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SHORT REPORT

Chronic Prescription of Renin-Angiotensin-Aldosterone System Inhibitors and Hospital Outcomes in Patients with Hypertension and COVID-19

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Introduction: A greater association of systemic arterial hypertension with worse prognosis in patients hospitalized with COVID-19 was described. Early in the pandemic, concerns were raised that the use of angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) could lead to unfavorable outcomes.

Objective: To evaluate whether there is an association between the use of the ACEi and ARB medications with unfavorable outcomes in hypertensive patients hospitalized with COVID-19.

Methods: This is a descriptive and retrospective study, collecting data through electronic medical records of patients with COVID-19 admitted to a University Hospital in 2020. Demographic data, use of ACEi or ARB medications, comorbidities, and outcomes, defined by the use of invasive ventilatory support (IVS), renal failure with progression to renal replacement therapy, and death were evaluated.

Results: 700 medical records were analyzed, 374 were of hypertensive individuals. The mean age of the patients was 66 ± 14 years, 51% were male, and 89% were white. There was a significantly higher prevalence of hospital discharge among patients who received ACEi/ARB compared to those who did not take these medications, (p-value = 0.027). There was no statistically significant difference in the use of ACEi/ARB for IVS (p-value = 0.062) and for renal replacement therapy (p-value = 0.587).

Conclusion: The use of ACEi/ARB drugs is not associated with worse outcomes in individuals with COVID-19. The present study demonstrated lower mortality rate associated with the use of these classes of drugs, similar to recent studies.

Keywords: hypertension, COVID-19, angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, hospital mortality

Introduction

Since the identification of SARS-COV-2 respiratory infection in China in 2019, several reports have demonstrated a greater association with systemic arterial hypertension leading to a worse prognosis in affected patients.[1]

Currently, the global number of COVID-19 cases exceeds 777 million and 7,087,731 deaths have been reported.[2] In Brazil, the numbers are alarming, with more than 39 million cases and 715,108 deaths recorded.[3]

Several reports have indicated that individuals with chronic degenerative diseases, such as hypertension, renal failure (RF) and diabetes mellitus (DM), had increased risk of hospitalization, morbidity and mortality due to COVID-19.[4]

There is controversy regarding the effect of antihypertensive drugs that act on the renin-angiotensin-aldosterone system (RAAS) and clinical outcomes related to COVID-19 infection.[5] Consequently, renin-angiotensin-aldosterone system (RAAS)

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inhibitors [angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)] are targets of research. RAAS inhibitors promote an upregulation of the angiotensin-converting enzyme 2 (ACE 2), which may be the key link for the entry of SARS-COV-2 into the body.[6]

RAAS inhibitors could act as facilitators of COVID-19 infection. At the beginning of the pandemic, the need to suspend this class of drugs in hospitalized patients was questioned.[6] However, an Italian study found no association between ACE inhibitors or ARBs with COVID-19-related clinical outcomes and, after correcting for other variables such as age and the presence of other cardiovascular diseases, hypertension alone was not a risk factor for worse outcomes.[7]

Corroborating a previous study, other researchers concluded that there is no need to avoid the use of these drugs in patients with COVID-19.[8] A detailed investigation demonstrated that the use of ACE inhibitors reduced the inflammatory process induced by the virus and increased the intrinsic anti-viral cellular response, while treatment with ARBs increased epithelial immune cell interactions.[9] A randomized study comparing the withdrawal or continuation of ACEIs or ARBs in patients hospitalized with mild to moderate COVID-19 did not observe a difference in mortality. Then, it is not recommended to discontinue these classes of drugs.[10]

Given the relevance of the topic, the present study aims to evaluate the use of drugs that act on the RAAS (ACE inhibitors and ARB) and their association with the outcomes of hypertensive patients hospitalized with COVID-19.

Methods

An exploratory, descriptive and retrospective study was carried out using data from electronic medical records of patients with COVID-19, admitted to a University Hospital in 2020. The research was approved by the local Research Ethics Committee (CAAE n° 58647722.0.0000.5415, dated July 15, 2022).

The inclusion criteria were hospitalized patients aged 18 years or older with confirmed COVID-19 infection and hypertension, as reported in their medical records according to American Hypertension Society criteria.[11] Polymerase Chain Reaction (PCR) or the COVID-19 antigen test was used to analyze samples from the upper airways to confirm COVID-19 positivity. Patients were hospitalized for COVID-19 between March and July 2020. The sample consisted of hypertensive patients and were separated into 2 groups according to previous use of RAAS inhibitors (yes or no).

The exclusion criteria were: patients on dialysis, kidney transplant patients, patients with terminal illnesses, pregnant women, and medical records with incomplete information.

The analysis included demographic data (age, sex, race), current medicine use (ACE inhibitor or ARB classes of medications), and comorbidities with the following complications being considered as outcomes: use of invasive ventilatory support (IVS), renal failure with progression to renal replacement therapy and death.

The analysis included descriptive statistics, such as the mean, standard deviation, percentiles, and frequencies and percentages for categorical variables. The behavior of continuous variables was assessed using descriptive statistics and the Shapiro–Wilk test to verify theoretical normality. The evaluation of data on the use of medications that act on the RAAS with the outcomes was conducted using the Mann–Whitney (non-normal) and Pearson's χ^2 (categorical data) tests. For the Mann–Whitney test, the effect size calculated was the point-biserial r, which ranges from −1 to 1, indicating the strength of the association between the variables and considering the cutoff points: r = 0.10 to 0.29 (small effect); r = 0.30 to 0.49 (medium effect); r ≥ 0.50 (large effect). For the Pearson's χ^2-test, the effect size calculated was Cramér's V. The statistical software R (v. 4.4.1, R Core Team, 2024) was used.

Results

A total of 700 patients were analyzed, 374 of whom were hypertensive. The mean age was 66 ± 14.43 years. Of the 374 individuals, 191 were male (51%) and 332 (89%) were white (Table 1).

Diabetes mellitus (DM) was reported in 174 (46%) of the cases, cardiovascular disease in 65 (17%) participants and previous non-dialysis chronic kidney disease (CKD) in 22 (6%) patients. ACE inhibitors or ARBs were used by 266 (71%) individuals. There was an association between the need for IVS and death. Among the individuals who died, 75% used IVS, while only 15% of those discharged from the hospital did (p-value < 0.001).

Table 1 Demographic Data, Comorbidities, Outcomes and Medications Used by Patients Hospitalized for COVID-19

Variables	N = 374
Age (years)	65.95 ± 14.43
Male	192 (51%)
Diabetes mellitus	174 (46.5%)
Invasive ventilatory support	131 (35%)
Renal replacement therapy	33 (9%)
Hospital death	121 (32%)
ACEi	102 (27.2%)
ARB	164 (43.7%)
Beta blockers	74 (19.8%)
Diuretics	89 (23.8%)
Antiplatelets	53 (14.2%)

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

There was no statistically significant difference in the use of ACE inhibitors/ARB in patients requiring IVS (p-value = 0.062) or renal replacement therapy (p-value = 0.587). However, the highest prevalence of hospital discharge occurred among patients who received ACEI/ARB (75%) compared to those who did not receive these medications (25%; p-value = 0.027), with an effect size of 0.10 (Table 2).

Table 2 Outcomes in Patients with Hypertension and COVID-19 in Angiotensin-Converting Enzyme Inhibitor (ACEi) and Angiotensin Receptor Blocker (ARB) Use

Invasive ventilatory support				
Variable	**No N = 243 (%)**	**Yes N = 131 (%)**	**p-value**	**Effect size (r)**
ACEi/ARB			0.062[a]	0.08[b]
No	62 (26)	46 (35)		
Yes	181 (74)	85 (65)		
Renal replacement therapy				
ACEi/ARB	**No N = 340 (%)**	**Yes N = 34 (%)**	**p-value**	**Effect size (r)**
No	98 (29)	12 (35)	0.587[a]	0.00[b]
Yes	242 (71)	22 (65)		

(*Continued*)

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Table 2 (Continued).

Outcomes				
ACEi/ARB	**Hospital discharge N = 253 (%)**	**Hospital Death N = 121 (%)**	**p-value**	**Effect size (r)**
No	64 (25)	44 (36)	0.027[a]	0.10[b]
Yes	189 (75)	77 (64)		

Notes: [a]Teste χ^2 de Pearson; Teste de Mann–Whitney. [b]Effect size; r biserial point.

Discussion

This study analyzed the use of ACE inhibitors or ARBs in a hypertensive population hospitalized with COVID-19 with the result being favorable in relation to mortality, thus the hospital discharge rate was higher in patients who used this class of medications. This finding is in agreement with the scientific literature, confirming that the use of ACE inhibitors/ARBs is not associated with an increase in mortality or severity.[8–10,12,13] On the contrary, there is a reduced chance of mortality for patients with COVID-19 who use of these medications.[14]

At the beginning of the COVID-19 pandemic, there was concern that drugs that act on the RAAS could be correlated to higher morbidity and mortality, since the SARS-CoV-2 virus utilizes ACE-2 as an entry receptor, primarily in lung and kidney cells.[15] As it was thought that the enzyme increases in patients taking ACE inhibitors and ARBs, this could potentially lead to a more severe infection due to enhanced viral entry into cells and subsequent replication.[16]

A prominent study conducted in Wuhan, China, among hospitalized patients with COVID-19, revealed a history of hypertension in 29.5% (850/2877) and identified it as a critical factor influencing disease severity. Furthermore, the relative risk of mortality was twice as high in the hypertensive population. However, this study shows that the regular use of antihypertensive medications brings health benefits, and it is recommended that hypertensive patients continue their prescribed treatment.[14]

Disorganization of the RAAS has been linked to damage and fibrosis in several organs such as the kidney, heart, and vascular wall. This contributes to increased cardiovascular risk in patients with hypertension, DM and previous cardiovascular disease. Therefore, the use of drugs that attenuate the activity of the RAAS has been shown to reduce cardiovascular events in high-risk individuals, reducing mortality mainly by preventing the progression of kidney disease.[17] In this sense, continuing to prescribe this class of drugs in hypertensive patients hospitalized with COVID-19 could offer cardiovascular protection.[18,19]

This study's findings show that the use of ACE inhibitors/ARBs was associated with a more favorable prognosis as evidenced by higher discharge rates. These findings are in line with other studies that indicate a possible clinical benefit with the use of these classes of antihypertensives in critical situations, including reduced mortality.[20]

The main strengths of this study are the exclusive sample of hypertensive patients, the diagnostic confirmation of COVID-19 by approved and accepted methods of viral detection and the data collection carried out in a single reference hospital specialized in the treatment of the disease.

Regarding limitations, retrospective studies are subject to the absence of complete information, as they depend on the quality and consistency of the available records.

Conclusion

The use of antihypertensive drugs that act on the RAAS is not associated with adverse clinical outcomes but is linked to reduced mortality from COVID-19. Despite the actions of this class of drugs in facilitating the entry of the virus into the lungs, the increase in the intrinsic antiviral cellular response and the reduction in cardiovascular risk associated with these drugs may have contributed to lower mortality in the present study.

Abbreviations

ACEi, Angiotensin-Converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; IVS, Invasive Ventilatory Support; RF, Renal Failure; DM, Diabetes Mellitus; CKD, Chronic Kidney Disease; RAAS, Renin-Angiotensin-Aldosterone System; PCR, Polymerase Chain Reaction; CAAE, Certificate of Ethical Appreciation; WHO, World Health Organization.

Data Sharing Statement

Data will be available upon reasonable request to the corresponding author.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of Medical School at Sao Jose Rio Preto (FAMERP) and followed the ethical principles of the Declaration of Helsinki (CAAE n° 58647722.0.0000.5415, dated July 15, 2022). As it was a retrospective study, the patient's consent form was waived. However, we declare that patient data is kept confidential.

Consent for Publication

All authors read and approved the final manuscript draft.

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Author Contributions

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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