Morbidity and mortality outcomes of COVID-19 patients with and without hypertension in Lagos, Nigeria: A retrospective cohort study

By

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Abstract

Background: The current pandemic of coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown epidemiological and clinical characteristics that appear worsened in hypertensive patients with COVID-19. The morbidity and mortality of the disease among hypertensive patients in Africa have yet to be well described.

Methods: In this retrospective cohort study all confirmed COVID-19 adult patients (≥18 years of age) in Lagos between February 27 to July 6 2020 were included. Demographic, clinical and outcome data were extracted from electronic medical records of patients admitted at the COVID-19 isolation centers in Lagos. Outcomes included dying or being discharged by July 6, 2020. Variables were compared between hypertensive and non-hypertensives using univariable and multivariable logistic regression, cox regression and Kaplan Meier survival analysis methods to assess hypertension as a risk factor associated with worsened disease severity and death.

Results: A total of 2075 adults with COVID-19 were included in this study. The prevalence of hypertension was 17.8% and it was the most common comorbidity followed by diabetes (7.2%) and asthma (2.0%). Overall mortality from COVID-19 was 4.2% while mortality among the hypertensives was 13.7%. Severe symptoms and mortality were significantly higher among the hypertensives and survival rates were significantly lowered by the presence of an additional comorbidity to 50% from 91% for those with hypertension alone and from 98% for all other patients (P<0.001). After adjustment for confounders, severe COVID-19 disease and death were higher for hypertensives (severe/critical illness: HR=2.41, P=0.001, 95%CI=1.4–4.0, death: HR=2.30, P=0.001, 95%CI=1.2–4.6, for those with hypertension only). Hypertension posed an increased risk of severe morbidity and death from coronavirus disease in the

presence of other comorbidities (severe/critical illness: HR=3.76, P=0.001, 95%CI=2.1–6.4, death: crude HR=6.63, P=0.001, 95%CI=3.4–1.6, for those with additional comorbidities).

Conclusion: The potential morbidity and mortality risks of hypertension especially with other comorbidities in COVID-19 could help direct efforts towards prevention and prognostication. This provides the rationale for improving preventive caution for people with hypertension and other comorbidities and prioritizing them for future antiviral interventions.

Keywords:

COVID-19, Nigeria, Hypertension, comorbidities, coronavirus, SARS-CoV-2 virus, pandemic

Introduction

Globally, there is an ongoing pandemic of Coronavirus disease (COVID-19), an infectious disease caused by a newly discovered coronavirus called the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). [1] The infection fatality rate (IFR) of this disease has been estimated at a range of around 0.5-1% [2,3], with higher rates among those aged 60 or older.[4] The majority of cases of COVID-19 experience mild to moderate respiratory illness and recover with supportive care. Serious illness is more likely with the elderly and those with underlying comorbidities like cardiovascular disease, chronic respiratory disease, diabetes, and cancer. [5, 6]

Much earlier in China, where COVID-19 was initially identified, it was found that 48% patients had a comorbidity, with hypertension being the most prevalent (30%), followed by diabetes (19%) and coronary heart disease (8%).[7] In Italy, it was reported that COVID-19 deaths were mostly among people with comorbidities (99%), the majority of these were hypertensive

(76.5%).[8, 9] Studies have shown that hypertension imposes on sufferers an increased risk of getting infected with COVID-19, experiencing worse symptomatology and complications and a 2-fold risk of dying from the infection. Hypertension was reported to have had a hazard ratio (HR) of 1.70 [95% confidence interval (CI) 0.92–3.14] to 3.05 (95% CI 1.57–5.92) for mortality in some unadjusted epidemiological studies in China.[10, 11]

High blood pressure is common among people over 60 years of age, prevalence being nearly as high as two-thirds of this population. Long-term ill health and aging leads to a weakened immune system increasing the susceptibility of people with chronic illnesses to coronavirus infection. Along with the increased risk of infection and worsened outcomes among hypertensives, there is a growing concern that some medications used in the treatment may influence mortality in patients with COVID-19. [12,13] These medications such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), cause a rise in blood levels of ACE2.[14] The theory is that the COVID-19 virus infects human cells by forming a bond with ACE2, a requirement for viral entry into host cells, [15] thus increasing individual susceptibility to infection and propagation of the virus.[16] Several other studies have however found no association between the use of these drugs and the severity of COVID-19.[17]

The epidemiological and clinical characteristics of patients with COVID-19 in terms of the detailed clinical course of illness, risk factors for mortality its spread and even its treatment are still being studied and documented. Understanding the potential effect of hypertension on the risk of mortality from COVID 19 could help clinicians to identify and characterize patients' prognosis at an early stage so as to provide timely intervention. This study, hence, was aimed at assessing the hypothesis that hypertension worsens the morbidity and mortality outcomes of confirmed COVID-19 patients.

Methodology

Study subjects and design

This retrospective observational study was conducted using data collected from 2075 adult COVID-19 patients (≥18 years of age) consecutively admitted across ten designated isolation and treatment centers and hospitals, with reverse transcription polymerase chain reaction (RT-PCR) test results confirming COVID 19. These patients received care at hospitals or isolation and treatment centers dedicated solely to the treatment of COVID-19, in Lagos, Nigeria from 27 February to 6 July 2020.

Data collection

Patients' data collected on admission included sociodemographic data, details of their medical history and comorbidities, symptoms, severity of symptoms on admission, clinical outcomes and end data (discharge or death). Data was collected at the hospital/isolation center using the electronic medical records created specifically for the Lagos State COVID-19 response. Data extracted for the purpose of this study was completely anonymized.

Description of variables

Sociodemographic data included the age, sex, health facility and epidemiological identifier. Details of their medical history were limited to the reported comorbidities. The patients' presenting symptoms were recorded and the severity of symptoms on admission were categorized as mild, moderate, severe, or critical. Asymptomatic patients were categorized as mild, while cases with cough, fever, respiratory rate <30 breaths per minutes and peripheral capillary oxygen saturation (spO2) >90% were categorized as moderate. Patients who had grunting respiration, respiratory rate >30 breaths per minute and spO2 <90% on admission were classified as severe. The patients categorized as critical cases were those in respiratory failure.[18]

History of hypertension

The data on comorbidities including hypertension was based the patient's report of previous diagnosis prior to the infection with SARS-CoV-2. Those who required antihypertensive medication during hospitalization with no prior prescription were treated with antihypertensives, while those who had been on medications prior to admission, were treated with their usual prescribed medication. These patients were not stratified according to whether or not they were receiving antihypertensive while on admission.

Outcomes and end data

The major endpoints during admission were discharge following recovery or mortality. Patients still receiving care as at 6/7/2020, who had neither been discharged, transferred nor had died were classified as 'yet undetermined'. Details of follow-up of patients after leaving the hospital or isolation center were not included in this dataset.

Data management and analysis

Data was analyzed using the SPSS version 20 and presented in frequencies and proportions. Descriptive statistics considered means ± standard deviation (SD) for continuous variables that were normally distributed and median ± interquartile range (IQR) for those identified as skewed. Bivariate analyses (chi square test (trend and non-trend) and the Fisher's exact test as required) were used in determining associations between variables. Kaplan–Meier survival analysis was done to compare mortality between hypertensives and non-hypertensives. The Cox proportional hazards model was used to quantify the risk of worse outcomes among hypertensives with COVID 19 and adjust for the effect of confounders. p-value ≤0.05 was considered statistically significant.

Results

The patients were predominantly less than 40 years of age and about a tenth of them were over 60 years of age. The median age of the patients was 40 (IQR=32 - 50) years, and the oldest

was 98 years. The male to female ratio was 2:1. About a third (23.3%) of the patients had at least one comorbidity including hypertension, other cardiovascular (CVS) diseases, diabetes, asthma, HIV, Hepatitis B, cancer, renal disease, sickle cell disease, tuberculosis and other lung diseases, while 17.8% had hypertension alone. Over 50% of them were asymptomatic at the time of admission. Severity on admission ranged between mild to critical and over half of them (56.9%) had mild symptoms; about 2% of them were in critical condition on admission and as at the end of the study period, there was about 4% mortality among those with the outcomes of interest (Table 1).

Table 1: Patient characteristics

Variable	**Frequency (N=2075)**	**%**
Age (in years)		
<40	1017	49.0
40-49	526	25.3
50-59	321	15.5
>-60	211	10.2
Total	**2075**	100.0
Median age(IQR), min-max	40(32 - 50), 18-98	
Sex		
Male	1379	66.5
Female	696	33.5
Total	**2075**	100.0
Comorbidities		
Yes	483	23.3
No	1588	76.7
Total	**2071**[a]	100.0
Type of comorbidity*		
Hypertension	369	17.8
Diabetes	150	7.2
Asthma	42	2.0
HIV/Hepatitis B	15	0.7
Other CVS diseases	14	0.6
Cancer	15	0.7
Renal disease	10	0.5
Sickle cell disease	6	0.3
Tuberculosis &other lung diseases	7	0.3
Symptoms		
Asymptomatic	1192	57.6

Symptomatic	879	42.4
Total	**2071**[b]	100.0
Severity on admission		
Mild	1179	56.9
Moderate	743	35.9
Severe	107	5.2
Critical	42	2.0
Total	**2071**[c]	100.0
Outcome		
Died	73	4.2
Discharged	1666	95.8
Total	**1739**[d]	100.0

[a] Missing=4(0.2%) [b]Missing=2(0.1%) [c]Missing=4 (0.2%) [d]Yet undetermined=336(16.3%)
*Multiple comorbidities reported by some patients

When the groups were stratified by the presence or absence of hypertension it was found that hypertensive cohorts were significantly older in age (55.68 ± 12.9 vs 38.68 ± 11.5) and there was an increasing proportion of hypertensives across the age groups (p for trend=0.001). Both cohorts were proportionately similar in sex distribution. A significant proportion of the hypertensive cohort suffered the worse forms of the COVID-19 disease; severe (14.4% vs 3.2%) and critical (6.8% vs 1.0%), compared to the non-hypertensive cohorts (p for trend <0.001). The time till endpoint of admission irrespective of outcome was significantly different between both cohorts. The hypertensive group experienced a relatively shorter time on admission before the final outcome, with median duration of admission shorter for hypertensives than for non-hypertensive (12(IQR=8 -14), 13(IQR=10 -14), respectively). The disease outcome was significantly different between the cohorts; 13.7% of those who were hypertensive died compared to 2.2% of the non-hypertensives (p=0.001) (Table 2).

Table 2: Comparison of patients' characteristics and morbidity/ mortality against hypertensive status

Variable	Hypertensive		**Total**	X^2	p-value
	Yes	No			
Age (in years)				457.47*	**0.001**
<40	33(8.9)	983(57.8)	1016**(49.1)**		

40-49	96(26.0)	429(25.2)	525**(25.4)**)		
50-59	118(32.0)	203(11.9)	321**(15.5)**		
>-60	122(33.1)	87(5.1)	209**(10.1)**		
Total	**369(100.0)**	**1702(100.0)**	**2071(100.0)**		
Mean age ± SD	55.68 ± 12.9	38.68 ± 11.5			
Sex				0.47	0.492
Male	251(68.0)	1126(66.2)	1377(64.5)		
Female	118(32.0)	576(33.8)	694(33.5)		
Total	**369(100.0)**	**1702(100.0)**	**2071(100.0)**		
Severity on admission				159.87*	**<0.001**
Mild	136(36.9)	1043(61.3)	1179(56.9)		
Moderate	155(42.0)	588(34.5)	743(35.9)		
Severe	53(14.4)	54(3.2)	107(5.2)		
Critical	25(6.8)	17(1.0)	42(2.0)		
Total	**369(100.0)**	**1702(100.0)**	**2071(100.0)**		
Time till endpoint				5.24*	**0.022**
< 14 days	197(66.1)	860(59.8)	1057(60.9)		
14-28	100(33.6)	557(38.7)	657(37.8)		
>28 days	1(0.3)	22(1.5)	23(1.3)		
Total	**298(100.0)**	**1439(100.0)**	**1737[a](100.0)**		
Median time (IQR)	12(8 -14)	13(10 -14)			
Mean ± SD	11.06 ± 5.47	12.4 ± 4.91			
Outcome				84.26	**0.001**
Died	41(13.7)	32(2.2)	73(4.2)		
Discharged	259(86.3)	1407(97.8)	1666(95.8)		
Total	**300(100.0)**	**1439(100.0)**	**1739[b](100.0)**		

*Chi square test for trend [a]Missing =334(16.1%) [b]Yet undetermined/missing=332(16.0%)

There was a statistically significant difference in mortality and survival (till discharge) among hypertensive patients who had hypertension only and those hypertensives with at least one additional comorbidity, and those who survived for less than 2 weeks and those died at 2 weeks and beyond. A higher proportion of hypertensives that had at least one other comorbidity died (26.3%) compared to those who had hypertension alone (7.8%) (p<0.001). The proportion of those who had died within the first 14 days (19.8%) was higher compared to those whose deaths occurred beyond two weeks (1.9%), implying that that death among hypertensives occurred mostly within the first 2 weeks of admission (p<0.001) (Table 3).

Table 3: Mortality among COVID 19 hypertensive patients (with or without other comorbidities, < or > 2week of admission)

Number of comorbidities	Died	Survived	Total	X^2	p-value
1 (Hypertension only)	16(7.8)	189(92.2)	205(100.0)	18.85	**<0.001**
≥ 2	25(26.3)	70(73.7)	95(100.0)		
Total	**41(13.6)**	**259(86.3)**	**300(100.0)**		
Time till endpoint					**0.001***
<14 days	39(19.8)	158(80.2)	197(100.0)		
14 - 28	2(1.9)	98(98.1)	100(100.0)		
>28	0(0.0)	1(100.0)	1(100.0)		
Total	**41(13.6)**	**257(86.3)**	**298(100.0)**		

*Fishers exact p

The Kaplan–Meier estimates indicated that the COVID-19 survival rate for the non-hypertensive patients was 94%, 91% for patients with hypertension only and 50% for those with hypertension with other comorbidities. The log-rank test indicated that there was a statistically significant difference between the three survival rates (p<0.001). The unadjusted hazard ratio (HR) indicated that in the risk of death there was a 4-fold increase among hypertensives and a 13-fold increase among hypertensives with additional comorbidities compared to non-hypertensives. Collectively, these results suggest that patients in the hypertensive group were less likely to survive (Figure 1).

Figure 1: Kaplan–Meier survival curves for mortality among COVID 19 patients with and without hypertension or with additional comorbidities.

In both the unadjusted and multivariate analysis (adjusting for sex and age), cox regression showed that the hypertensive groups had increased rates of severe COVID-19 disease and mortality. Prior to adjustment, severe/critical illness and death from COVID-19 were significantly associated with being hypertensive (severe/critical illness: crude HR=4.21, p=0.001, 95%CI=2.7–6.5) (death: crude HR=3.70, p=0.001, 95%CI=2.0–6.7) and having an additional

comorbidity (severe/critical illness: crude HR=7.35, p=0.001, 95%CI=4.5–11.8) (death: crude HR=12.68, p=0.001, 95%CI=7.5 – 21.4). After adjustment for confounders, the HR for severe illness and death were still higher than for non-hypertensives (severe/critical illness: aHR=2.41, p=0.001, 95%CI=1.4–4.0, death: aHR=2.30, p=0.001, 95%CI=1.2–4.6, for those with hypertension only) (severe/critical illness: aHR=3.76, p=0.001, 95%CI=2.1–6.4, death: aHR=6.63, p=0.001, 95%CI=3.4–1.6, for those with additional comorbidities). The hypertension-only patients were about 2 times as likely as non-hypertensives to develop severe disease and 2 times as likely as non-hypertensives to die while those with additional comorbidities were about 4 times as likely as non-hypertensives to develop severe disease and about 7 times as likely to die of COVID 19 compared to non-hypertensives (Table 4).

Table 4: Cox regression for risk of increased severity and death among patients with hypertension compared with non-hypertensives

Variable		**Unadjusted**			**Adjusted**		
		HR	**95%CI**	**p-value**	**aHR**	**95%CI**	**p-value**
Severity (Severe/critical)							
	HTN	4.21	2.7 – 6.5	**0.001**	2.41	1.4 – 4.0	**0.001**
	HTN+	7.35	4.5 – 11.8	**0.001**	3.76	2.1 – 6.4	**0.001**
Outcome (death)							
	HTN	3.70	2.0 – 6.7	**0.001**	2.30	1.2 – 4.6	**0.019**
	HTN+	12.68	7.5 – 21.4	**0.001**	6.63	3.4 -12.6	**0.001**

HTN = hypertension HTN+ = hypertension plus other comorbidities HR = Hazard ratio
aHR=Adjusted hazard ratio

Discussion

The coronavirus disease (COVID-19) is a relatively new and hence understudied disease, however the available data has identified the importance of hypertension in the morbidity and mortality picture of the disease. The age and sex distribution found in this study is similar to the

findings of a meta-analysis of the clinical characteristics and comorbidities among 1786 coronavirus patients with a median age of 41 years a male to female ratio of 1.4:1. [19] The same study found a hypertension prevalence of 15.8%, lower than was found in this study. Another study in Wuhan, China found almost a 2-fold higher prevalence.[20] However, in all three studies the spectrum of comorbidities was the same and hypertension was the most common comorbidity.

Reports of increased incidence and severity of COVID-19 have stated that the severity is skewed towards the elderly population who have a higher prevalence of hypertension and are apparently at particular risk of being infected with SARS-CoV-2 virus.[21] This study found that severity is related to hypertension and that the hypertensive group also experienced a significantly shorter time on admission before the final outcome. This could be explained by the significantly higher proportion of worse disease outcome (death) among the hypertensives. While there is an overrepresentation of hypertension among hospitalized and critically ill COVID-19 patients, expert reports have expressed uncertainty whether hypertension is more causal or if other confounders such as age and other comorbidities associated with hypertension augment its role.[22] In the current study, adjustment for confounders meant that patients with hypertension were at a greater risk of increased severity and death from COVID 19 as was seen in a much smaller study in Wuhan, China. [23] Meanwhile, even though it was found in another study that there was a significant two-fold higher risk of mortality due to hypertension when compared with patients with no hypertension,[17] the current study found in addition, a significant difference in the potential of dying or surviving among hypertensives to be augmented in the presence of at least one additional comorbidity.

To corroborate the finding of this study that hypertension posed a greater risk of death among COVID-19 patients, a study in China reported that chronic hypertension was more frequent among COVID-19 patients who died compared with those who recovered.[24] Also similar to the

finding that hypertension had an HR of 3.70 (crude) for death in 369 patients admitted for COVID 19 another study found an HR of 3.05 in 191 hypertensive patients with COVID-19. [20] Another study however, found that hypertension has a lower HR of 1.70 for death in 201 patients with COVID-19. [25]

This study was limited because data on hypertensive medication were not included in the dataset. It would have been useful to consider this because there is currently limited clinical evidence of the influence of antihypertensive medication on the prognosis of COVID-19. Nevertheless, continuing a patient's usual antihypertensive treatment is recommended.[26] Also, the patients in this study were only studied till the end of their stay in the COVID-19 isolation ward. It would have been interesting and beneficial to study the patient beyond the time of discharge.

Conclusion

Several studies have observed an overrepresentation of hypertension among COVID-19 patients, as has his study but the role of other comorbidities worsening the severity and outcome of hypertension has been highlighted in this study. Studies that demonstrate causation would be beneficial as understanding about COVID 19 improves. Until more information is available to guide treatment and management of COVID 19 patients with hypertension, it is important to control blood pressure according to current clinical practice guidelines.

List of abbreviations

ACE Angiotensin-converting enzyme

ARBs Angiotensin receptor blockers

HTN Hypertension

HTN+ Hypertension with other comorbidities

HR Hazard ratio

aHR Adjusted hazard ratio

Declarations:

Ethics approval and consent to participate

Ethical approval was obtained from The Lagos State University Teaching Hospital Health Research Ethics Committee. Ethical review provided a waiver of written informed consent for the purpose of this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because of ethical restrictions but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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the design of the study, and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' contributions

A A[1], AO[2,3], JI[1], and RA[1], contributed to the conceptualization and design of the study.

AB[4], BA[5], IA[1], BM[6], BS[6], SY[7], RA[1], OO[3], EE[3], JO[8], OA[4], SA[4], YO[2], IA[9], SO[4], contributed to data generation and quality as well as manuscript review.

OKO[2], OW[5], FE[10], contributed to data cleaning analysis and interpretation.

AO[2,3], OKO[2], JI[1], and RA[1], contributed to manuscript development

SO[1], AO[1], DL[1], HAR[1], NO[1], KA[11], contributed to manuscript review

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Authors' information (optional)

All authors involved in this study are members of Epidemic Response Team at the Emergency Operations Centre set up to respond to the COVID-19 outbreak in Lagos State, Nigeria.

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