Mortality associated with COVID-19 and hypertension in sub-Saharan Africa. A systematic review and meta-analysis

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Abstract
Hypertension is a common comorbidity in COVID-19 patients. However, little data is available on mortality in COVID-19 patients with hypertension in sub-Saharan Africa (SSA). Herein, the authors conducted a systematic review of research articles published from January 1, 2020 to July 1, 2021. Our aim was to evaluate the magnitude of COVID-19 mortality in patients with hypertension in SSA. Following the PRISMA guidelines, two independent investigators conducted the literature review to collect relevant data. The authors used a random effect model to estimate the odds ratio, or hazard ratio, with a 95% confidence interval (CI). Furthermore, the authors used Egger’s tests to check for publication bias. For mortality analysis, the authors included data on 29,945 COVID-19 patients from seven publications. The authors assessed the heterogeneity across studies with the I² test. Finally, the pooled analysis revealed that hypertension was associated with an increased odds of mortality among COVID-19 inpatients (OR 1.32; 95% CI, 1.13–1.50). Our analysis revealed neither substantial heterogeneity across studies nor a publication bias. Therefore, our prespecified results provided new evidence that hypertension could increase the risk of mortality from COVID-19 in SSA.

KEYWORDS
Africa, COVID-19, hypertension, mortality

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), a new emerging acute respiratory disease, is transmitted mainly through respiratory droplets and results in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of July 22, 2021, COVID-19 has affected 42,385,317 people worldwide, with 650,684 deaths. In Africa, COVID-19 accounted for 4,634,617 infections with 109,711 deaths, a case fatality rate of 0.23%.

In symptomatic patients with COVID-19, the clinical presentation is mild in 80%, moderate to severe in 15%, and critical in 5%.
Severe cases are at risk of developing acute respiratory distress syndrome (ARDS), shock, thromboembolic events, multi-organ failure, and death.\(^2\)

Hypertension affects more than 1 billion people worldwide, which makes it one of the most important public health problems globally.\(^3\) However, our knowledge of the impact of hypertension on SARS-CoV-2 infection is limited, especially in sub-Saharan Africa. Several clinical studies have shown that hypertension is one of the most common comorbidities in patients with SARS-CoV-2.\(^4-5\) A cohort study on 1099 ambulatory and hospitalized patients with COVID-19 found a history of hypertension in 15% of the patients.\(^7\)

Few meta-analyses have established the association between hypertension and mortality in patients with COVID-19 across the world.\(^8-13\) However, Africa has often been omitted in these meta-analyses. As of July 22, 2021, we did not find a single meta-analysis from Africa on the association between hypertension and mortality in patients with COVID-19. In sub-Saharan Africa (SSA), several observational studies were conducted on the predictors of mortality in patients with COVID-19 to determine the contribution of hypertension as a comorbidity to COVID-19 mortality. The results were discordant. Some African studies have found hypertension to be a predictor of mortality,\(^14-16\) while others have not.\(^17-21\) These studies had different study designs and study populations and have therefore produced different estimates and effect sizes. Consequently, a comprehensive and systematic analysis was needed to minimize such variability. In this review paper, we conducted a systematic review and meta-analysis, the first in SSA to our best knowledge, to investigate the association between hypertension and mortality in patients with COVID-19 in SSA. We hypothesized that hypertension would be significantly associated with mortality in COVID-19 patients in Africa.

2 | METHODS

2.1 | Data sources

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and conducted a systematic review using PubMed, Google Scholar, and Web of Science between January 1, 2020, and July 1, 2021.

We conducted our literature search on PubMed as follows. We scored with 0 points if not reported, 1 point if inadequately reported, and 2 points if adequately reported, which made a total of 24 points maximum. A study was labeled either “high quality” if the total score was ≥17 or “low quality” if the total score was <17.\(^22-23\)

2.2 | Study selection

Two independent investigators selected potentially eligible studies based on the appropriateness of the title and abstract. They then reviewed the full texts according to the eligibility criteria. Reviews, editorials, case reports, and family studies were not included for the analysis. Clinical studies that did not clearly indicate death as an outcome were also not included. In cases where the same author had more than one study on the same patient (duplicate publications), we included only the paper with the highest quality (Figure 1).

2.3 | Data extraction

Two investigators independently used our data extraction form, which included information on authors, year of publication, country, study design, study location (number of study sites), sample size, age, sex, outcome, mortality rate, history of hypertension, diabetics, cardiovascular disease, and chronic lung disease. This information was obtained independently by two investigators. A third investigator double checked the filled data extraction forms for completion, and compared the data per review paper to remove duplicates and resolve any discrepancies.

2.4 | Quality assessment

Two independent reviewers used the methodological items for non-randomized studies (MINORS) list (Table 1) to assess the methodological quality of individual studies. Each of the 12 MINORS items was scored with 0 points if not reported, 1 point if inadequately reported, and 2 points if adequately reported, which made a total of 24 points maximum. A study was labeled either “high quality” if the total score was ≥17 or “low quality” if the total score was <17.\(^22-23\)

2.5 | Data analysis

We did statistical analysis using STATA software version 14 and used the odds ratio (OR) or hazards ratio (HR) with a 95% confidence interval (CI) to estimate the correlation between hypertension and mortality in patients with COVID-19. We assessed heterogeneity across studies using the \(I^2\) statistic and the \(X^2\) test. For the \(X^2\) test,
significant heterogeneity between studies was indicated by a Cochran’s Q p value < .10. Heterogeneity was considered low if the I² value was less than 25%, moderate if the I² value was from 25% to 50%, or high if the I² value was greater > 50%. In the case of high heterogeneity, we did a sensitivity analysis and had to remove a study from the meta-analysis. We used forest plots to show visually the effect estimates of the included studies. We used Egger’s test to assess a potential publication bias. A p < .05 at both ends was considered statistically significant.

3 | RESULTS

3.1 | Study selection and characteristics

The flow chart shows the studies in our meta-analysis (Figure 1). A total of seven studies (all retrospective except one and all of high quality) involving 29,945 patients from eight Sub-Saharan African countries were finally included in our study. Based on the criteria described previously (Table 1). The studies were published from January 2020 to July 2021. The number of confirmed COVID-19 cases in each study ranged from 105 to 22,308. All the included studies in the meta-analysis were retrospective (Table 2). The proportion of patients with hypertension ranged from 1.18% to 34%.

3.2 | Mortality analysis

Patients with COVID-19 and hypertension had an increased probability of death as compared to those without hypertension. OR = 1.32; 95% CI [1.13–1.50] (Figure 2).
TABLE 2 Characteristics of the included study

| First author and year of publication | Country | Study site | Sex ratio | Age [median, interquartile range] | Sample size | Mortality rate* (%) | Diabetes n (%) | Hypertension n (%) | Cardiovascular diseases n (%) | Chronic pulmonary diseases n (%) |
|--------------------------------------|---------|------------|-----------|-----------------------------------|-------------|---------------------|----------------|-------------------|-----------------------------|-----------------------------|
| Matangila et al., 2020               | DRC     | One hospital in Kinshasa | 1.04      | 54 years old [38-64]              | 160         | 20                  | 31 (19)       | 55 (34)           | 11 (7)                      | 5 (3)                       |
| Nachega et al., 2020                | DRC     | Seven largest health facilities in Kinshasa | 1.90      | 46 years old [34-58]              | 766         | 13.2                | 107 (14)      | 194 (25.4)        | 30 (3.9)                    | 26 (3.4)                    |
| Abraha et al., 2021                 | Ethiopia| One district health center in Mekelle city | 1.72      | 29 years old [24-38]              | 2617        | 0.8                 | 82 (3.1)      | 82 (3.1)          | -                           | 73 (2.8)                    |
| Jaspard et al., 2021                | Guinea and Burkina | Three hospitals in Burkina and Guinea | 1.77      | 41 years old [30-57]              | 1805        | 29                  | 219 (12)      | 386 (21)          | -                           | -                           |
| Osibogun et al., 2021               | Nigeria | 10 health centers in Lagos | 1.92      | 43 years old [35-55]              | 2184        | 3.3                 | 149 (6.8)     | 365 (16.7)        | 2 (2.22)                    | -                           |
| Ghada                               | Sudan   | One health center | 1.69      | -                                 | 105         | 29                  | 53 (49)       | 53 (49)           | -                           | -                           |
| Boule et al., 2020                  | South Africa | western Cape Provincial Health Centers of Public sector health | 0.85      | -                                 | 22308       | 2.8                 | 3123 (14)     | 5131 (23)         | -                           | 1562 (7)                    |

*The only outcome was mortality in all seven selected studies that were all retrospective except one.

FIGURE 2 Forest plot for the association between hypertension and mortality in patients with COVID-19
3.3 | Heterogeneity across studies

No heterogeneity was evident between studies ($I^2 = 0.0\%$, Cochran Q test 5.82, $p = 0.439$) (Figure 2).

3.4 | Publication bias

Egger’s test found no publication bias ($p = .254$) (Table 3).

4 | DISCUSSION

In our meta-analysis, we found that the risk of death was higher in hypertensive patients with COVID-19 as compared to non-hypertensive ones. It has been shown that hypertensive patients tend to be severely affected and are more likely to die from COVID-19. Among possible mechanistic explanations for such an association, angiotensin converting enzyme (ACE2) could most likely be involved. Indeed, ACE2 is a type 1 integral membrane glycoprotein in the epithelial cells of multiple organs (heart, kidney, lung, and stomach). There are several situations that can promote overexpression of ACE2. Firstly, arterial hypertension itself leads to an increased activation of the renin-angiotensin system (RAS). Secondly, regular use of antihypertensive drugs such as angiotensin II receptor blockers (ARB) and ACE inhibitors increases the expression of ACE2. These two mechanisms may synergistically interact in a hypertensive patient taking such antihypertensive medication. The overexpression of ACE2 facilitates the entry of SARS-CoV-2 into pneumocytes. Such enhanced viral uptake favors respiratory infection, which significantly increases the severity and mortality rate of COVID-19 in hypertensive patients taking ARBs and/or ACEIs. After viral uptake, ACE2 overexpression, which is thought to provide lung protection, is downregulated as the enzyme is decreased, resulting in reduced angiotensin II degradation, increased aldosterone secretion, and loss of potassium from the urine and subsequent hypokalemia.

The association between hypertension and mortality was stronger in studies with a high proportion of male patients with COVID-19. Almost all the studies in the meta-analysis had a male predominance. It is known that males are more exposed to severe COVID-19. A greater expression and activation of angiotensin II type I receptor (AT1R) has been observed in hypertensive male patients, most likely due to vasoconstriction, a proinflammatory response, with increased oxidative stress, leading to acute respiratory distress syndrome (ARDS). This condition helps explain the higher incidence of severe COVID-19 in males as compared to females. Estrogen has been thought to predispose females to a “good” renin-angiotensin-aldosterone system (RAS).

Most of our studies had patients with a median age greater than 40 years old. It is known in the literature that older individuals with hypertension have lower ACE2 levels and higher RAS signaling, leading to increased hypertension. A higher RAS signaling that evolves to extremely low ACE2 levels and markedly elevated RAS signaling after COVID-19 infection results in a more severe disease. In contrast, younger individuals without hypertension have higher ACE2 and lower RAS signaling, which progresses to slightly lower ACE2 levels and slightly increased RAS signaling after COVID-19 infection, resulting in a potentially higher disease incidence but less severe disease.

Diabetes mellitus, cardiovascular disease, and chronic lung disease were the main comorbidities in patients with COVID-19. A recent study found that hypertension alone was not an independent predictor of disease outcome, but only in association with diabetes mellitus or another risk factor. Importantly, some studies have found that hypertension and diabetes have no effect on disease outcome in COVID-19 patients whereas other studies have found that hypertension and diabetes, with or without obesity, are independently associated with a poor outcome.

A study of nearly 4000 critically ill patients with COVID-19 hospitalized in intensive care has shown that hypertension, diabetes, cardiovascular disease, hypercholesterolemia, chronic kidney disease, and other comorbidities were predictive of mortality. However, of these comorbidities, only diabetes and hypercholesterolemia were independent predictors. A study of only hypertensive patients has reported that diabetes was not an independent prognostic factor, whereas age and chronic kidney disease were independent predictors. This study has found that diabetes, hypertension, and obesity were independent predictors of severe COVID-19 regardless of patients’ sex; the strongest predictor in patients younger than 50 years old was obesity, whereas no association was found between age and either hypertension or diabetes. However, the authors did not adjust for all comorbidities as in the first mentioned study of the same patient cohort.

The National Cohort Study in England studied 19 256 ICU admissions related to COVID-19 and found that patients with type 2 diabetes had an increased risk of mortality independent of hypertension, chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, or other potential risk factors. Another study has shown no association between hypertension and mortality or acute respiratory distress syndrome (ARDS) in patients with COVID-19. The authors have shown that either hypertension or diabetes, individually or in comorbidity, was an independent predictor of ARDS and mortality in patients with COVID-19. Gupta and coworkers have revealed that only body mass index ≥ 40 kg/m² and coronary artery disease were independent predictors of 28-day mortality in COVID-19 patients. Hypertension, diabetes, heart failure, and chronic

### Table 3: Egger’s test to analyze selected review papers for publication bias

| Standard effect | Slope  | Bias  |
|-----------------|--------|-------|
| Coefficient     | 0.19   | 0.87  |
| Standard error  | 0.12   | 0.67  |
| T               | 1.57   | 1.29  |
| p value         | 0.177  | 0.254 |
| 95% IC Confidence interval | -0.13 – 0.52 | -0.87 – 2.61 |
obstructive pulmonary disease were not independently associated with mortality in these patients.39-38

5 | LIMITATIONS

The results of this meta-analysis should be interpreted with caution. First, the observational and retrospective nature of the selected individual studies limited our ability to draw causal inferences. Therefore, our results may be affected by reverse causality bias or other unknown confounders that were not adjusted for in these studies. Second, individual studies did not provide data on the use of antihypertensive medications, duration of hypertension, and systolic and diastolic blood pressure. Third, only seven studies met our inclusion criteria. A larger prospective study is needed to confirm our results. Despite these limitations, our study has important strengths. We performed extensive database searches to ensure that all relevant and published studies were identified. We did not find heterogeneity among the selected individual studies.

6 | CONCLUSIONS

We found an increased risk of COVID-19 mortality among hypertensive patients in sub-Saharan Africa. Hypertension could be one of the potential predictive variables for COVID-19 mortality that Sub-Saharan hospitals should look for during triage. To minimize in-hospital mortality in COVID-19, patients with a history of hypertension should strictly follow COVID-19 preventive measures and social distancing and be prioritized for COVID-19 vaccination initiatives in sub-Saharan Africa.

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AUTHOR CONTRIBUTIONS

The study was conceived and designed by B.B. The literature searches and data extraction were carried out by B.B. and O.O. The first draft was written by B.B., H.S., M.S., and J.N. B.B. conducted the analysis. The final text was co-authored by all authors, who double-checked for essential intellectual substance. The text was approved by all authors in its current form.

DATA AVAILABILITY STATEMENT

The data sets reside with the authors of the original papers evaluated.

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