Results of Statistical Analyses version 1

Clinical profile and predictors of mortality of hospitalized patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 in Nigeria: A retrospective analysis of high burden states

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Background

The current COVID 19 pandemic has resulted in a high number of deaths and associated disruption of public health and socioeconomic activities of countries and populations. As at 9th of April 2021, Nigeria had recorded 163,581 confirmed cases, with 150,005 cases discharged, 7,518 cases on admission and 2,058 deaths with a significant increase in the number of confirmed cases and concurrent deaths since the beginning of the second wave of infections. Most of these deaths have been in-hospital. Little is known about the deaths in the community due largely to poor community records of deaths and other vital statistics. The weak Nigerian health system is thought to have led to a considerably high in-hospital mortality especially in settings where critical care services and resources are scarce. Underlying morbidities such as malnutrition, anemia, HIV/AIDs, and chronic respiratory conditions, diabetes and heart failure have been shown to be important contributors to high global mortality in the current COVID 19 pandemic.

Even though several global reports have been written about the impact of the COVID 19 pandemic on clinical outcomes especially the attendant morbidity and mortality, little is known about the situation in Nigeria. Understanding the relative contributions and probable mechanism through which sociodemographic, clinical and laboratory factors relate to the high in-hospital mortality in Nigeria could help us identify weak points within the health system that can be improved upon for current and future responses. In addition, such review will also help us plan and prioritize health infrastructure and resource allocation for better health outcomes in our public health system.

The aim of this study was to describe clinical characteristics and factors associated with mortality and time to mortality for patients hospitalized with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Nigeria.

Data Analysis Plan

Study Setting

Nigeria is Africa's most populous country. We studied patients with laboratory-confirmed SARS-CoV-2 infection from 28 COVID 19 treatment centers across 15 states in Nigeria including the Federal Capital Territory (see Figure 1).

Study Design

This study was a retrospective cross-sectional study.

Power analysis

TODO

Data Collection

We extracted data from the World Health Organization (WHO) nCOV database platform (OpenClinica Electronic Data Capture [EDC] System) for 28 sites across 15 states in Nigeria (see Figure 1). Two states (Delta

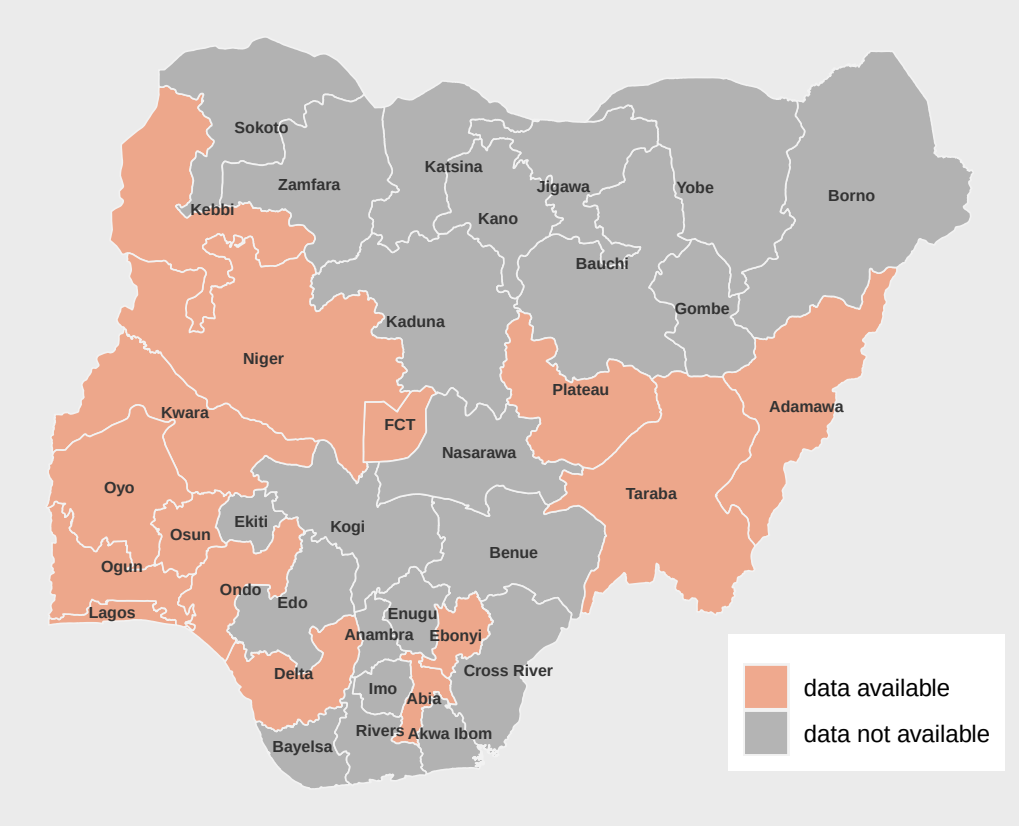

Figure 1: States with available data

and Taraba) were excluded because the states both had less than 10 records. We retrieved data on date of admission, enrollment date, demographic data (patients' sex, age, health worker), data on pre-existing morbidity (chronic cardiac disease, hypertension, chronic pulmonary disease, asthma, chronic kidney disease, chronic neurological disorder, HIV, diabetes, current smoking, tuberculosis, asplenia, malignant neoplasm), pre-admission and chronic medication (ACE inhibitors, angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs in the 14 days prior to admission), medications received on day of admission or following (antiviral, corticosteroid, chloroquine/hydroxychloroquine), admitted to ICU or HDU, supplemental oxygen given, use of non-invasive ventilation, use of invasive ventilation, outcome (discharged alive, hospitalized, transfer to other facility, death, palliative discharge), and outcome date.

Study Variables

The primary study outcome was death for a PCR confirmed infection with SARS-COV-2 virus. The secondary study outcome was time from enrollment to death. We coded the primary study outcome as 1 if the patient died or 0 if outcome was censored. Time following admission was right-censored at 84 days post-enrollment. The main explanatory variable was severity of disease. We defined severity of disease as a composite score derived from any or all of:

1. Received supplemental oxygen therapy on any day during hospitalization,
2. Admitted to the ICU or HDU at any point during hospital stay,

3. Received non-invasive ventilation (CPAP/BIPAP) on any day during hospitalization, and
4. Received invasive ventilation (mechanical ventilator) on any day during hospitalization

These variables were assigned a score of 1 if reported in the database or 0, otherwise. The severity score was calculated as the sum of these individual scores with a range of 0 to 4. The other explanatory variables were demographic (age, sex, healthcare worker), pre-existing morbidity, malaria, HIV infection, pre-admission and chronic medications, and medications received on admission or following admission. These explanatory variables were coded as 1 if reported or 0 if not reported or missing.

Statistical Analysis

According to Subramanian (2004), the term multilevel refers to individuals at a lower level who are nested within spatial units at higher levels. Multilevel methods are suitable for the statistical analysis of data with a nested structure, which is typically hierarchical. Multilevel regression modeling was a proper approach for the data analyis used in this study. These data are from several COVID-19 treatment sites across Nigeria with patients clustered by site. The sites in turn may be considered to be nested by facility type e.g. tertiary hospital, non-tertiary hospital, and other treatment site.

Multilevel statistical modeling incorporates models at each level of analysis into a full multilevel model. For example, in a two-level nested model, the model at the first level is expressed as

$$y_{ij} = \beta_{0j} + \beta_1 x_{1ij} + e_{0ij}$$

Where where y_{ij} is the measure of the dependent variable for the ith individual in the jth group. The term β_{0j} is a constant and is the measure of the dependent variable for the jth group, and β_1 is the fixed marginal effect of the predictor variable (x_{1ij}) on the dependent variable.

The individual or the level-1 residual term, e_{0ij}, is assumed to have a normal distribution with a mean of 0 and a variance, $\sigma^2_{e_0}$. In multilevel modeling, the coefficients at level-1 become the outcome variables at level-2. Thus, the model at level-2 can be written as

$$\beta_{0j} = \beta_0 + u_{0j}$$

meaning the mean measure of the dependent variable for the jth group is split into β_0 (the average for the dependent variable across all groups), and u_{0j}, the effect specific to the jth group, and u_{0j} can be treated similar to individual-level residuals. Combining the two equations above yields the full model. This full model is known as a random-intercepts or variance components model:

$$y_{ij} = \beta_0 + \beta_1 x_{1ij} + (u_{0j} + e_{0ij})$$

In this multilevel statistical model, the variance at level-2, $\sigma^2_{u_0}$, measures the group differences after accounting for the compositional effect of the predictor variable and thus separates the effects of the individual-level variables from the contextual differences between group-level variables (see Subramanian, 2004). Therefore using multilevel modeling we can (a) model the variation in patient-level regression coefficients across

sites, (b) account for the patient- and site-level variation in estimating site-level coefficients, and (c) estimate regression coefficients for particular groups (Gelman & Hill, 2007).

We performed univariate analysis using the Fisher exact test, or the Wilcoxon test as appropriate to describe characteristics of patients who had non-missing outcomes. We also did univariate survival analysis using the Kaplan-Meir method to assess the relationship between time from enrollment to development death.

We further fitted adjusted and unadjusted mixed effects logistic regression models and Cox proportional hazards regression models to assess predictors of COVID-19 hospital death. Study site and facility type were included in the models as random effects while severity score, patients' sex, age, health worker, chronic cardiac disease, hypertension, respiratory disease, chronic kidney disease, chronic neurological disorder, HIV, diabetes, current smoking, malignant neoplasm, malaria, pre-admission and chronic medication (ACE inhibitors, angiotensin II receptor blockers, non-steroidal anti-inflammatory drugs in the 14 days prior to admission), medications received on day of admission or following (antiviral, corticosteroid, azithromycin, chloroquine/hydroxychloroquine) were included as fixed effects. We report the models with the smallest AIC selected by stepwise regression. All statistical analysis were conducted using R version 4.1.1. Mixed effects Cox regression was done using the `coxme` package.

Results

Patient characteristics

Table 1: Patient characteristics

	Died		
Variables	**No**, *N* = 3,249	**Yes**, *N* = 213	*p* value
Days from enrollment to outcome, Median (IQR)	12 (7, 15)	2 (1, 10)	<**0.001**
Age, Median (IQR)	39 (28, 53)	61 (48, 70)	<**0.001**
Age group			<**0.001**
<18	252 (8.1%)	4 (1.9%)	
18-45	1,688 (54.4%)	39 (18.7%)	
46-65	894 (28.8%)	95 (45.5%)	
66-75	183 (5.9%)	41 (19.6%)	
>75	87 (2.8%)	30 (14.4%)	
Male	1,947 (59.9%)	152 (71.4%)	<**0.001**
Health care worker	144 (4.4%)	3 (1.4%)	**0.034**
Chronic cardiac disease (not hypertension)	19 (0.6%)	13 (6.1%)	<**0.001**
Diabetes	237 (7.3%)	62 (29.1%)	<**0.001**
Hypertension	506 (15.6%)	88 (41.3%)	<**0.001**
Current smoking	18 (0.6%)	4 (1.9%)	**0.042**
Respiratory disease	55 (1.7%)	4 (1.9%)	0.782
Chronic neurologic disease	12 (0.4%)	0 (0%)	>0.999
Malignant neopllasm	8 (0.2%)	2 (0.9%)	0.122
Chronic kidney disease	10 (0.3%)	6 (2.8%)	<**0.001**
HIV	24 (0.7%)	4 (1.9%)	0.09
Malaria	78 (2.4%)	6 (2.8%)	0.702
Antiviral	457 (14.1%)	24 (11.3%)	0.253
ACE-i/ARB	94 (2.9%)	10 (4.7%)	0.136
Azithromycin	1,515 (46.6%)	104 (48.8%)	0.534
Corticosteroid	180 (5.5%)	54 (25.4%)	<**0.001**
CQ/HCQ	968 (29.8%)	71 (33.3%)	0.275
NSAIDs	31 (1%)	3 (1.4%)	0.463
Systemic anticoagulation	58 (1.8%)	15 (7%)	<**0.001**
Severity score			<**0.001**
0	2,916 (89.8%)	89 (41.8%)	
1	249 (7.7%)	71 (33.3%)	
2	78 (2.4%)	47 (22.1%)	
3	5 (0.2%)	5 (2.3%)	
4	1 (0%)	1 (0.5%)	

Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Logistic regression model

As seen in the table below, we fitted a logistic mixed model estimated using maximum likelihood and the bound optimization by quadratic approximation (BOBYQA) algorithm to predict mortality with severity, age group, male gender, health worker status, chronic cardiac disease, diabetes, respiratory disease (), chronic kidney disease, malaria, azithromycin and chloroquine. The model included site and facility type as random effects. The model's total explanatory power is substantial (conditional $R^2 = 0.55$) and the part related to the fixed effects alone (marginal R^2) is of 0.25. Confidence Intervals (CIs) at the 95% level and p-values were computed using the Wald approximation.

Table 2: Mixed effects logistic regression model of predictors of mortality

Predictor	**OR**	**95% CI**	*p* value
Severity score	3.5	2.73, 4.49	<0.001
Age group			
<18	—	—	
18-45	1.81	0.58, 5.61	0.307
46-65	3.93	1.29, 12	0.016
66-75	5.37	1.68, 17.1	0.005
>75	6.81	2.04, 22.8	0.002
Male	1.78	1.23, 2.56	0.002
Health care worker	0.22	0.06, 0.79	0.02
Chronic cardiac disease (not hypertension)	3.07	1.2, 7.86	0.019
Diabetes	2.16	1.41, 3.31	<0.001
Respiratory disease	0.34	0.09, 1.2	0.094
Chronic kidney disease	11	2.74, 44.2	<0.001
Malaria	0.45	0.16, 1.28	0.134
Azithromycin	0.33	0.19, 0.58	<0.001
CQ/HCQ	0.07	0.03, 0.14	<0.001
Azithromycin * CQ/HCQ	9.69	4.08, 23	<0.001
N = 3,462. AIC = 1,050.6. Conditional $R^2 = 0.55$. Marginal $R^2 = 0.25$			
OR = Odds Ratio, CI = Confidence Interval			

Cox regression model

Kaplan Meier Plots

Interaction Plots