# Correlation of In-Hospital Antihypertensive Therapy with Clinical Outcomes in Hypertensive Patients Admitted with COVID-19: A Retrospective Single-Centre Study in South Africa

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*Receive date:16/11/2024*
*Revise date:4/8/2025*
*Accept date:9/9/2025*
*Publish date:15/9/2025*
*Keywords:*
*Hypertension, COVID-19, ACEIs/ARBs, Mortality, South Africa, Black population*

**Background and study aim:** Hypertension has been associated with severe COVID-19 manifestations and increased mortality rates, particularly in low- and middle-income countries. This study aimed to elucidate the impact of inpatient antihypertensive therapy on COVID-19 outcomes among hypertensive patients in a predominantly black population in South Africa, focusing on the role of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

**Patients and Methods:** A retrospective analysis was conducted at King Edward VIII Hospital, South Africa, encompassing hypertensive patients hospitalised with laboratory-confirmed SARS-CoV-2 infection from June 2020 to December 2021. Data on demographics, comorbidities, antihypertensive therapy, clinical signs, laboratory markers, and outcomes were analysed. Statistical methods included univariate and multivariate logistic regression to identify predictors of mortality.

**Results:** The study included 205 hypertensive patients with COVID-19, of whom 115 received ACEI/ARB therapy. Patients on ACEI/ARBs exhibited significantly lower requirements for oxygen therapy, steroid therapy, and mechanical ventilation. Notably, ACEI/ARB therapy was associated with a significant reduction in mortality (aOR=0.144, p<0.001), higher median oxygen saturation (p=0.002), and lower inflammatory markers on presentation (p<0.05). Conversely, initial findings suggested an increased mortality risk with calcium channel blocker use (OR=2.783, p=0.001), which did not remain significant after adjusting for confounders (aOR=1.388, p=0.544).

**Conclusion:** ACEI/ARB use was associated with improved outcomes in hypertensive patients hospitalised with COVID-19 in a predominantly black population in South Africa. These findings support the continuation of ACEI/ARB therapy in hypertensive patients with COVID-19. Further research is warranted to explore the mechanisms underlying these associations and to validate these findings in larger, prospective studies.

## INTRODUCTION

The emergence of COVID-19 as a global pandemic has unveiled the complex interplay between chronic illnesses and infectious diseases, particularly highlighting the vulnerability of individuals with pre-existing conditions [1,2,3]. Among these, hypertension has emerged as a significant factor. Through extensive international research, the correlation between this chronic condition and SARS-CoV-2 infection has been better understood – hypertension is not only a common underlying condition in severe COVID-19 cases, but is also linked to an increased risk of serious illness and death in hospitalised patients [4,5,6,7,8,9,10,11.[

In addition to the abovementioned adverse effects of the disease itself, matters are further complicated by theoretical concerns regarding the influence of certain antihypertensive therapies - angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in particular - on COVID-19 outcome [4].

The entry of SARS-CoV-2 into human cells occurs through the attachment of the virus's spike protein to the angiotensin converting enzyme-2 (ACE-2) receptor on the host cell surface. The physiological consequence of ACE-2 binding results in the production of angiotensin (1-7) which, via the Mas receptor, exerts vasodilatory, natriuretic, diuretic, anti-proliferative and anti-fibrotic functions. There is a theoretical concern that the use of ACEIs and ARBs upregulate ACE-2 expression which may facilitate viral entry into the cell – potentially elevating the risk of infection and severity [4 .[

Conversely, several mechanisms of potential benefit of these drugs have also been postulated. Increased ACE-2 expression may raise the levels of angiotensin (1-7) with its resultant beneficial effects. Additionally, the use of these drugs may increase the interaction between angiotensin 2 and the ACE-2 receptor, with possibly reduced binding affinity for this virus. Furthermore, the blanket discontinuation of these medications in individuals with heart failure, for which these drugs have a clear mortality benefit, may lead to increased admissions and mortality [4 .[

Although initial studies suggested a higher risk of death associated with the use of ACEIs and ARBs in patients with COVID-19 and coexistent hypertension, numerous reports since then have demonstrated a lack of a significant association with in-hospital mortality and disease severity [12,13,14,15,16]. Interestingly, some studies even demonstrate a lower risk of death with the inpatient use of these agents [15,16,17,18,19,20]. Additionally, some studies demonstrate a possible protective effect with the pre-hospital use of ACEIs and ARBs as well, possibly resulting from a reduced inflammatory response [21,22]. As a result, most societies recommend against routine discontinuation of ACEIs and ARBs, unless indicated for other reasons [4,23.[

Although extensive research has explored the link between hypertension and COVID-19, there remains a significant lack of data focused on predominantly African populations. Black hypertensives are more likely to have severe and resistant hypertension, as well as lower plasma renin and aldosterone levels compared to other race groups – potentially influencing response rates to treatment with ACEIs and ARBs [24,25]. This highlights the importance of conducting targeted research within this population to more clearly understand the relationship between hypertension and COVID-19 in African communities.

Addressing this gap, our study sought to explore the effect of antihypertensive therapy on COVID-19 outcomes in South Africa, aiming to enrich both local and global understanding of this association. This endeavor not only contributes to the body of knowledge but also aims to inform policies and treatment strategies in the face of future SARS-CoV-2 outbreaks.

## PATIENTS AND METHODS

**Aim:**

This study sought to assess the relationship between antihypertensive therapy and COVID-19 outcomes in a primarily African patient population .

**Study Design/Setting:**

A retrospective observational study was undertaken at King Edward VIII Hospital (KEH), a tertiary care institution located in the KwaZulu-Natal province of South Africa .

**Sample Selection:**

The study included all hypertensive patients aged 13 years and older with a laboratory-confirmed diagnosis of COVID-19 admitted to KEH between 1 June, 2020 and 31 December, 2021. Pregnant patients and those without necessary data available were excluded from the study .

**Data Collection and Ethical Consideration:**

Ethical approval for this study was obtained from the University of KwaZulu-Natal Biomedical Research and Ethics Committee (BREC/00005457/2023) along with authorisation from the Department of Health and local site approval from King Edward VIII Hospital. The need for informed consent was waived by the Biomedical Research and Ethics Committee due to the retrospective nature of the study .

The following data, sourced from the medical records of the sample population, was


DOI: 10.21608/aeji.2025.336759.1430

examined and interpreted in alignment with the objectives of the research study:

- Demographics
- Comorbidities
- Antihypertensive therapy
    - Drug classes
    - Number of agents
- Baseline clinical signs
- Baseline inflammatory markers
- Treatment received
- Outcome:
    - Survivor
    - Non-survivor
- Duration to death or discharge

**Statistical Analysis:**

The data was analysed using SPSS v27.0 and Stata version 17. Depending on the data distribution, data was reported as mean (standard deviation) (SD) or median (interquartile range) (IQR), and compared using Student's t-test or the Mann-Whitney U-test, respectively. Categorical data was displayed as frequencies and percentages and compared using chi-squared test or Fisher's exact test for smaller frequencies. To determine factors predicting mortality related to antihypertensive therapy, both univariate and multivariate logistic regression analyses were conducted – expressing both unadjusted and adjusted odds ratios with their respective confidence interval. A log rank test compared survival rates between individuals using ACEIs/ARBs versus those not using ACEIs/ARBs. A p-value less than 0.05 represented statistical significance .

**Study Procedure:**

The sample population comprised hypertensive patients hospitalised with COVID-19; all of whom were receiving antihypertensive therapy. The sample was divided into those receiving ACEIs/ARBs and those not receiving ACEIs/ARBs with comparisons made in terms of demographics, clinical features, and patient outcome. The cohort was also divided into survivors and non-survivors with comparisons made to identify predictors of mortality. Blood pressure was recorded using standardised automated devices equipped with appropriately-sized arm cuffs. The primary outcome of intertest was in-patient mortality.

**Definitions:**

COVID-19 was diagnosed with a positive SARS-CoV-2 polymerase chain reaction test result. Non-survivors were defined as patients who died during their hospital stay, while survivors were those that were either discharged home or transferred to another facility without demise during hospitalisation. Hypertension was defined as patients already receiving antihypertensive therapy at admission, or those with blood pressure readings exceeding 140/90mmHg during hospitalisation and requiring initiation of antihypertensive therapy .

## RESULTS

A total of 205 hypertensive patients with COVID-19 were included. This comprised 115 patients that received ACEI/ARBs (either alone or in combination with other agents) for their hypertension, and 90 patients that received antihypertensive therapy that did not include an ACEI/ARB.

Patients in the ACEI/ARB cohort had significantly less participants that required oxygen therapy, required steroid therapy and received mechanical ventilation compared to those that did not receive ACEI/ARBs. Additionally, there was a significantly greater number of patients that survived. (Table 1)


DOI: 10.21608/aeji.2025.336759.1430

**Table 1: Demographics, comorbidities, treatment and outcome – comparison between those receiving ACEIs/ARBs vs. those not receiving ACEIs/ARBs**

| | | Total (n = 205) | ACEI/ARB (n = 115) | No ACEI/ARB (n = 90) | p value |
|---|---|---|---|---|---|
| | | f (%) | f (%) | f (%) | |
| Age (years) | 10-19 | 1 (0.5) | 1 (0.9) | 0 (0) | 0.371 |
| | 20-29 | 4 (2) | 1 (0.9) | 3 (3.3) | |
| | 30-39 | 9 (4.4) | 4 (3.5) | 5 (5.6) | |
| | 40-49 | 20 (9.8) | 10 (8.7) | 10 (11.1) | |
| | 50-59 | 60 (29.3) | 40 (34.8) | 20 (22.2) | |
| | 60-69 | 62 (30.2) | 35 (30.4) | 27 (30) | |
| | 70-79 | 37 (18.1) | 17 (14.8) | 20 (22.2) | |
| | 80-89 | 9 (4.4) | 6 (5.2) | 3 (3.3) | |
| | 90-99 | 3 (1.5) | 1 (0.9) | 2 (2.2) | |
| | Total | 205 | 115 | 90 | |
| Gender | Female | 120 (58.5) | 62 (53.9) | 58 (64.4) | 0.129 |
| | Male | 85 (41.5) | 53 (46.1) | 32 (35.6) | |
| | Total | 205 | 115 | 90 | |
| Race | Black African | 165 (80.5) | 98 (85.2) | 67 (74.4) | 0.142 |
| | White | 16 (7.8) | 8 (7) | 8 (8.9) | |
| | Coloured | 1 (0.5) | 0 (0) | 1 (1.1) | |
| | Asian | 23 (11.2) | 9 (7.8) | 14 (15.6) | |
| | Total | 205 | 115 | 90 | |
| Comorbidities | Diabetes | 112 (54.6) | 63 (54.8) | 49 (54.4) | 0.962 |
| | COPD/Asthma | 13 (6.3) | 8 (7) | 5 (5.6) | 0.683 |
| | HIV | 46 (22.4) | 23 (20) | 23 (25.6) | 0.344 |
| | Chronic Kidney Disease | 35 (17.1) | 18 (15.7) | 17 (18.9) | 0.541 |
| Required Steroid Therapy | Yes | 167 (81.5) | 86 (74.8) | 81 (90) | 0.005 |
| | No | 38 (18.5) | 29 (25.2) | 9 (10) | |
| | Total | 205 | 115 | 90 | |
| Required Oxygen Therapy | Yes | 169 (82.4) | 87 (75.7) | 82 (91.1) | 0.004 |
| | No | 36 (17.6) | 28 (24.4) | 8 (8.9) | |
| | Total | 205 | 115 | 90 | |
| Required Mechanical Ventilation | Yes | 45 (22) | 17 (14.8) | 28 (31.1) | 0.005 |
| | No | 160 (78.1) | 98 (85.2) | 62 (68.9) | |
| | Total | 205 | 115 | 90 | |
| Outcome | Non-survivor | 113 (55.1) | 28 (24.4) | 64 (71.1) | <0.001 |
| | Survivor | 92 (44.9) | 87 (75.7) | 26 (28.9) | |
| | Total | 205 | 115 | 90 | |

ACEIs: Angiotensin-Converting Enzyme Inhibitors
ARBs: Angiotensin Receptor Blockers

Examination of age distribution showed no significant difference between the two cohorts, with a median age of 60 years (53 - 67) for the ACEI/ARB group and 62 years (52 - 70) for the non-ACEI/ARB group (p = 0.598).
Participants on ACEI/ARB therapy exhibited a significantly higher median oxygen saturation at 92% (84 - 97) compared to 87% (76 - 93) in those not on these medications (p = 0.002).

Notable differences also emerged in laboratory parameters. The white cell count (WCC) was lower in the ACEI/ARB group with a median of 8.9 $x10^9$/l (6.8 - 11.5) as compared to 10.45 $x10^9$/l (7.3 - 14.7) in the non-ACEI/ARB group (p = 0.005). Additionally, C-reactive protein (CRP) levels were significantly lower in participants receiving ACEI/ARB, with a median of 100 mg/l (40 - 158), in contrast to 147 mg/l (96 - 242) in those not receiving these medications (p < 0.001). (Table 2)

**Table 2: Age, admission vital signs and laboratory variables – comparison between those receiving ACEIs/ARBs vs. those not receiving ACEIs/ARBs**

| | Total (n = 205) | | ACEI/ARB (n = 115) | | No ACEI/ARB (n = 90) | | p value |
|---|---|---|---|---|---|---|---|
| | Median (IQR) | Mean (SD) | Median (IQR) | Mean (SD) | Median (IQR) | Mean (SD) | |
| Age (years) | 61 (52-69) | | 60 (53-67) | | 62 (52-70) | | 0.598 |
| Oxygen Saturation (%) | 89 (80-96) | | 92 (84-97) | | 87 (76-93) | | 0.002 |
| Respiratory rate (breaths/minute) | 22 (20-25) | | 22 (20-24) | | 22 (20-26) | | 0.016 |
| Heart rate (bpm) | 97 (87-110) | | 94 (87-107) | | 100 (88-113) | | 0.226 |
| Systolic blood pressure (mmHg) | 130 (118-145) | | 129 (118-142) | | 130.5 (119-151) | | 0.297 |
| Diastolic blood pressure (mmHg) | | 78.12 (14.7) | | 78.10 (14.2) | | 78.16 (15.3) | 0.977 |
| Pulse pressure (mmHg) | 52 (43-64) | | 52 (43-62) | | 54.5 (42-66) | | 0.208 |
| Shock Index | 0.74 (0.66-0.83) | | 0.74 (0.66-0.81) | | 0.73 (0.66-0.88) | | 0.921 |
| Temperature (ºC) | 36.5 (36.4-36.7) | | 36.5 (36.3-36.7) | | 36.55 (36.4-36.7) | | 0.622 |
| Glucose (mmol/l) | 9.6 (7.1-15) | | 8.6 (6.9-14.2) | | 10.15 (7.5-16.1) | | 0.078 |
| White cell count (WCC)(x$10^9$/l) | 9.6 (6.9-12.3) | | 8.9 (6.8-11.5) | | 10.45 (7.3-14.7) | | 0.005 |
| C-reactive protein (CRP) (mg/l) | 120 (59-191) | | 100 (40-158) | | 147 (96-242) | | <0.001 |

ACEIs: Angiotensin-Converting Enzyme Inhibitors
ARBs: Angiotensin Receptor Blockers

The 205 participants comprised 113 survivors and 92 non-survivors.

The study notably found a significant difference in outcomes related to the use of ACEI/ARB medications; 77% of survivors were on ACEI/ARB therapy, in contrast to 30.4% of non-survivors ($p < 0.001$). Similarly, the distribution of specific antihypertensive therapy drug classes revealed significant findings. Patients on ACEI/ARBs showed significantly higher survival rates ($p < 0.001$), while those on calcium channel blockers presented a notable disparity, with a higher prevalence among non-survivors (47.8%) compared to survivors (24.8%) ($p = 0.001$). Other classes of antihypertensives, such as loop diuretics, thiazide diuretics, potassium-sparing diuretics, beta blockers, alpha blockers, and centrally-acting agents did not demonstrate significant differences in distribution between survivors and non-survivors.

In addition, there was no significant difference in the survival outcomes based on the number of medications taken ($p = 0.344$). (Table 3)

**Table 3: Comparison between survivors and non-survivors (categorical variables)**

| | | Total (n = 205) | Survivors (n = 113) | Non-survivors (n = 92) | p value |
|---|---|---|---|---|---|
| | | f (%) | f (%) | f (%) | |
| Age (years) | 10-19 | 1 (0.5) | 1 (0.9) | 0 (0) | 0.301 |
| | 20-29 | 4 (2) | 2 (1.8) | 2 (2.2) | |
| | 30-39 | 9 (4.4) | 7 (6.2) | 2 (2.2) | |
| | 40-49 | 20 (9.8) | 12 (10.6) | 8 (8.7) | |
| | 50-59 | 60 (29.3) | 37 (32.7) | 23 (25) | |
| | 60-69 | 62 (30.2) | 28 (24.8) | 34 (40) | |
| | 70-79 | 37 (18.1) | 18 (15.9) | 19 (20.7) | |
| | 80-89 | 9 (4.4) | 7 (6.2) | 2 (2.2) | |
| | 90-99 | 3 (1.5) | 1 (0.9) | 2 (2.2) | |
| | Total | 205 | 113 | 92 | |
| Gender | Female | 120 (58.5) | 69 (61.1) | 51 (55.4) | 0.416 |
| | Male | 85 (41.5) | 44 (38.9) | 41 (44.6) | |
| | Total | 205 | 113 | 92 | |
| Race | Black African | 165 (80.5) | 96 (85) | 69 (75) | 0.199 |
| | White | 16 (7.8) | 7 (6.2) | 9 (9.8) | |
| | Coloured | 3 (1.5) | 1 (0.9) | 0 (0) | |
| | Asian | 23 (11.2) | 9 (8) | 14 (15.2) | |
| | Total | 205 | 113 | 92 | |
| ACEI vs. Non-ACEI/ARB | ACEI/ARB | 115 (56.1) | 87 (77) | 28 (30.4) | <0.001 |
| | Non-ACEI/ARB | 90 (43.9) | 26 (23) | 64 (69.6) | |
| | Total | 205 | 113 | 92 | |
| Specific Antihypertensive therapy drug class | ACEI/ARB | 115 (56.1) | 87 (77) | 28 (30.4) | <0.001 |
| | Calcium channel blocker | 72 (35.1) | 28 (24.8) | 44 (47.8) | 0.001 |
| | Thiazide diuretic | 57 (27.8) | 27 (23.9) | 30 (32.6) | 0.166 |
| | Beta blocker | 25 (12.2) | 11 (9.7) | 14 (15.2) | 0.233 |
| | Potassium-sparing diuretic | 6 (2.9) | 4 (3.5) | 2 (2.2) | 0.693 |
| | Loop diuretic | 65 (31.7) | 30 (26.6) | 35 (38) | 0.079 |
| | Centrally-acting agents (Methyldopa) | 4 (2) | 0 (0) | 4 (4.4) | 0.039 |
| | Alpha blocker | 3 (1.5) | 2 (1.8) | 1 (1.1) | 0.685 |
| Number of antihypertensive agents | 1 | 98 (47.8) | 58 (51.3) | 40 (43.5) | 0.344 |
| | 2 | 80 (39) | 38 (33.6) | 42 (45.7) | |
| | 3 | 21 (10.2) | 12 (10.6) | 9 (9.8) | |
| | 4 | 4 (2) | 3 (2.7) | 1 (1.1) | |
| | 5 | 2 (1) | 2 (1.8) | 0 (0) | |
| | Total | 205 | 113 | 92 | |

ACEIs: Angiotensin-Converting Enzyme Inhibitors
ARBs: Angiotensin Receptor Blockers

The use of ACEIs/ARBs emerged as a significant protective factor against mortality. Univariate analysis showed a reduced odds ratio (OR) of 0.131 (95% CI 0.070 – 0.244, p < 0.001). This remained significant after multivariate analysis with an adjusted OR of 0.144 (95% CI 0.051 – 0.401, p < 0.001).

Conversely, calcium channel blockers were initially associated with an increased risk of death on univariate analysis (OR 2.783, 95% CI 1.540 – 5.027, p = 0.001), but this association did not remain significant after adjustment for confounders (adjusted OR 1.388, 95% CI 0.482 – 4, p = 0.544).

Other drug classes of antihypertensive therapy did not demonstrate significant associations with mortality on either univariate or multivariate analyses. (Table 4)

**Table 4: Predictors of mortality - univariate and multivariate logistic regression analysis**

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Unadjusted OR | 95% CI | p value | Adjusted OR | 95% CI | p value |
| ACEI/ARB | 0.131 | 0.070 – 0.244 | <0.001 | 0.144 | 0.051 – 0.401 | <0.001 |
| Calcium channel blocker | 2.783 | 1.540 – 5.027 | 0.001 | 1.388 | 0.482 – 4 | 0.544 |
| Thiazide diuretic | 1.541 | 0.834 – 2.848 | 0.167 | 1.705 | 0.537 – 5.413 | 0.366 |
| Beta blocker | 1.664 | 0.716 – 3.867 | 0.236 | 0.287 | 0.534 – 1.542 | 0.146 |
| Potassium-sparing diuretic | 0.606 | 0.108 – 3.382 | 0.568 | 0.755 | 0.041 – 13.757 | 0.850 |
| Loop diuretic | 1.699 | 0.939 – 3.073 | 0.080 | 1.322 | 0.409 – 4.270 | 0.641 |
| Alpha blocker | 0.610 | 0.054 – 6.834 | 0.688 | 0.294 | 0.003 – 25.812 | 0.592 |

ACEIs: Angiotensin-Converting Enzyme Inhibitors
ARBs: Angiotensin Receptor Blockers
OR: Odds Ratio

The difference in survival rates between the ACEI/ARB cohort and the non-ACEI/ARB cohort is displayed in figure 1. A log rank test demonstrated significantly lower survival rates in those participants not receiving an ACEI/ARB ($p < 0.001$), with a mean time to death of 10.9 days. Whereas, those in the ACEI/ARB cohort had a mean time to death of 11.8 days.

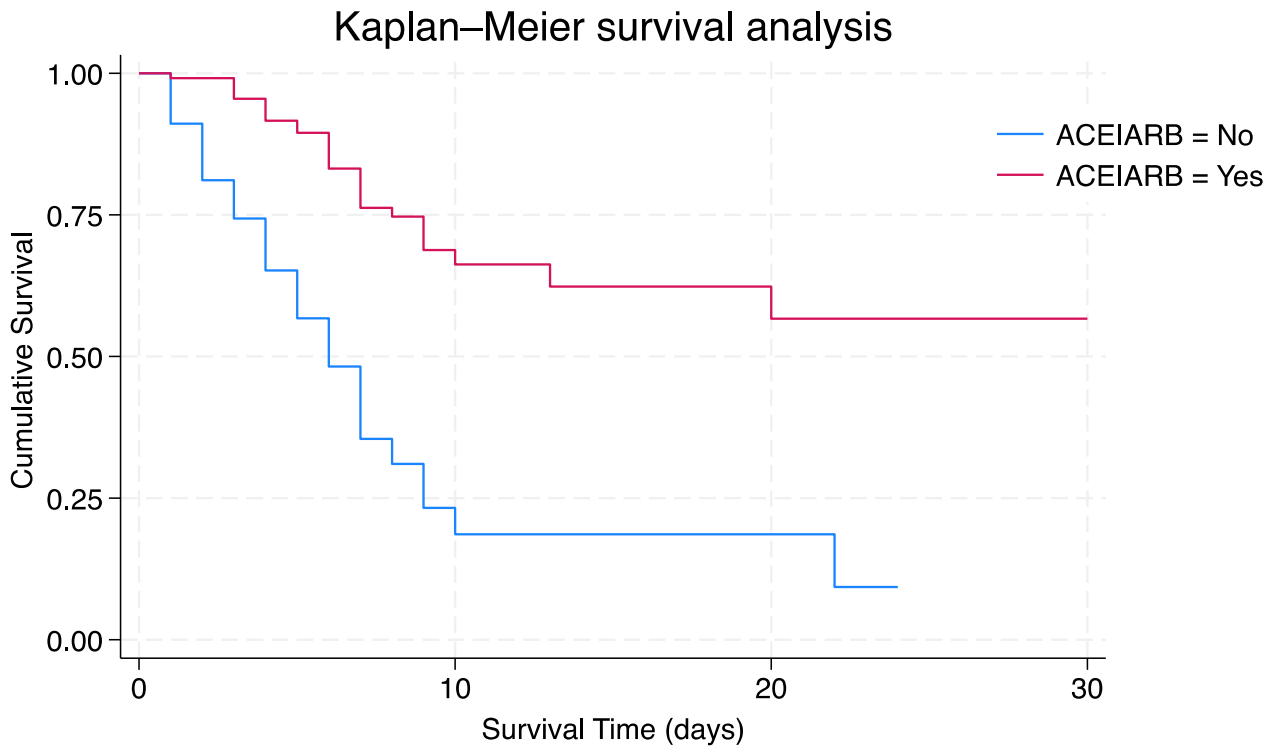


**Fig 1: Kaplan-Meier Survival Analysis – time to death (days) for participants receiving ACEIs/ARBs vs. not receiving ACEIs/ARBs**

Conversely, figure 2 demonstrates a significantly lower survival rate in those using a calcium channel blocker ($p < 0.001$).

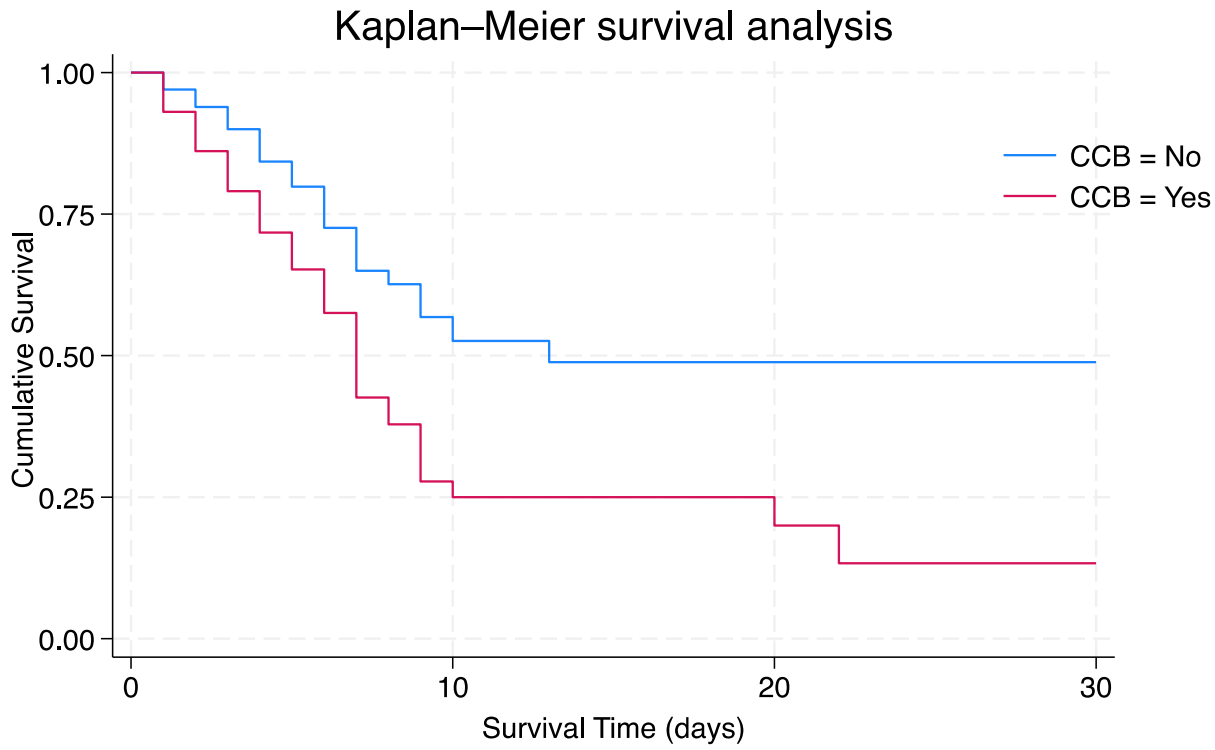


**Fig 2: Kaplan-Meier Survival Analysis – time to death (days) for participants receiving CCB vs. not receiving CCB**

## DISCUSSION

This study sought to evaluate the impact of antihypertensive therapy, particularly the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, on the outcomes of hypertensive patients hospitalised with COVID-19 - providing critical insights into the association between specific antihypertensive therapies and COVID-19-related mortality, highlighting the protective role of ACEI/ARB therapy in this patient population .

Our findings reveal a significant reduction in mortality among hypertensive patients receiving ACEI/ARB therapy, with both univariate and multivariate analyses indicating a substantial protective effect. Additionally, we found a lower prevalence of oxygen, steroid and mechanical ventilation requirements, as well as higher oxygen saturation and lower CRP and white cell count values on presentation – indicating milder disease. This result aligns with previous studies suggesting that ACEIs/ARBs may confer a protective advantage in COVID-19 outcomes [15,16,17,18,19,20,21,22]. The theoretical concerns regarding the upregulation of ACE-2 expression and facilitated viral entry did not translate into increased mortality in our cohort. Instead, our data supports the hypothesis that the modulation of the renin-angiotensin-aldosterone system (RAAS) by ACEIs/ARBs may offer beneficial effects in the context of COVID-19, potentially through the attenuation of inflammation and the prevention of acute lung injury [4.[

Calcium channel blockers (CCBs) are one of the most commonly prescribed antihypertensives and work primarily by inhibiting calcium influx into vascular smooth muscle cells with subsequent vasodilation [26]. CCBs were initially associated with increased mortality in our study, however this association did not remain significant after multivariate analysis – and thus, should be cautiously interpreted. Interestingly, several meta-analyses have been conducted and demonstrate improved survival rates with the use of calcium channel blockers in hypertensive patients with SARS-CoV-2 infection [26,27,28].


DOI: 10.21608/aeji.2025.336759.1430

Previous studies, that may be extrapolated to SARS-COV-2, indicate that SARS-CoV and MERS-CoV utilize calcium-dependent mechanisms for viral entry into cells and reduction of intracellular calcium levels may inhibit this viral entry [26]. It is also postulated that the vasodilatory properties of CCBs in both systemic and pulmonary blood vessels may help counteract inflammation and localised vasoconstriction triggered by SARS-CoV-2 infection – thereby improving oxygen delivery and enhancing survival of host cells [27]. The potential protective effects of CCBs in the context of SARS-CoV-2 infection warrants further investigation through large-scale prospective studies .

The lack of significant associations between mortality and other classes of antihypertensive medications in our study suggests that the protective effect observed may be unique to ACEI/ARB therapy. These findings contribute to the growing body of evidence advocating against the routine discontinuation of ACEI/ARB therapy in hypertensive individuals with COVID-19, unless clinically warranted for other reasons .

Our study suggests that the benefits of continuing ACEI/ARB therapy in hypertensive patients with COVID-19 may outweigh the risks. Healthcare providers should consider these findings when managing hypertensive patients with COVID-19 - considering the potential protective effects of ACEI/ARB therapy on outcomes.

This study adds valuable evidence to the ongoing debate regarding the use of ACEI/ARB therapy in hypertensive patients with COVID-19 and – to the best of our knowledge – is the first of its kind conducted within an African population. The protective effect observed with ACEI/ARB therapy highlights the need for a nuanced approach to the management of hypertension in the context of COVID-19, underscoring the potential benefits of these medications in improving patient outcomes. Further large-scale prospective research, particularly in diverse populations and settings, is essential to fully understand the implications of antihypertensive therapy on COVID-19 mortality and to guide optimal treatment strategies.

The study's limitations include its retrospective nature, which might introduce bias, and dependence on medical record accuracy, potentially affecting the reliability of comorbidity, treatment, and outcome data. Conducted in a single tertiary hospital, the findings may not be generalisable across different settings or regions. Furthermore, the small sample size and the evolving dynamics of the COVID-19 pandemic could limit the relevance of the results over time.

## CONCLUSION

Our investigation into the influence of antihypertensive therapy, especially the use of ACEIs and ARBs, on the outcomes of hypertensive patients hospitalised with COVID-19 yields significant findings, affirming the protective role of ACEI/ARB therapy. In a landscape where data on African populations remain sparse and, given the distinctive clinical presentation of hypertension in these groups, our research fills a crucial gap, reinforcing the necessity for specific studies within this demographic.

**Acknowledgments:**

Not applicable .

**Abbreviations:**

ACEI - Angiotensin-Converting Enzyme Inhibitor

ARB - Angiotensin Receptor Blocker

aOR - Adjusted Odds Ratio

BREC - Biomedical Research Ethics Committee

CCB – Calcium Channel Blocker

COPD - Chronic Obstructive Pulmonary Disease

COVID-19 - Coronavirus Disease 2019

CRP - C-Reactive Protein

IQR - Interquartile Range

KEH - King Edward VIII Hospital

OR - Odds Ratio

PCR - Polymerase Chain Reaction

RAAS - Renin-Angiotensin-Aldosterone System

SD - Standard Deviation

SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

SPSS - Statistical Package for the Social Sciences

WCC - White Cell Count

**Ethics approval and consent to participate:**

The University of KwaZulu-Natal Biomedical Research and Ethics Committee (BREC/00005457/2023) granted ethical clearance for this study, with additional approval from the Department of Health and the respective site (KEH). To ensure privacy, data was anonymised before analysis. The need for informed consent was waived by the Biomedical Research and Ethics Committee due to the retrospective nature of the study. All research activities adhered strictly to applicable guidelines and regulatory standards.

**Availability of data and materials:**

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

**Competing interests:**

The authors declare that they have no competing interests .

**Funding:**

None.

**Author contributions:**

A.S.I contributed towards data collection, writing of the article, analysis and interpretation of data. S.P contributed towards writing and proofreading of the article. All authors have read and approve the final manuscript, and give consent for publication .

## HIGHLIGHTS

- Use of ACEIs/ARBs exhibited a significant survival benefit (aOR = 0.144, $p < 0.001$) in patients hospitalised with COVID-19, as well as milder disease with lower inflammatory markers, reduced oxygen and steroid requirements, and less need for mechanical ventilation.
- Calcium channel blocker use was initially associated with higher mortality, but this did not remain statistically significant after adjusting for confounders.
- No mortality benefit or harm was associated with other antihypertensive drug classes (beta blockers, thiazide diuretics, loop diuretics, potassium-sparing diuretics, alpha blockers.(

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**Cite as:** Ikram, A., Pillay, S. Correlation of In-Hospital Antihypertensive Therapy with Clinical Outcomes in Hypertensive Patients Admitted with COVID-19: A Retrospective Single-Centre Study in South Africa. *Afro-Egyptian Journal of Infectious and Endemic Diseases*, 2025; (): -. doi: 10.21608/aeji.2025.336759.1430