THE RELATIONSHIP BETWEEN COVID-19 SEVERITY AND THE USAGE OF ANGIOTENSIN-II RECEPTOR BLOCKERS IN HYPERTENSIVE PATIENTS

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ABSTRACT

Purpose of the study: As demonstrated by numerous epidemiological studies, the high incidence of hypertension among patients with coronavirus disease 2019 (COVID-2019) appears to be associated with an elevated risk of mortality. The angiotensin-converting enzyme (ACE) system is not expressed uniformly throughout the human population, and contemporary variations may account for part of the global disparities in infection prevalence. In addition, animal investigations have demonstrated that the ACE2 receptor is a potential infection route for the COVID-19-causing SARS-CoV-2 virus. As two-thirds of hypertension patients take ACE inhibitors/angiotensin receptor blockers, a number of concerns have been raised regarding the harmful or beneficial effects of contemporary antihypertensive medications in COVID-19. This study presents the most recent evidence for and against the impact of ACE blockade administration in the age of COVID-19 on the cohort of hypertension patients in Bangladesh (N = 300). **Methods:** We included in this study 300 patients who had a record of a COVID-19 test performed between July 2021 and September 2021 using RT-PCR. All the patients had a history of hypertension two years before the index date, based on the International Classification of Diseases codes (Tenth Revision, Clinical Modification, ICD-10-CM). All of them have been taking anti-hypertensive drugs for 1–2 years. We used logistic regression to estimate the odds ratio (OR) and the 95% confidence interval (CI) of COVID-19 severity in patients prescribed Angiotensin Receptor Blockers (ARB) versus those not prescribed ARB. We selected a cohort of 300 Bangladeshi patients who were covid positive and had been taking hypertensive medications for 1-5 years. **Results:** Among COVID-19-positive patients with hypertension, the use of ARB is associated with increased odds of hospitalization, including all patients admitted to ICU or CCU (OR = 1.008, (0.440, 2.309) and OR= 2.31, (0.024, 2.452) respectively). Participants receiving ARB have a lower odds ratio of using BiPAP, CPAP, and Ventilation (0.592, 0.010, and 0.031, respectively; p-value < 0.5) compared to the non-ARB users. **Research Implications:** We noticed a statistically significant association between ARB administration and mechanical ventilation in our study. Since ARB use was also related to a decreased likelihood of needing additional oxygen support, such as nasal cannula, BiPAP, and CPAP, there is sufficient evidence from other clinical factors to indicate a consistent connection between ARB use and oxygen assistance among covid-positive patients. Further research is required to determine the molecular relationship between ARB use and oxygen level in Covid-positive individuals.

KEYWORDS: SARS-CoV-2, ACE2 Receptor, Hypertension, Angiotensin Receptor Blockers (ARB)

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has spread across the globe at an unprecedented rate. Patients infected with the virus causing COVID-19, the severe acute respiratory syndrome coronavirus (SARS-CoV-2), vary in disease severity. Statistics showed around 1,952,162 cases of covid positive in Bangladesh till April 2022. Twenty-nine thousand one hundred twenty-four patients died, causing a 1.5% fatality rate and 96.8% recovery rate. The same source of statistics showed 1283 critical cases treated in ICU, which forms 0.1% of the total infected patients. Seven covid vaccines are approved in Bangladesh, and around 70% of the population are already fully vaccinated. Those with pre-existing medical conditions such as hypertension are particularly vulnerable to severe outcomes of COVID-19 (Fang, Karakiulakis and Roth, 2020a). According to a study done in 2020, the prevalence of hypertension is high and rising in Bangladesh (Chowdhury *et al.*, 2020a). The study identified that hypertension prevalence ranges from 1.10% to 75.0%, and the overall weighted pooled prevalence of hypertension is 20.0% (Chowdhury *et al.*, 2020b). Angiotensin receptor

blockers (ARBs) are widely prescribed for hypertension (Heran *et al.*, 2008). Previous studies have reported that ARBs could diminish the potential for acute respiratory distress syndrome, myocarditis, or acute kidney injury, occurring in COVID-19 patients. ARBs have been suggested to treat COVID-19 and its complications (Gurwitz, 2020; Rothlin *et al.*, 2020; Saavedra, 2020).

ARBs have been in clinical use since 1995 and are known to be effective antihypertensive agents with excellent tolerability profiles. ARBs have additive BP-lowering effects when combined with thiazide diuretics and dihydropyridine CCBs, without increasing adverse event rates(Burnier and Brunner, 2000). The renin-angiotensin-aldosterone system has been a significant target pathway for developing antihypertensive medications(Appel and Appel, 2004). The four drugs involved in this pathway include ACE inhibitors, angiotensin II receptor blockers (ARBs), aldosterone antagonists, and direct renin inhibitors. The interest in this pathway is due to the action of angiotensin II on the vascular system, renal sodium and water handling, and cellular proliferation (Weir, 1999). Inhibition of ACE only partially inhibits the formation of angiotensin II. Angiotensin II activates two types of angiotensin II receptors (ATR): ATR1 and ATR2. ATR1 is abundant in the vessels, brain, heart, kidney, adrenal gland, and nerves. At the same time, ATR2 is prominently expressed in the fetus. Still, it decreases during the postnatal period, where they are only available in small numbers in the adult kidney, adrenal gland, heart, brain, uterus, and ovary. Activation of ATR1 causes generalized vasoconstriction from contraction of vascular smooth muscle and increases in aldosterone, resulting in increased sodium reabsorption in the proximal tubule and cell growth in the arteries and heart (Israili, 2000). The ARBs specifically block the interaction of angiotensin II at the AT1 receptor, thereby relaxing smooth muscle, increasing salt and water excretion, reducing plasma volume, and decreasing cellular hypertrophy. These agents mainly exert their blood pressure-lowering effect by reducing peripheral vascular resistance, usually without a rise in heart rate(Fang, Karakiulakis and Roth, 2020b).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to target cells through the angiotensin-converting enzyme 2 (ACE2), which is expressed by the epithelial cells of the lungs, intestine, kidney, and blood vessels ***(Figure 1)*** (Hoffmann *et al.*, 2020). Interest has been directed to the use of angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs) because these drugs may affect the ability of SARS-CoV-2 to infect cells through upregulation of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2 cell entry(Li *et al.*, 2003; Zhang *et al.*, 2020). Literature surveys have failed to identify any reports associating ACEI/ARB with a higher risk of COVID-19 infection, severity, or mortality(Liu *et al.*, 2020; Xu *et al.*, 2021). Meta-analysis of studies of ACEI/ ARB usage among COVID-19 patients showed no significant increase in COVID- 19 infection risk but did show a decreased risk of severe COVID-19 and mortality in patients receiving ACEI/ARB therapy(Baral, White and Vassiliou, 2020; Barochiner and Martínez, 2020). Furthermore, a meta-analysis of twenty-six studies involving 8,104 hypertensive ACEI/ARB users and 8,203 hypertensive non-ACEI/ARB users reported a significantly lower mortality risk and a lower need for ventilator use among ACEI/ARB users(Wang *et al.*, 2021). Another study showed the possible benefit of ARBs in COVID-19 patients through a case series(Lee *et al.*, 2021). There has been no studies regarding this in Bangladesh. We thus sought to investigate the anti-hypertension medication, ARB for its different associations with COVID-19 occurrence and severity by using a cohort of 300 patients.

Methodology

Study population

We included in this study 300 patients who had a record of a COVID-19 test performed between July 2021 and September 2021 using RT-PCR. The data was collected from Central Police Hospital, Popular Medical College Hospital, Dhaka Medical College Hospital, Better Life Hospital, Dr. Sirajul Medical College and Hospital, and Bangabandhu Sheikh Mujib Medical University Hospital situated in Dhaka, Bangladesh. The study participants were admitted to the isolation unit, HDU, and ICU. All the patients had a history of hypertension two years before the index date, based on the International Classification of Diseases codes (Tenth Revision, Clinical Modification, ICD-10-CM). All of them have been taking anti-hypertensive drugs for 1–2 years.

Delineation

Patients positive for COVID-19 were defined by a positive nucleic acid RT-PCR test done in the respective hospitals. The index date is determined as the date of the first positive or first negative test or the date of the hospital admission closest (within 15 days) to the date of the first positive or negative test. Prescription of anti-hypertension medication, ARB, constituted medication exposure within two years of the index date. Patients identified with ARB prescriptions were compared to those without ARB prescriptions. If a patient was not prescribed an ARB within two years of the index date, they were not considered exposed to ARB. Other anti-hypertension medications, such as alpha-blockers, beta-blockers, or calcium channel blockers, have been prescribed to the unexposed participants. Among the 300 patients, 127 (42.33%) were prescribed at least one of these non-ARB medications. The evaluation of all medication use was based on prescriptions written in the two years preceding the COVID-19 test date (index date).

Using a four-level severity scale, the severity of COVID-19 was defined as mild, moderate, severe, or critical disease stages. The World Health Organization's criteria, including mild, moderate, severe, and critical disease, are the most frequently used classification system for clinical prediction of COVID-19 severity (Organization, 2020). The severity of our COVID-19-positive patients who were still alive 28 days after the index date was classified using a four-level severity measure: level 1—mild disease and hospitalized in the general ward; level 2—moderate disease, hospitalized, using oxygen mask and not requiring mechanical ventilation; level 3—severe disease, admitted to ICU but without mechanical ventilation; level 4—critical disease requiring mechanical ventilation.

Outcomes

We looked into the follow-up data of the patients after 14 days and 28 days. The outcomes were divided into patients being admitted to the general ward, ICU, CCU, and patients discharged without oxygen. The worst outcome was death. Next, the covid severity was also measured by the oxygen requirement of the patients. The outcomes were categorized as room air, nasal cannula, face mask, BiPap, CPAP, and ventilation.

Covariates and demographics

In this study, age at the index date and gender were considered to be demographic factors. All of the patients were permanent residents of Bangladesh, so race and ethnicity are not included in the demographics. Diabetes, pulmonary disease, kidney disease, coronary atherosclerotic heart disease (CAHD), chronic liver disease, dyslipidemia, cancer, smoking status, heart failure, and asthma were among the COVID-19-relevant comorbidities that were defined based on inpatient and outpatient ICD-10 codes from the two-year period preceding the index date.

Statistical analysis

We used logistic regression to estimate the odds ratio (OR) and the 95% confidence interval (CI) of COVID-19 severity in patients prescribed ARB versus those not prescribed ARB. We performed multinomial logistic regression analysis using IBM SPSS Statistics ('IBM Corp. Released 2019. IBM SPSS Statistics for Windows.', no date). We used propensity score weighting (PSW) to control for confounding in sensitivity analyses due to the potential imbalance among covariates. All analyses were adjusted for relevant covariates, such as age, gender, and comorbidities. We used nominal logistic regression with and without PSW to examine the association between ARB and the four-level COVID severity measure in COVID-19-positive patients. In analyses focusing on severity, the reference group consisted of COVID-19-positive patients discharged without oxygen after 14 days of follow-up (least severe). We used maximum likelihood estimation to calculate the OR with 95 percent confidence intervals and set the level of statistical significance (alpha) to 0.05. To examine the robustness of the observed associations, we estimated the CI of the primary findings (regression coefficients) from logistic regression models using a bootstrapping procedure. Because it is asymptotically more accurate than the standard confidence intervals derived from sample variance and assumptions of normality, the bootstrapping procedure was used as a sensitivity analysis to control and verify the stability of the results (DiCiccio and Efron, 1996; Platt, Hanley and Yang, 2000).

Results

Characteristics of the patients

Our study population consisted of 152 (50.6%) female and 148 (49.4%) male patients. All patients were Covid positive and took the hypertensive drug for 1-5 years. The mean age (± SD) at the index date for patients was 58.22 ± 11.47 years. Patients were identified with various comorbidities, among which significant were diabetes (43.3%), ischemic heart disease (20.67%), dyslipidemia (13.67%), and asthma and bronchial asthma (10%) ***(Table 1)***. Patients were categorized as ARB and non-ARB users depending on the anti-hypertensive drugs. 173 (57.67%) patients received ARB as an anti-hypertensive drug, and 127 (42.33%) patients took non-ARB drugs for hypertension. Among non-ARB hypertensive drugs were medications such as alpha-blockers, beta-blockers, or calcium channel blockers ***(Table 2)***. The mean age (± SD) at the index date for patients receiving ARB was 56.65 ± 10.60 years compared to 60.40± 12.25 mean age (± SD) at the index date for patients receiving non-ARB. Male patients were 88 (50.8%) compared to 85 (49.2%) female patients among ARB users. On the other hand, male patients were 62 (48.8%) compared to 65 (51.2%) female patients among non-ARB users.

Table 1. Comorbidities of patients with hypertension and COVID-19 infection.

Co-Morbidity	Yes	No
Diabetes Mellitus	130 (43.3%)	170 (56.7%)
Heart Failure	13 (4.3%)	287 (95.7%)
Asthma	25 (8.3%)	275 (91.7%)
Bronchial Asthma	5 (1.67%)	295 (98.33%)
Ischemic Heart Disease (IHD)	62 (20.67%)	238 (79.3%)
Chronic obstructive pulmonary disease (COPD)	13 (4.3%)	287 (95.7%)
Dyslipidemia	41 (13.67%)	259 (86.33%)
Osteoarthritis (OA)	3 (1%)	297 (99%)

Hypothyroidism	16 (5.3%)	284 (94.7%)
Chronic kidney disease (CKD)	15 (5%)	285 (95%)
coronary artery bypass graft (CABG)	3 (1%)	297 (99%)
Rheumatoid Arthritis	3 (1%)	297 (1%)
Acute kidney injury (AKI)	3 (1%)	297 (1%)
Diffuse Parenchymal Lung Disease (DPLD)	2 (0.67%)	298 (99. 33%)
Hepatocellular carcinoma (HCC)	1 (0.33%)	299 (99.67%)

Table 2. Statistics of patients receiving ARB and non-ARB hypertensive drugs. Abbreviations: AHT, Anti-Hypertensive; ARB, Angiotensin Receptor Blocker.

AHT Drug Class	**Number of cases**	
ARB (57.67%)	173	
	AT1 receptor antagonist	173 (100%)
Non-ARB (42.33%)	127	
	Beta blocker	53 (42.1%)
	Ca^{2+} channel blocker	53 (41.2%)
	Diuretics	21 (16.7%)
Total	**300**	

Association of ARB with follow-up outcomes of patients

Firstly, we looked into the follow-up data for the participants after 14days ***(Table 3)***. Patients who used ARB had a lower odds ratio of being discharged without Oxygen and at home with Oxygen (0.695 and 0.682 respectively, p-value < 0.5) compared to patients who received non-ARB as anti-hypertensive drugs. However, the ICU and CCU odds ratio was higher for ARB-receiving patients than the patients taking non-ARB drugs (OR = 1.008 and 5.611, respectively).

Table 3. Association of ARB use with the follow-up of Covid-positive patients after 14 and 28 days. The table shows odds ratio, 95% confidence interval (CI) and p-value of logistic regression analysis.

Follow-up after 14 days				
Condition	**Class of drug used**	**Odds**	**95% CI**	**p-value**
Discharged without oxygen	ARB	0.695	(0.068, 0.7068)	0.759
At home with Oxygen	ARB	0.682	(0.245, 1.900)	0.465
CCU	ARB	2.311	(0.024, 2.452)	0.536
In Hospital in General ward	ARB	1.570	(0.772, 3.192)	0.213
In ICU	ARB	1.008	(0.440, 2.309)	0.985
Death	ARB	0.304	(0.098, 0.942)	0.039
Follow-up after 28 days				
Condition	**Class of drug used**	**Odds**	**95% CI**	**p-value**
Discharged without oxygen	ARB	0.077	(0.011, 0.535)	0.009
At home with Oxygen	ARB	0.993	(0.163, 6.055)	0.994
In Hospital in General ward	ARB	2.207	(0.592, 8.224)	0.238
Death	ARB	0.910	(0.354, 2.345)	0.846

Next, we tried to look into the follow-up data of the participants after 28days. The results were paralleled with the data of follow-up after 14days ***(Figure 2)***. Patients who used ARB have a lower odds ratio of being discharged without Oxygen and at home with Oxygen (OR = 0.077 and 0.993 respectively, p-value < 0.5) compared to patients who received non-ARB as anti-hypertensive drugs. In contrast, the odds ratio of patients admitted to the hospital after 28days of the Covid-positive test was higher for ARB users than for non-ARB users (2.207, p-value <0.5).

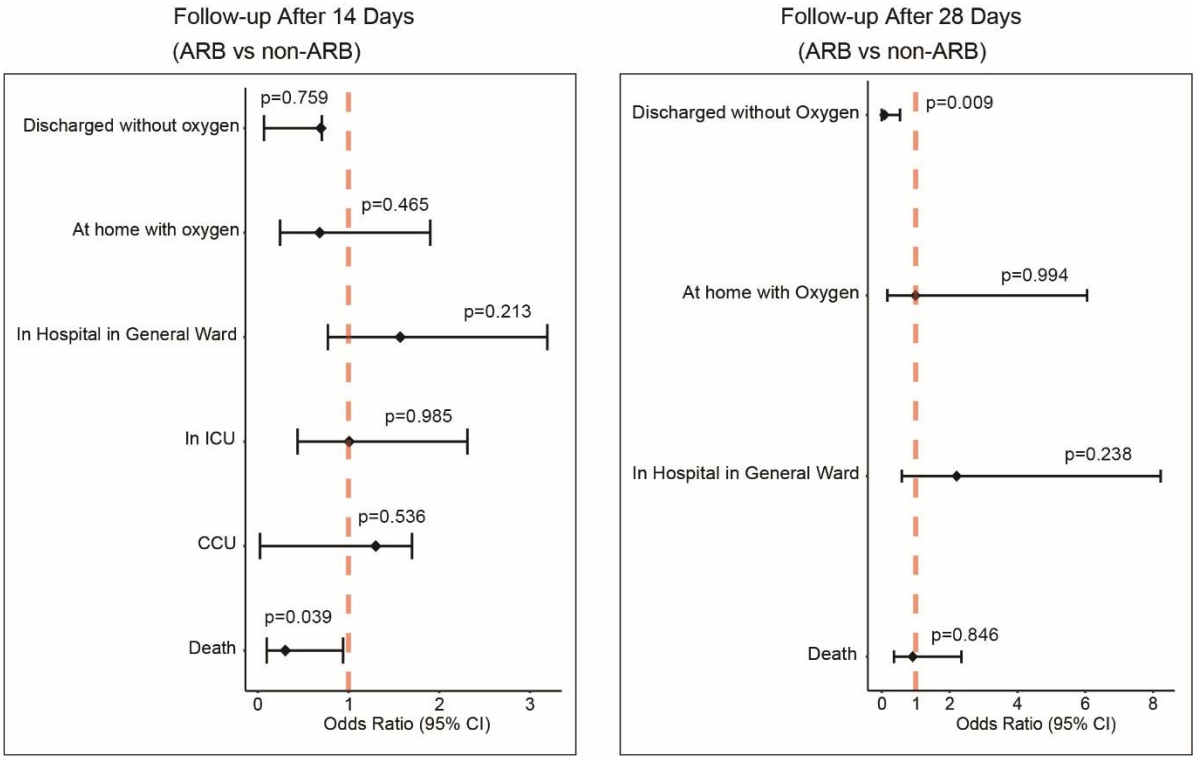

Figure 1. Odds ratios of severity of Covid-positive patients after follow up of 14 days and 28 days respectively with records of using ARB. Patients with records of having been prescribed ARB were compared to those with no record of having been prescribed ARB using a logistic regression model. Among COVID-19-positive patients with hypertension, the use of ARB is associated with increased odds of hospitalization (including all patients admitted to ICU or CCU). The use of ARB was not associated with mortality. No significant association was observed between ARB use and death of the patients.

Association of ARB with the oxygen support of Covid-positive patients

Afterwards, we tried to look into the association of maintenance of oxygen of patients (using room air, nasal cannula, BiPAP or CPAP, mechanical ventilation etc.) with the use of ARB as antihypertensive drug ***(Table 4, Figure 3)***. Here, to further get a clear view, we divided the participants into three age groups, such as, 25-45 age, 46-65 age, 66-85 age. There were 52 participants from age group of 25-45, 169 participants from age group 46-65 and 79 participants from age group 66-85. The results are almost consistent in all age groups. Participants receiving ARB have a lower odds ratio of using BiPAP, CPAP, and Ventilation compared to the non-ARB users in all age groups. However, the odds ratio for patients (ARB users) who had to use Nasal Cannula was 1.003 times more than the non-ARB users in age group 46-65 and 1.120 times in age group 66-85. But in all other cases of oxygen requirement, such as, BiPAP, CPAP, high flow nasal cannula, the odds of ratio was less for ARB users compared to non-ARB in all age groups. It can be said from the overall analysis that the odds ratio for oxygen requirement was less for ARB users compared to non-ARB users.

Table 4. Association of ARB use with the maintenance of oxygen for Covid-positive patients. The table shows odds ratio, 95% confidence interval (CI) and p-value of logistic regression analysis.

Oxygen requirement	Age Group	Class of drug used	Odds	95% CI	p-value
Room Oxygen	25-45	ARB	0.465	(0.323, 0.775)	1.00
	46-65	ARB	0.382	(0.019, 7.857)	0.533
	66-85	ARB	0.754	(0.565, 0.855)	0.466
BiPAP	25-45	ARB	0.567	(0.156,0.237)	0.000
	46-65	ARB	0.692	(0.222, 1.581)	0.296
	66-85	ARB	0.343	(0.565, 1.122)	0.001
CPAP	25-45	ARB	0.082	(0.030, 0.121)	0.002
	46-65	ARB	0.075	(0.010, 0.430)	0.005
	66-85	ARB	0.076	(0.002, 1.023)	0.78
Face mask	25-45	ARB	0.451	(0.120, 0.768)	0.001
	46-65	ARB	0.522	(0.127, 0.813)	0.016

	66-85	ARB	1.232	(0.667, 2.457)	1.267
High Flow Nasal cannula	25-45	ARB	0.366	(0.180, 0.562)	0.005
	46-65	ARB	0.277	(0.060, 1.160)	0.078
	66-85	ARB	0.436	(0.230, 0.953)	0.064
Nasal cannula	25-45	ARB	0.998	(0.030, 0.988)	1.22
	46-65	ARB	1.003	(0.409, 2.474)	0.000
	66-85	ARB	1.120	(0.568, 2.303)	0.899
Non rebreather mask	25-45	ARB	0.071	(0.050, 0.998)	0.054
	46-65	ARB	0.068	(0.026, 0.163)	0.000
	66-85	ARB	0.031	(0.005, 0.851)	0.089
Ventilation	25-45	ARB	0.146	(0.006, 0.541)	0.005
	46-65	ARB	0.098	(0.031, 0.271)	0.000
	66-85	ARB	0.087	(0.005, 0.377)	0.778

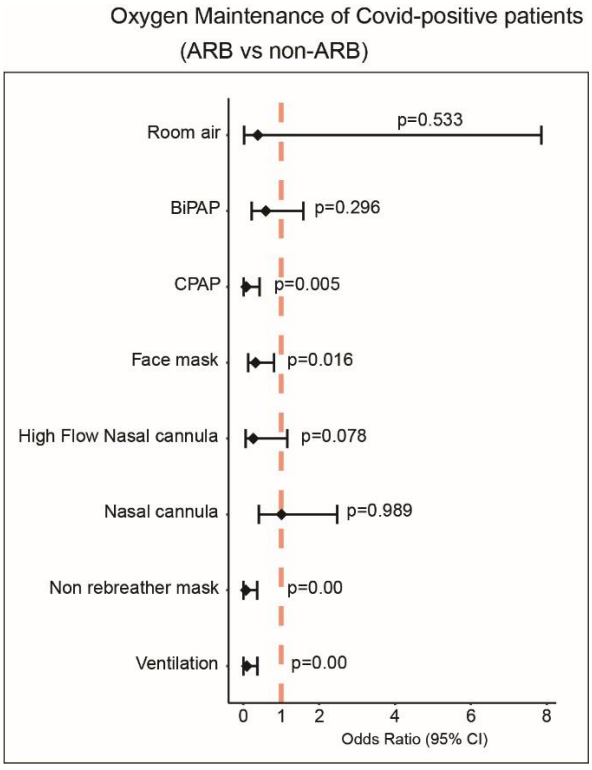

Figure 2. Odds ratios of maintenance of oxygen of Covid-positive patients with records of using ARB. Patients with records of having been prescribed ARB were compared to those with no record of having been prescribed ARB using a logistic regression model. Among COVID-19-positive patients with hypertension, the use of ARB is associated with decreased odds of using BiPAP, CPAP and Ventilation.

Association of ARB with the requirement of ICU/HDU/BiPAP/CPAP/Mechanical Ventilation of Covid-positive patients

We also attempted to understand the relationship between ARB use and Covid severity by examining the odds ratio of ARB-using patients who required severe Covid measures such as ICU, HDU, BiPAP, CPAP, or mechanical ventilation. It is observed that, patients receiving ARB has a decreased odds ratio of being admitted in ICU, HDU or using BiPAP, CPAP and mechanical ventilation (OR = 0.566, (0.334, 0.958), p-value = 0.034) ***(Figure 4)***.

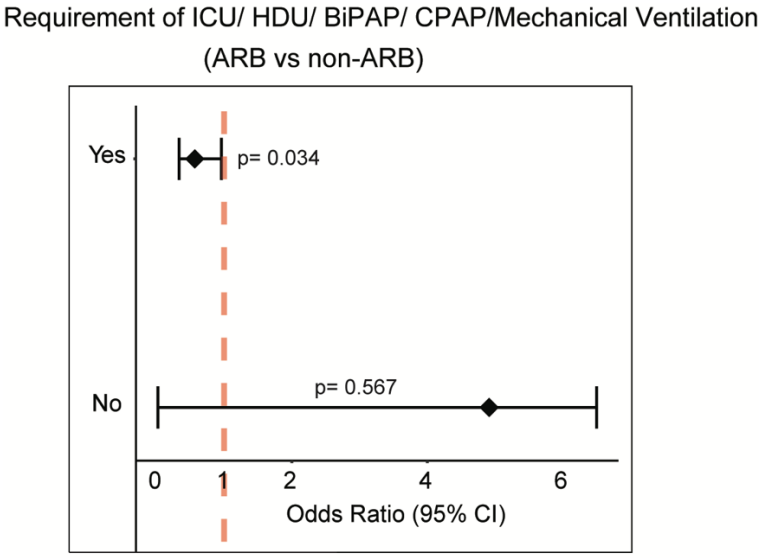

Figure 3. Odds ratios of the requirement of ICU, HDU, BiPAP, CPAP, or Mechanical Ventilation by patients with records of using ARB.

Discussion

Adjusting for baseline comorbidities, this study demonstrated no significant connection between prior ARB usage and death or severe COVID-19 in individuals diagnosed with COVID-19 while evaluating the patients' follow-up reports after 14 and 28 days. In assessments of oxygen need, however, ARB usage was associated with a lower mechanical ventilation/BiPAP/CPAP rate than other antihypertensive medication users.

The interaction between SARS-CoV-2 and the RAAS has prompted contradictory hypotheses on the influence of RAAS inhibitors on the progression of COVID-19 (Vaduganathan, Vardeny, Michel, J. J. V. McMurray, *et al.*, 2020a). Because animal studies demonstrated that ACEIs and ARBs upregulate expression of ACE2, a receptor important in the SARS-CoV-2 infection of host target cells, it was hypothesized that these drugs might facilitate viral binding and cell entrance (Soler *et al.*, 2008). In contrast, RAAS inhibitors may be beneficial for COVID-19 patients due to their effects on angiotensin II expression and consequent elevations in angiotensin 1-7 and 1-9, which have vasodilatory and anti-inflammatory properties that may mitigate lung damage (Vaduganathan, Vardeny, Michel, J. J. V. McMurray, *et al.*, 2020b). In mice infected with SARS-CoV, a close viral sibling of SARS-CoV-2, ARBs appear to have an innate protective effect against COVID-19 pneumonia by minimizing lung damage (Imai *et al.*, 2005). A case study was done under the title to find possible benefit of Angiotensin II Receptor Blockers in COVID-19 Patients. It is hypothesized that angiotensin II receptor blockers (ARBs) reduce interleukin-6 (IL-6) levels via RAAS regulation. Four COVID-19 patients treated with ARBs were examined for changes in angiotensin II and interleukin-6 levels in the study and their report supported the potential benefit of ARBs to improve the clinical outcomes of COVID-19 patients by controlling RAAS dysfunction.

A study analyzed the mechanisms of action of ACEIs and ARBs on the renin-angiotensin-aldosterone system, as well as the rationale for why these medications may influence the virulence of COVID-19 (Vaduganathan, Vardeny, Michel, J. J. V. McMurray, *et al.*, 2020b). The authors concluded that clinical recommendations on the use of ACEI/ARBs required further information on this topic. The notion that ACE2 inhibition may result in worse results in COVID-19 is supported by animal studies providing suggestive mechanistic insights (Diaz, 2020; Esler and Esler, 2020; Fang, Karakiulakis and Roth, 2020b). The new SARS-CoV-2 utilizes the cell membrane protein ACE2 as a receptor for entry into cells. There does not appear to be a clear mechanistic relationship between ACE2 overexpression and COVID-19 pathogenicity and consequences, as demonstrated by contradictory results from animal model studies (Zhong *et al.*, 2011; Burchill *et al.*, 2012). The ACE2 enzyme is widely expressed in the body, particularly in the epithelial cells of the alveoli, which serve as the entrance route for SARS-CoV-2 (Hamming *et al.*, 2004). Different relationships were seen between ACEI and ARB and a positive COVID-19 test and severity outcomes, potentially reflecting their distinct molecular biological targets. ACEI inhibits ACE, whereas ARB inhibits angiotensin II receptor AT1R; both routes are balanced by ACE2, the SARS-CoV-2 viral receptor. Infection with SARS-CoV-2 virus induces a number of physiological reactions. Earlier studies demonstrated that treatment with ACEI or ARB leads to upregulation of ACE2 in patients with type 1 or type 2 diabetes (Wan *et al.*, 2020) or in patients with hypertension (Li, Zhang and Zhuo, 2017). However, a recent study suggests that ACEI/ARB do not increase expression of the ciliary ACE2 receptor, and therefore, they may not

increase susceptibility to SARS-CoV-2 infection (Lee *et al.*, 2020). This is corroborated by the lack of convincing evidence associating ACEIs and ARBs to an increase in the severity of COVID-19 in human investigations (Patel and Verma, 2020; Vaduganathan, Vardeny, Michel, J. J. v McMurray, *et al.*, 2020). In COVID-19 patients with hypertension, it is unclear if the use of ACEIs alters the levels of ACE2 and provides SARS-CoV-2 with additional entry sites into cells, resulting in more harm. SARS-CoV (not SARS-CoV-2) decreases the amount of ACE2 and induces acute lung failure in mice (Kuba *et al.*, 2005). The viral load of SARS-CoV-2 is decreased when human cellular organoids are treated with recombinant ACE2 protein, and a similar effect has been described with ARB (Ferrario *et al.*, 2005). Consequently, the levels of ACE2 may fluctuate in the presence of ACEI or ARB, resulting in distinct physiological effects.

Hypertension is a significant comorbidity in COVID-19 patients. Recent evidence suggests that immunological dysfunction may contribute to poor outcomes in COVID-19 individuals with hypertension (Pan *et al.*, 2020). In light of the significance of managing hypertension, it has been demonstrated that when long-term drugs are discontinued during hospitalization, they are frequently not resumed owing to clinical inertia, consequently decreasing long-term results (Fonarow *et al.*, 2008). The findings of this study support the continuing treatment of ACEIs or ARBs in hospitalized COVID-19 patients. All of the patients in this trial had hypertension, and more than half were obese, two comorbidities that enhance the likelihood of poor outcomes with COVID-19 (Drager *et al.*, no date; Mcinnes and Mcmurray, 2020).

In the nested case-control susceptibility study, past usage of ACEI/ARB was not related with COVID-19 infection, according to research based on the Danish COVID-19 registries of 4,480 individuals gathered between February 22, 2020 and May 4, 2020. This retrospective cohort analysis did not find any association between ACEI/ARB and death or a composite outcome of death/severity of COVID-19 (Fosbøl *et al.*, 2020). Patients with hypertension or other comorbidities have a weak or nonexistent connection between ACEI/ARB and disease severity or mortality, according to global studies with small sample sizes. Studies involving 1,178 COVID-19-positive hospitalized patients in China (Li *et al.*, 2020), 1,200 inpatients in the United Kingdom (Bean *et al.*, 2020), 5,179 patients in Korea (Jung *et al.*, 2020), 111 patients in France (Lafaurie *et al.*, 2021), 1,603 patients in Italy (Bravi *et al.*, 2020), 338 patients in Saudi Arabia (Hakeam *et al.*, 2021a), 659 patients in Brazil (Lopes *et al.*, 2021), and 1,449 patients in the United States (Bauer *et al.*, 2021) revealed no statistically significant associations. The uncertainty around the function of RAAS inhibitors in COVID-19 patients has increased as a result of observational data and a systematic review. During the COVID-19 epidemic, scientific bodies have urged that patients not quit ACEI or ARB medication (*European Society of Cardiology Council on Hypertension. Position statement on ACE-inhibitors and angiotensin receptor blockers*, no date; Bozkurt, Kovacs and Harrington, 2020). No randomized clinical studies have been conducted to assess if ACEIs or ARBs are useful, detrimental, or neutral in terms of clinical outcomes in COVID-19 patients. We tried to investigate the manner of relationship between ARB use and Covid-19 severity from already published articles ***(Table 5)***.

Table 5. Use of ACEIs and ARBs and the risk of poor clinical outcome of COVID-19 from published articles.

Title of the study	**Year of the study**	**Country**	**Characteristics of population**	**Antihypertensive drug used**	**No. of exposed participants**	**No. of unexposed participants**	**OR (95% Class Interval, CI)**
Association between angiotensin blockade and COVID-19 severity in Hong Kong (Cheung, Hung and Leung, 2020)	2020	China	COVID-19	ARB	N.A.	N.A.	1.86 (0.31, 9.97)
Clinical Characteristics and Disease Progression in Early-Stage COVID-19 Patients in South Korea. (Choi *et al.*, 2020)	2020	Korea	COVID-19	ARB	16	277	1.60 (0.41, 6.23)
Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective	2020	France	COVID-19	ARB	36	983	18.4 (6.28, 53.9)

analysis of 1061 cases in Marseille, France. (Million *et al.*, 2020)							
Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. (Fosbøl *et al.*, 2020)	2020	Denmark	COVID-19	ARB	630	3585	0.90 (0.71, 1.14)
Risk of severe COVID-19 in hypertensive patients treated with renin-angiotensin-aldosterone system inhibitors. (Golpe *et al.*, 2020)	2020	Spain	COVID-19 with HTN	ARB	89	68	0.29 (0.1, 0.88)
Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with the Risk of Hospitalization and Death in Hypertensive Patients with Coronavirus Disease-19. (Khera *et al.*, 2020)	2020	US	COVID-19 with HTN	ARB	731	810	0.877 (0.611, 1.258)
Antihypertensive drugs in COVID-19 infection. (Pinto-Sietsma *et al.*, 2020)	2020	Netherland, Germany	COVID-19 (including clinical diagnosis)	ARB	91	678	0.94 (0.56, 1.58)
Role of Drugs Affecting the Renin-Angiotensin-Aldosterone System on Susceptibility and Severity of COVID-19: A Large Case-Control Study from Zheijang Province, China. (Yan *et al.*,	2020	China	COVID-19	ARB	N.A.	N.A.	0.77 (0.36, 1.63)

2020)							
Association Between Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19 Infection in South Korea. (Son, Seo and Yang, 2020)	2020	Korea	COVID-19 with HTN and taking anti-HTN medication	ARB	101	35	0.972 (0.424, 2.226)
Predictors of severe or lethal COVID-19, including Angiotensin Converting Enzyme inhibitors and Angiotensin II Receptor Blockers, in a sample of infected Italian citizens. (Bravi *et al.*, 2020)	2020	Italy	COVID-19 with HTN	ARB	228	315	0.83 (0.50, 1.40)
Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 in a western population. CARDIOVID registry. (López-Otero *et al.*, 2021)	2020	Spain	COVID-19	ARB	N.A.	N.A.	1.02 (0.28, 3.64)
Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). (Mehta *et al.*, 2020)	2020	US	COVID-19	ARB	98	1637	1.12 (0.59, 2.12)
Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. (Reynolds *et al.*, 2020)	2020	US	COVID-19	ARB	664	639	0.96 (0.77, 1.21)

Pre-existing traits associated with Covid-19 illness severity. (Ebinger *et al.*, 2020)	2020	US, China	COVID-19	ARB	N.A.	N.A.	1.38 (0.56, 3.42)
Association between chronic ACE inhibitor exposure and decreased odds of severe disease in patients with COVID-19. (Şenkal *et al.*, 2020)	2020	Turkey	COVID-19	ARB	105	78	0.61 (0.27, 1.40)
Comparative Impacts of ACE (Angiotensin-Converting Enzyme) Inhibitors Versus Angiotensin II Receptor Blockers on the Risk of COVID-19 Mortality. (Zhou *et al.*, 2020)	2020	China	COVID-19	ARB	560	2240	0.31 (0.18, 0.53)
Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. (Grasselli *et al.*, 2020)	2020	Italy	Critically ill COVID-19 patient in ICU	ARB	N.A.	N.A.	1.05 (0.85, 1.29)

Using a four-level COVID-19 severity scale, we did not discover a consistent relationship between ACEI or ARB usage and illness severity. A recent analysis of 590 COVID-19 patients from a single facility (78 ACEI/ARB users vs. 512 non-users) found no significant connection between ACEI/ARB usage and hospitalization, ICU admissions, mechanical ventilation, length of hospital stay, use of inotropes, or all-cause death (Bae *et al.*, 2020). There were no significant relationships between ACEI/ARB usage and hospitalization, ICU admission, mechanical ventilation, or death in a multicenter analysis of 338 patients. Nevertheless, the same study indicated that continued ACEI/ARB usage while hospitalization substantially reduced the risk of mortality (Hakeam *et al.*, 2021b). The link between ACEI/ARB usage and ICU/mortality was not significant in a study of 614 hospitalized COVID-19 patients with hypertension. However, ICU admission and death were significantly reduced among inpatients who continued ACEI/ARB therapy (Lam *et al.*, 2020). In a cohort of 826 COVID-19-positive individuals, there was no connection between the dosage of ACEI/ARB and COVID-19 infection or hospitalization (Dublin *et al.*, 2021). There is no research from Bangladesh that report on the connection between ARB and Covid severity. Using the medical records of Bangladeshi patients who had been diagnosed with covid-positive and previous hypertension and had been exposed to antihypertensive medicines for a period of 1-5 years, we sought to investigate this crucial research topic.

We noticed a statistically significant connection between ARB use and mechanical ventilation in our study. The finding that exposure to ARB is related with decreased likelihood of needing mechanical ventilators among COVID-19-positive hypertensive inpatients may be attributed to proximal factors, such as unmeasured clinical characteristics that may obfuscate these results. Since ARB use was also related with a decreased likelihood of needing additional oxygen support, such as nasal cannula, BiPAP, and CPAP, there is sufficient evidence from other clinical factors to indicate a consistent connection between ARB use and oxygen assistance among covid-positive patients. Further research is required to determine the molecular relationship between ARB use and oxygen level in Covid-positive individuals. Patients who used ARB had a reduced chances ratio of being released without Oxygen and at

home with Oxygen compared to patients who got non-ARB as anti-hypertensive medicines, however the ICU and CCU odds ratio was greater for ARB-receiving patients compared to non-ARB-receiving patients. So, we could not reach to a conclusion of whether ARB has a beneficial or detrimental effect in Covid-positive patients.

Conclusion

In our investigation, we observed a statistically significant correlation between ARB usage and mechanical ventilation. Exposure to ARB is associated with a lower chance of requiring mechanical ventilation in COVID-19-positive hypertensive individuals. ARB usage was also associated with a lower risk of requiring supplemental oxygen support, such as nasal cannula, BiPAP, and CPAP, indicating a continuous link between ARB use and oxygen assistance among covid-positive patients. ARB usage increases hospitalization risk among COVID-19-positive hypertensive patients (including all inpatients admitted to ICU or CCU). ARB usage and patient mortality were not significantly linked.

Patient Involvement and Research Ethics Approval

The protocols adhered to the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki and were approved by the institutional ethics committee at Central Police Hospital, Dhaka. All patients provided written informed consent according to local guidelines.

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Authors' Contributions

FM, MRS, KMA, SMA, DD, MZA, MSI, MNSUA, and MS contributed to the conception, and data collection, and made necessary laboratory arrangements regarding the study. FKR and MS designed and developed the methodology. FKR curated the data, performed all statistical and exploratory analyses, and prepared the figures. SMA and DD helped to develop the figures and tables generated. FKR interpreted all the results and wrote the first draft. FKR, FM, MRS, KMA, SMA, DD, MZA, MSI, MNSUA, and MS revised and edited the manuscript. All authors have read and agreed to submit the final version of the manuscript.

Data Availability

Kindly contact the corresponding author at the given email (mousumi_sanyal85@yahoo.com) for data availability. Data will be provided upon request.

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