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Impact of angiotensin receptor blocker as antihypertensive in assessing mortality in patients of COVID-19: A single tertiary care center study

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Abstract:

BACKGROUND: The angiotensin-converting enzyme 2 (ACE2) receptor, a membrane receptor present in the respiratory system, the gastrointestinal tracts, the heart, and the kidney is the entry point for SARS-CoV-2 to enter human cells. Concerns were raised about the influence of using antihypertensive drugs like angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in individuals with COVID-19 due to its tight relationship with the ACE2 receptor. The aim of this study was to investigate the impact of being on an Angiotensin Receptor Blockers (ARB) on mortality in patients consecutively diagnosed with COVID-19.

MATERIAL AND METHODS: This is the retrospective observational study done in all patients consecutively diagnosed with COVID-19 from January 2021 to June 2021. All related patient information and clinical data was retrieved from the hospitals electronic medical record system.

RESULTS: In this study, out of 500 patients, 51 died, having mean age of 66.92 ± 10.85 years. 144 (28.8%) patients were on angiotensin receptor blockers as antihypertensive treatment, 142 (28.4%) having other antihypertensive and 214 (42.8%) were not on any treatment. Out of 51 Death 7 (4.9) patients were on ARBs, 15 ± 10.6 were on other medication [OR 2.31 (0.94–6.22, $P = 0.077$) univariable; OR 2.57 (1.00–7.23, $P = 0.058$) multivariable] and 29 ± 13.6 had no treatment at all [OR 3.07 (1.38–7.80, $P = 0.010$) univariable; OR 3.36 (1.41–9.08, $P = 0.010$) multivariable].

CONCLUSION: Use of ARB medications for the hypertensive patients who acquire COVID-19 infection has shown protective effects of such medications on COVID-19 disease severity in the term of mortality and the mortality rate among hypertensive patients on COVID-19 with ARBs/ACE inhibitors showed significant differences as compared to other antihypertensives.

Keywords:

ARB (Angiotensin II receptor blocker), COVID – 19, ICU (intensive care unit), mortality

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Introduction

In December 2019, a new coronavirus (SARS-CoV-2) caused Coronavirus Disease 2019 (COVID-19) in Wuhan, Hubei Province, China. With a slew of instances in practically every country, this sickness has put doctors all across the world on high alert.[1] SARS-CoV-2 infects alveolar cells by attaching to the S-receptor binding domain and the angiotensin-converting enzyme (ACE) 2 receptor, similar to SARS viruses, and induces a cascade of clinical alterations in patients.[2]

Previous studies on SARS-CoV have shown that the elevation of angiotensin II contributes to the occurrence and aggravation of acute pneumonia, and that SARS-CoV infection induces a decrease in

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the expression of tissue ACE 2.[3] Based on these findings, researchers have advocated for the use of RAS inhibitors such as ACEI or ARBs to treat SARS-CoV-2-induced pneumonia.[4] Other investigations, however, have raised concerns by demonstrating that several RAS inhibitors increase ACE2 expression[5]; thus, using RAS inhibitors in COVID-19 patients may worsen the condition.[6] ACE2 regulates blood pressure and fluid balance by modulating the RAAS, a key neurohormonal pathway.[5]

Angiotensin II, the RAAS's final product, is a crucial vasoactive hormone that binds to angiotensin II receptor type 1 (AT1) in the heart, lungs, blood vessels, kidneys, and adrenal glands, and is involved in myocardial hypertrophy and fibrosis, inflammation, vascular remodeling, and atherosclerosis.[7] ACE2 inactivates angiotensin II, thus reducing its vasoconstrictive and myeloproliferative effects, which has impact on numerous human tissues including the nasal epithelium, heart, kidneys, and lungs.[7]

SARS-CoV-2 uses its spike(S) protein to connect to the ACE2 receptor, allowing it to enter host cells. This complex is endocytosed, resulting in ACE2 downregulation and local angiotensin II build up. Local stimulation of the RAAS is hypothesized as a mechanism for severe lung injury, which is a characteristic of COVID-19 and a key cause of morbidity and mortality.[8,9]

Concerns have been raised concerning the potential risk associated with RAAS inhibitors due to the overrepresentation of hypertension among critically ill COVID-19 patients. Recent debates have centered on whether ACE-Is and ARBs increase ACE2 expression, making COVID-19 infection easier or leading to a more severe infection.[10] ACE2, one of the renin-angiotensin system's components, is, on the other hand, one of the antihypertensive medicines' targets. Many COVID-19 patients are hypertensive, which has sparked a lot of debate over how to treat hypertension individuals.

There is currently no research on the systematic and thorough epidemiology and clinical aspects of COVID-19-positive hypertensive individuals. In addition, more research on whether hypertension impacts the clinical results of COVID-19 patients is needed. This study highlights about relationship between ARBs/other antihypertensives and clinical outcomes in patients with COVID-19.

Materials and Method

Study design and setting: This retrospective observational study was conducted in the Department of Medicine, Datta Meghe Institute of Medical Sciences, Wardha, Maharashtra, India, from period of 21 January 2021 to 21 May.

Ethical consideration

Ethical clearance has been obtained from the institutional ethics committee (IEC number: DMIMS DU/IEC/2022/834).

Study participants and sampling

Inclusion criteria were COVID-19 patients who tested positive by RT-PCR aged 30 years or above were diagnosed case of hypertension irrespective of medication they are on. Exclusion criteria were patients less than 30 years, pregnant females, and other comorbidities like ischemic heart disease, diabetes mellitus, chronic kidney disease, hematological disorders.

Data collection tool and technique

A total of 1250 patients admitted for COVID-19 infection were considered for this study. After applying exclusion criteria, a total of 500 patients meeting the inclusion criteria were included in the study. The parameters measured in this study included age, gender, comorbidities, the medication used for hypertension, laboratory parameters, HRCT score, outcome of the patient. The DxH 800 hematology analyzer (Beckman Coulter, South Drive, IN) was used to assess the whole blood count, while the Vitros 5600 was used to examine all inflammatory markers, renal function tests, and liver function tests (Ortho Clinical Diagnostics, Raritan, NJ). Within 48 hours of admission, all of the patients had a high-resolution computed tomography (HRCT) scan. Comorbidities such as hypertension, diabetes, and bronchial asthma were screened in all recruited patients. All of the patients were monitored until they were cured or died. Figure 1 shows the flowchart of methodology for this study.

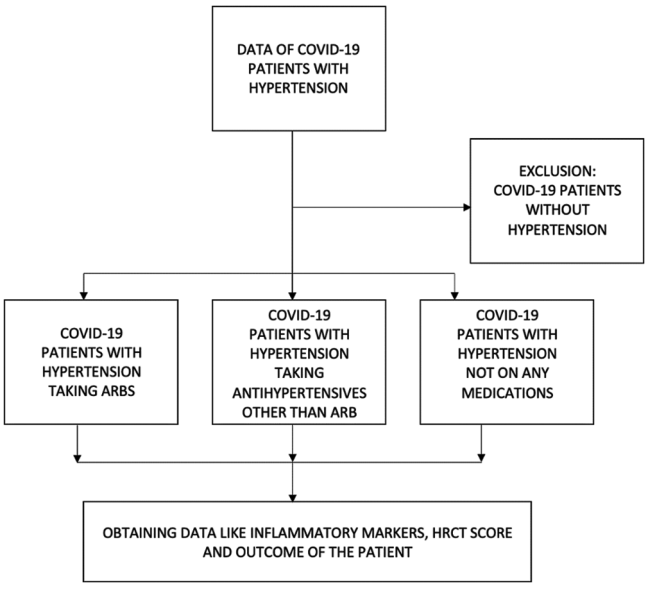

Figure 1: Flow chart of the study

Statistics

For continuous data, descriptive statistics were used to report mean and standard deviations, and for categorical variables, frequency statistics were used to determine numbers and percentages. For continuous variables, the independent t-test was employed, and for categorical variables, the Chi-squared test was utilized. Odds Ratio (OR) with 95% Confidence Intervals (CI) was calculated. Statistical significance was set at P value < 0.05.

Result

In this study out of 500 patients, 51 died, having mean age of 66.92 ± 10.85 years. Total duration of hypertension was 7.10 ± 6.19 years. 144 (28.8%) patients were on angiotensin receptor blockers (ARBs) as antihypertensive treatment, 142 (28.4%) having other antihypertensive and 214 (42.8%) were not on any treatment. Other base line characteristics are shown in Table 1.

Regression analysis showed mean duration of hypertension as 7.2 ± 5.3 years. Out of 51 deaths, 7 (4.9%) patients were on ARBs; odds ratio in these group of patients were not significant as others odds ratio were calculated in comparison with ARBs

Table 1: Baseline parameters

All parameters	Mean±SD
Age (years)	66.92±10.85
Male	335 (67%)
Female	165 (33%)
Duration of hypertension (years)	7.10±6.19
Treatment	
ARBs	144 (28.8%)
Other antihypertensive treatment	142 (28.4%)
Hypertensive but not on treatment	214 (42.8%)
Compliant (yes)	286 (57.2%)
Medications	
ARBs	144 (50.3%)
Other medications	142 (49.7%)
HRCT Score	14.83±2.85
HRCT Severity	
Moderate	231 (46.2%)
Severe	269 (53.8%)
Hemoglobin (g/dL)	11.92±2.42
TLC (per mm^3)	12330.02±8111.04
Platelet Count (Lac)	16.42±321.91
ESR (mm/Hr)	47.13±24.07
CRP (mg/L)	17.02±35.17
D-Dimer	3.23±4.32
Ferritin	572.71±372.52
Uric Acid	6.14±4.09
LDH	892.61±1028.54
S. Vitamin D	34.62±20.83
Outcome	
Discharge	449 (89.8%)
Death	51 (10.2%)

treatment. 15 ± 10.6 patients died who were on other medication [OR 2.31 (0.94–6.22, P = 0.077) univariable; OR 2.57 (1.00–7.23, P = 0.058) multivariable] and 29 ± 13.6 had no treatment at all [OR 3.07 (1.38–7.80, P = 0.010) univariable; OR 3.36 (1.41–9.08, P = 0.010) multivariable], as shown in Table 2.

The area under the ROC curve (AUROC) for duration of hypertension (years) predicting outcome as death was 0.53 (95% CI: 0.451–0.61), thus demonstrating poor diagnostic performance. It was not statistically significant (p = 0.473). At a cut-off of duration of hypertension (years) ≥3, it predicts sensitivity of 84% and a specificity of 24% as shown in Figure 2.

Discussion

Among COVID-19 positive patients, the present study found a significant association between ARBs use and mortality when compared with those who are on other anti-hypertensive medication as well as with those who are not taking any antihypertensive treatment. Several studies have postulated that the use of ARBs may influence COVID-19 severity, it's even been linked to poorer outcomes, according to several studies. This came as a result of their preliminary findings which showed that these medicines were linked to worsening COVID-19 illness severity.

The use of ARBs was not linked with COVID-19 disease severity or mortality in a retrospective study of 1,178 hospitalized COVID-19 disease patients in Wuhan City, although the study did not control for confounding variables.[11]

Among a survey of 558 hospitals in patients admitted with COVID-19 disease, Tetlow *et al*.[12] found no link

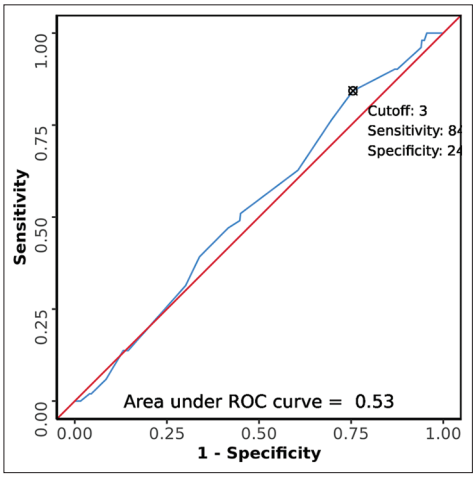

Figure 2: ROC curve analysis showing diagnostic performance of duration of hypertension (years) in predicting outcome: Death vs. discharge

Table 2: The regression analysis for the dependent variable using all the predictor variables

Dependent: Outcome	Discharge	Death	OR (univariable)	OR (multivariable)
Age (years)				
Mean (SD)	67.1 (10.9)	65.5 (10.0)	0.99 (0.96-1.01, *P*=0.316)	0.98 (0.96-1.01, *P*=0.277)
Duration of hypertension (years)				
Mean (SD)	7.1 (6.3)	7.2 (5.3)	1.00 (0.95-1.05, *P*=0.914)	1.03 (0.97-1.09, *P*=0.271)
Treatment				
ARBs	137 (95.1)	7 (4.9)	-	-
Other medications	127 (89.4)	15 (10.6)	2.31 (0.94-6.22, *P*=0.077)	2.57 (1.00-7.23, *P*=0.058)
Non-treatment	185 (86.4)	29 (13.6)	3.07 (1.38-7.80, *P*=0.010)	3.36 (1.41-9.08, *P*=0.010)
HRCT score				
Mean (SD)	14.9 (2.9)	14.2 (2.7)	0.92 (0.83-1.02, *P*=0.118)	0.90 (0.80-1.01, *P*=0.075)

between ARB use and acute renal injury, macrovascular thrombi, or mortality.

Furthermore, an observational study by Braude *et al*.[13] on 1,371 patients revealed that ACEI/ARB use was not related with higher mortality, and it was found to be associated with shorter in-hospital stay.

Similarly, Senkal *et al*.[14] found that 165 COVID-19 patients had severe disease (hospitalization for more than 14 days, ICU admission, or death), and that taking an ACEI was associated with lower disease severity, milder infiltrations on CT, lower levels of C-reactive protein and ferritin, and shorter hospital stay.

Zhou *et al*.[15] examined 15,504 patients from 17 different hospitals in China to see if there was a link between in-hospital ACEI/ARB use and COVID-19 all-cause death after 28 days. After adjusting for unbalanced factors and in-hospital drugs in which patients were matched for age, gender, illness severity, co-morbidities, and calcium channel blocker use, ACEI/ARB use was linked to a lower risk of 28-day all-cause mortality from COVID.

Bean *et al*.[16] examined the risk of COVID-19 disease severity in 1,200 individuals, which was similar to the current study. 399 (33%) patients, who were on ACE inhibitor or an ARB, had a decreased risk of ICU admission or mortality [OR, 0.63 (95% CI: 0.47–0.84)].

In a study by Flacco *et al*., total of 9,890 patients with hypertension on ACEI/ARB use was linked to severe or lethal COVID-19 disease. They found no significant link between ACEI [CI 0.65–1.26] or ARB [CI 0.75–1.12] use and severe or lethal COVID-19 disease.[17,18]

All the patients of COVID-19 should undergo 2D-echocardiography to assess the ejection fraction as it may impact the effect of ACEI or ARB.[19,20]

Limitation and recommendation

Limitations—This study was limited to a single hospital at Wardha district so that it cannot be generalized. We also did not collect data on medication dose and have not investigated the differences between the use of ACEI or ARB. People who are not on ACEI or ARB may be on an alternate treatment or not on any treatment also resulted in confounding. Data on dose and duration of the medication was not collected which added up to the limitations.

Conclusion

The preventive effects of ARB on COVID-19 disease severity and mortality are becoming clearer over time in both waves of this pandemic, and the findings of this study support the use of this medicine in such patients. As compared to other antihypertensives, the death rate for COVID-19 hypertension patients taking ARBs/ACE inhibitors was significantly less. In hypertensive patients with COVID-19, angiotensin II receptor blockers (ARBs)/ACE inhibitors shouldn't be stopped.

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Conflicts of interest

There are no conflicts of interest.

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