sato et al. [7], the in-hospital death rate was lower in patients taking ACEI/ARB, but the length of hospital stay, both inside and outside the intensive care unit, was longer. Nonetheless, other studies have demonstrated alternative findings, such as increased AKI in COVID-19 patients [37]. Therefore, the specific implications of the aforementioned data demonstrated by our study and those of multiple other studies are unclear at this time. Further studies regarding these specific variables are needed to draw more concrete, evidence-based, and meaningful conclusions.

In a general sense, our observations that RAAS blockade is not implicated in COVID-19 mortality are aligned with results from similar studies that explored the association of RAAS blockade with COVID-19 outcomes. A study by Li et al. [38] investigated associations between COVID-19 progression and severity for not only RAAS

Table 5. Multivariable logistic regression analysis for acute DVT/PE in hospitalized COVID-19 patients

	B	S.E.	Wald	df	Sig. (*p* value)	Exp(B) (OR)	95% CI for Exp(B)	
							lower	upper
Gender (male)	−0.265	0.638	0.173	1	0.678	0.767	0.220	2.679
On RAAS inhibitors	−0.356	0.675	0.278	1	0.598	0.700	0.187	2.630
Diabetes mellitus	2.802	1.074	6.801	1	0.009	16.480	2.006	135.368
Hypertension	−0.175	0.860	0.042	1	0.838	0.839	0.156	4.529
CAD	0.809	1.154	0.491	1	0.484	2.245	0.234	21.565
CKD	−0.490	0.785	0.390	1	0.532	0.613	0.131	2.854
CLD	0.927	1.101	0.709	1	0.400	2.528	0.292	21.875
Recategorized race			0.651	3	0.885			
Non-Hispanic whites	18.092	3,487.048	0.000	1	0.996	71,999,681.016	0.000	
Non-Hispanic blacks	−0.390	0.935	0.174	1	0.677	0.677	0.108	4.232
Native Americans	0.167	1.078	0.024	1	0.877	1.182	0.143	9.782
Dichotomized age (<65 years)	−0.607	0.725	0.701	1	0.402	0.545	0.132	2.256
Constant	3.015	1.097	7.561	1	0.006	20.397		

Table 6. Multivariable logistic regression analysis for readmission in COVID-19 patients

	B	S.E.	Wald	df	Sig. (*p* value)	Exp(B) (OR)	95% CI for Exp(B)	
							lower	upper
Gender (male)	−0.029	0.331	0.008	1	0.931	0.972	0.508	1.860
On RAAS inhibitors	0.339	0.348	0.951	1	0.329	1.404	0.710	2.777
Diabetes mellitus	0.230	0.332	0.477	1	0.490	1.258	0.656	2.414
Hypertension	−0.826	0.568	2.120	1	0.145	0.438	0.144	1.331
CAD	−0.178	0.367	0.234	1	0.628	0.8376	0.408	1.719
CKD	−0.813	0.358	5.168	1	0.023	0.443	0.220	0.894
CLD	−0.474	0.366	1.677	1	0.195	0.22	0.304	1.276
Recategorized race			1.375	3	0.711			
Non-Hispanic whites	0.703	0.659	1.140	1	0.286	2.021	0.556	7.351
Non-Hispanic blacks	0.568	0.637	0.795	1	0.373	1.765	0.506	6.157
Native Americans	0.392	0.662	0.350	1	0.554	1.480	0.404	5.421
Dichotomized age (<65 years)	0.311	0.357	0.755	1	0.385	1.364	0.677	2.748
Constant	2.112	0.729	8.407	1	0.004	8.268		

blockade but also calcium channel blockers, beta-blockers, and combinations of these drugs. No statistically significant associations were observed regarding COVID-19 severity or mortality, even when stratified for specific variables such as patients with CAD, cerebrovascular disease, diabetes, neurologic disease, or CKD [38]. This was also demonstrated in a retrospective analysis [38] and a large meta-analysis of observational studies [39]. Bezabih et al. [40] although determined that RAAS inhibition may confer a protective effect on patients with severe COVID-19 when compared with non-RAAS antihypertensives, this significance was lost when compared with specific groups of these medications, except in the case of beta-blockers. The significance of this observation remains unclear. In another study, ACEI, but not ARB, was actually associated with an increased risk of severe COVID-19, while calcium channel blockers were associated with lower hospitalization risk [30]. Nevertheless, our analysis did not show any significant difference in adverse outcomes in patients taking RAAS inhibitors compared to those not, except in the specific incidences mentioned in the preceding paragraphs.

A study performed by Mancia et al. [8] investigating the risk of COVID-19 infection similarly demonstrated no statistically significant associations between antihypertensives, including not only RAAS blockers, beta-blockers, and

Table 7. Multivariable logistic regression analysis for mortality in hospitalized COVID-19 patients

	B	S.E.	Wald	df	Sig. (*p* value)	Exp(B) (OR)	95% CI for Exp(B)	
							lower	upper
Gender (male)	−0.332	0.273	1.472	1	0.225	0.718	0.420	1.227
On RAAS inhibitors	0.266	0.292	0.830	1	0.362	1.305	0.736	2.315
Diabetes mellitus	0.029	0.274	0.011	1	0.916	1.029	0.601	1.762
Hypertension	−0.112	0.414	0.074	1	0.786	0.894	0.397	2.010
CAD	0.359	0.325	1.214	1	0.270	1.431	0.756	2.709
CKD	−0.474	0.318	2.223	1	0.136	0.623	0.334	1.161
CLD	−0.092	0.327	0.078	1	0.780	0.913	0.480	1.733
Recategorized race			2.793	3	0.425			
Non-Hispanic whites	−0.009	0.621	0.000	1	0.989	0.991	0.293	3.349
Non-Hispanic blacks	−0.475	0.608	0.609	1	0.435	0.622	0.189	2.048
Native Americans	−0.519	0.628	0.683	1	0.408	0.595	0.174	2.037
Dichotomized age (<65 years)	1.071	0.296	13.042	1	<0.001	2.917	1.632	5.215
Constant	1.354	0.642	4.451	1	0.035	3.872		

calcium channel blockers, but also various types of diuretics, as well as antihyperglycemic drugs, lipid-lowering agents, cardiovascular drugs, and respiratory drugs. It should be noted that within this study, the term "RAAS blockade" was extended to include mineralocorticoid receptor antagonists, indicating that in a more general sense, blockage of essentially any stage of the RAAS was not associated with an increased risk of COVID-19 [8]. Although our study did not directly investigate the risk of COVID-19 infection, implications of the ACE2 receptor on COVID-19 infection versus mortality are, without a doubt, interrelated.

Furthermore, another intriguing observation in our study involves procalcitonin, which appeared to be significantly lower in COVID-19 patients treated with RAAS blockers (0.65 vs. 0.74, $p = 0.05$). Procalcitonin is an acute phase reactant which can assist in diagnosing lower respiratory infections of bacterial etiology [41]. Although inconsistent, previous data have indicated that ACE inhibitors and ARBs may confer a protective role in patients with community-acquired pneumonia [42]. Given that bacterial superinfection is a relatively common complication in patients with COVID-19, one could theorize, a posteriori, that these medications may offer an additional layer of protection for patients in whom superimposed bacterial pneumonia arises. Additional research is needed to determine whether a true link exists between usage of RAAS blockade in COVID-19 patients diagnosed with parallel bacterial pulmonary infections and corresponding outcomes.

Finally, our study results revealed another interesting observation. A relatively higher proportion of Native Americans using some form of RAAS blockade developed COVID-19 infections when compared to those who were not using them. Studies observing racial disparities have shown that the rate and severity of COVID-19 infection are higher among black, Hispanic, and Asian populations compared to whites [43–45]. Furthermore, Native Americans are more vulnerable to COVID-19 infection and develop disease with a higher severity [46]. Nonetheless, no studies have investigated the role of RAAS blockers in COVID-19 infectivity and severity among Native Americans, and more studies are needed to validate our findings.

Limitations

Although our study provides significant information to the existing literature regarding RAAS usage in COVID-19 patients, it should be noted that the sample size is relatively small, especially at the subgroup level of analysis. Hence, large-scale studies are required to validate our findings. The study site was a single-center small community hospital with a patient population that may not be largely representative. However, our study provides invaluable results for future meta-analysis, given the significant benefits of RAAS blockers in patients with cardiovascular diseases.

Conclusion

Among hospitalized patients with COVID-19, we found no statistically significant relationship between RAAS blockade and acute cardiovascular events, acute DVT/PE, length of hospitalization, readmission, and overall mortality rate. However, among COVID-19

patients using RAAS blockers, Native Americans trended toward a higher rate of COVID-19 infection. Procalcitonin was significantly lower in the RAAS group, indicating these medications may offer protection against superimposed bacterial pneumonia. Further observations were lower odds of hypoxia among hypertensives, lower odds of mechanical ventilation among males, higher odds of acute DVT/PE in diabetics, and higher odds of hypoxia and mortality in patients 65 years old or younger. Nonetheless, further studies are needed to establish stronger and more specific linkages between RAAS blockade and COVID-19 infection outcomes.

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Statement of Ethics

Approval was obtained from the Institutional Review Board (IRB) at the University of North Carolina (UNC) Health Southeastern Hospital (SRMC IRB Study No. 20.311), and the study has been granted an exemption from requiring written informed consent by SRMC IRB.

Conflict of Interest Statement

Authors have no conflict of interest to declare.

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Author Contributions

Poornima Vinod: writing – original draft, writing and editing, visualization, supervision, resources, project administration, methodology, investigation, data curation, and conceptualization. Vinod Krishnappa and William Rathell Jr.: writing – original draft, review, and editing, resources, investigation, data curation, and conceptualization. Godwin Dogbey: statistical analysis, methodology, investigation, data curation, conceptualization, writing, and editing. Hiten Patel and William Herzog: writing – review and editing, conceptualization, and supervision.

Data Availability Statement

The manuscript contains all the required data, and for any further inquiries, the corresponding author can be contacted.

References

1 WHO. Coronavirus Global Situation. 2023; Available from: https://covid19.who.int
2 Konstam MA, Gheorghiade M, Burnett JC, Grinfeld L, Maggioni AP, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007;297(12):1319–31. https://doi.org/10.1001/jama.297.12.1319
3 Johns Hopkins University. Coronovirus resource center. Johns Hopkins University of Medicine; 2023.
4 Chomistek AK, Liang C, Doherty MC, Clifford CR, Ogilvie RP, Gately RV, et al. Predictors of critical care, mechanical ventilation, and mortality among hospitalized patients with COVID-19 in an electronic health record database. BMC Infect Dis. 2022;22(1):413. https://doi.org/10.1186/s12879-022-07383-6
5 Jugdutt BI. Expanding saga of the renin-angiotensin system: the angiotensin II counter-regulatory AT2 receptor pathway. Circulation. 2015;131(16):1380–3. https://doi.org/10.1161/CIRCULATIONAHA.115.016328
6 Tsampasian V, Corballis N, Vassiliou VS. Renin-angiotensin-aldosterone inhibitors and COVID-19 infection. Curr Hypertens Rep. 2022;24(10):425–33. https://doi.org/10.1007/s11906-022-01207-3
7 Sato K, White N, Fanning JP, Obonyo N, Yamashita MH, Appadurai V, et al. Impact of renin-angiotensin-aldosterone system inhibition on mortality in critically ill COVID-19 patients with pre-existing hypertension: a prospective cohort study. BMC Cardiovasc Disord. 2022;22(1):123. https://doi.org/10.1186/s12872-022-02565-1
8 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. 2020;382(25):2431–40. https://doi.org/10.1056/NEJMoa2006923
9 Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020;38(5):781–2. https://doi.org/10.1097/HJH.0000000000002450
10 Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie 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(12):1671–81. https://doi.org/10.1161/CIRCRESAHA.120.317134
11 Jarcho JA, Ingelfinger JR, Hamel MB, D'Agostino RB Sr, Harrington DP. Inhibitors of the renin-angiotensin-aldosterone system and covid-19. N Engl J Med. 2020;382(25):2462–4. https://doi.org/10.1056/NEJMe2012924
12 Litchfield WR, Anderson BF, Weiss RJ, Lifton RP, Dluhy RG. Intracranial aneurysm and hemorrhagic stroke in glucocorticoid-remediable aldosteronism. Hypertension. 1998;31(1 Pt 2):445–50. https://doi.org/10.1161/01.hyp.31.1.445
13 Welander J, Larsson C, Bäckdahl M, Hareni N, Sivlér T, Brauckhoff M, et al. Integrative genomics reveals frequent somatic NF1 mutations in sporadic pheochromocytomas. Hum Mol Genet. 2012;21(26):5406–16. https://doi.org/10.1093/hmg/dds402
14 Augustine R, Abhilash S, Nayeem A, Salam SA, Augustine P, Dan P, et al. Increased complications of COVID-19 in people with cardiovascular disease: role of the renin-angiotensin-aldosterone system (RAAS) dysregulation. Chem Biol Interact. 2022;351:109738. https://doi.org/10.1016/j.cbi.2021.109738
15 Rizk JG, Sanchis-Gomar F, Henry BM, Lippi G, Lavie CJ. Coronavirus disease 2019, hypertension, and renin-angiotensin-aldosterone system inhibitors. Curr Opin Cardiol. 2022;37(5):419–23. https://doi.org/10.1097/HCO.0000000000000982

16 Alhaddad MJ, Almulaify MS, Alshabib AA, Alwesaibi AA, Alkhameys MA, Alsenan ZK, et al. Relation between renin-angiotensin-aldosterone system inhibitors and COVID-19 severity. Cureus. 2022;14(3):e22903. https://doi.org/10.7759/cureus.22903
17 Schieffer E, Schieffer B. The race for ACE: targeting angiotensin-converting enzymes (ACE) in SARS-CoV-2 infection. J Renin Angiotensin Aldosterone Syst. 2022;2022:2549063. https://doi.org/10.1155/2022/2549063
18 Paulsson-Habegger L, Snabaitis AK, Wren SP. Enzyme inhibition as a potential therapeutic strategy to treat COVID-19 infection. Bioorg Med Chem. 2021;48:116389. https://doi.org/10.1016/j.bmc.2021.116389
19 Zanza C, Tassi MF, Romenskaya T, Piccolella F, Abenavoli L, Franceschi F, et al. Lock, stock and barrel: role of renin-angiotensin-aldosterone system in coronavirus disease 2019. Cells. 2021;10(7):1752. https://doi.org/10.3390/cells10071752
20 Zimmermann T, Walter JE, Lopez-Ayala P, Strebel I, Amrein M, Koechlin M, et al. Influence of renin-angiotensin-aldosterone system inhibitors on plasma levels of angiotensin-converting enzyme 2. ESC Heart Fail. 2021;8(2):1717–21. https://doi.org/10.1002/ehf2.13249
21 Fagyas M, Bánhegyi V, Úri K, Enyedi A, Lizanecz E, Mányiné IS, et al. Changes in the SARS-CoV-2 cellular receptor ACE2 levels in cardiovascular patients: a potential biomarker for the stratification of COVID-19 patients. Geroscience. 2021;43(5):2289–304. https://doi.org/10.1007/s11357-021-00467-2
22 Haslbauer JD, Stalder A, Zinner C, Bassetti S, Mertz KD, Went P, et al. Immunohistochemical and transcriptional analysis of SARS-CoV-2 entry factors and renin-angiotensin-aldosterone system components in lethal COVID-19. Pathobiology. 2022;89(3):166–77. https://doi.org/10.1159/000520221
23 Kang SH, Lee DH, Han KD, Jung JH, Park SH, Dai AM, et al. Hypertension, renin-angiotensin-aldosterone-system-blocking agents, and COVID-19. Clin Hypertens. 2021;27(1):11. https://doi.org/10.1186/s40885-021-00168-0
24 Rodrigues R, Costa de Oliveira S. The impact of angiotensin-converting enzyme 2 (ACE2) expression levels in patients with comorbidities on COVID-19 severity: a comprehensive review. Microorganisms. 2021;9(8):1692. https://doi.org/10.3390/microorganisms9081692
25 Ventura D, Carr AL, Davis RD, Silvestry S, Bogar L, Raval N, et al. Renin angiotensin aldosterone system antagonism in 2019 novel coronavirus acute lung injury. Open Forum Infect Dis. 2021;8(10):ofab170. https://doi.org/10.1093/ofid/ofab170
26 Rubin SJS, Falkson SR, Degner NR, Blish CA. Safety of ACE-I and ARB medications in COVID-19: a retrospective cohort study of inpatients and outpatients in California. J Clin Transl Sci. 2021;5(1):e8. https://doi.org/10.1017/cts.2020.489
27 Ozkan G, Ulusoy Ş, Erdem Y, Altun B, Yılmaz R, Ata N, et al. The effect of hypertension and antihypertensive therapies on the course of COVID-19 infection: Turkish national health system data. Clin Exp Hypertens. 2022;44(6):502–6. https://doi.org/10.1080/10641963.2022.2071923
28 Barbieri L, Trabattoni D, Stefanini GG, Vizzardi E, Tumminello G, Assanelli E, et al. Impact of RAAS inhibitors on clinical outcome and mortality in patients with STEMI during the COVID-19 era: a multicenter observational study. Front Cardiovasc Med. 2021;8:792804. https://doi.org/10.3389/fcvm.2021.792804
29 Mahanaimy M, Finkel U, Barda N, Rottman E, Balicer R, Berliner Senderey A, et al. Association of renin-angiotensin-aldosterone inhibitors with COVID-19 infection and disease severity among individuals with hypertension. Isr Med Assoc J. 2022;24(5):310–6.
30 Ma Y, Zhang Y, Li S, Yang H, Li H, Cao Z, et al. Sex differences in association between anti-hypertensive medications and risk of COVID-19 in middle-aged and older adults. Drugs Aging. 2021;38(10):921–30. https://doi.org/10.1007/s40266-021-00886-y
31 Kurdi A, Mueller T, Weir N. An umbrella review and meta-analysis of renin-angiotensin system drugs use and COVID-19 outcomes. Eur J Clin Invest. 2023;53(2):e13888. https://doi.org/10.1111/eci.13888
32 Loader J, Taylor FC, Lampa E, Sundström J. Renin-angiotensin aldosterone system inhibitors and COVID-19: a systematic review and meta-analysis revealing critical bias across a body of observational research. J Am Heart Assoc. 2022;11(11):e025289. https://doi.org/10.1161/JAHA.122.025289
33 Oliveira J, Gameiro J, Bernardo J, Marques F, Costa C, Branco C, et al. Impact of chronic RAAS use in elderly COVID-19 patients: a retrospective analysis. J Clin Med. 2021;10(14):3147. https://doi.org/10.3390/jcm10143147
34 Aparisi A, Catalá P, Amat-Santos IJ, Marcos-Mangas M, López-Otero D, Veras C, et al. Chronic use of renin-angiotensin-aldosterone inhibitors in hypertensive COVID-19 patients: results from a Spanish registry and meta-analysis. Med Clin. 2022;158(7):315–23. https://doi.org/10.1016/j.medcle.2021.04.026
35 Khodneva Y, Malla G, Clarkson S, Fu R, Safford MM, Goyal P, et al. What is the association of renin-angiotensin-aldosterone system inhibitors with COVID-19 outcomes: retrospective study of racially diverse patients? BMJ Open. 2022;12(4):e053961. https://doi.org/10.1136/bmjopen-2021-053961
36 Lumbers ER, Head R, Smith GR, Delforce SJ, Jarrott B, H Martin J, et al. The interacting physiology of COVID-19 and the renin-angiotensin-aldosterone system: key agents for treatment. Pharmacol Res Perspect. 2022;10(1):e00917. https://doi.org/10.1002/prp2.917
37 Lee SA, Park R, Yang JH, Min IK, Park JT, Han SH, et al. Increased risk of acute kidney injury in coronavirus disease patients with renin-angiotensin-aldosterone-system blockade use: a systematic review and meta-analysis. Sci Rep. 2021;11(1):13588. https://doi.org/10.1038/s41598-021-92323-8
38 Li XL, Li T, Du QC, Yang L, He KL. Effects of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors on COVID-19. World J Clin Cases. 2021;9(20):5462–9. https://doi.org/10.12998/wjcc.v9.i20.5462
39 Sharma R, Kumar A, Majeed J, Thakur AK, Aggarwal G. Drugs acting on the renin-angiotensin-aldosterone system (RAAS) and deaths of COVID-19 patients: a systematic review and meta-analysis of observational studies. Egypt Heart J. 2022;74(1):64. https://doi.org/10.1186/s43044-022-00303-8
40 Bezabih YM, Bezabih A, Alamneh E, Peterson GM, Bezabhe W. Comparison of renin-angiotensin-aldosterone system inhibitors with other antihypertensives in association with coronavirus disease-19 clinical outcomes. BMC Infect Dis. 2021;21(1):527. https://doi.org/10.1186/s12879-021-06088-6
41 Self WH, Balk RA, Grijalva CG, Williams DJ, Zhu Y, Anderson EJ, et al. Procalcitonin as a marker of etiology in adults hospitalized with community-acquired pneumonia. Clin Infect Dis. 2017;65(2):183–90. https://doi.org/10.1093/cid/cix317
42 Caldeira D, Alarcão J, Vaz-Carneiro A, Costa J. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. BMJ. 2012;345:e4260. https://doi.org/10.1136/bmj.e4260
43 Tanne JH. Covid-19: US studies show racial and ethnic disparities in long covid. BMJ. 2023;380:535. https://doi.org/10.1136/bmj.p535
44 Fu J, Reid SA, French B, Hennessy C, Hwang C, Gatson NT, et al. Racial disparities in COVID-19 outcomes among Black and white patients with cancer. JAMA Netw Open. 2022;5(3):e224304. https://doi.org/10.1001/jamanetworkopen.2022.4304
45 Lopez L 3rd, Hart LH 3rd, Katz MH. Racial and ethnic health disparities related to COVID-19. JAMA. 2021;325(8):719–20. https://doi.org/10.1001/jama.2020.26443
46 Silberner J. Covid-19: how Native Americans led the way in the US vaccination effort. BMJ. 2021;374:n2168. https://doi.org/10.1136/bmj.n2168