ORIGINAL RESEARCH

Demographic characteristics, clinical presentation and in-hospital outcome among patients with Covid-19 in a Nigerian tertiary hospital

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Abstract

Background

We described the demographic/clinical characteristics and in-hospital outcome of patients with COVID-19 at the University of Nigeria Teaching Hospital (UNTH) during the first wave to inform evidence-based responses during subsequent waves in Africa.

Methodology

We conducted retrospective cohort analyses of adult patients ≥18 years with PCR or GeneXpert-confirmed SARS-CoV-2 infection. Data was extracted from patients' medical records from 1st May to 30th September 2020. Based on disease severity, patients were either hospitalized (82) or managed at home (90). Logistic regression and cox-proportional hazard models were used to determine predictors of severe COVID-19 disease and in-hospital mortality, respectively.

Results

Of 172 cases, 113 (65.7%) were males, and the mean age was 45 ± 19 years. The majority were urban dwellers (72.1%), 19.8% had a positive history of contact with a confirmed/suspected case, 15.7% were healthcare workers while 68 (39.5%) had co-morbidities. Symptomatic patients comprised 73.3% of cases. Fever (p=0.02) and breathlessness (p=0.03) were commoner in males while diarrhoea (p<0.01) was predominant in females. On multivariate analysis, severe COVID-19 was predicted by the presence of co-morbidity (AOR= 14.44, 95% C.I= 4.79- 43.58, p <0.001)and prior antibiotic/antimalarial use (AOR= 6.35, 95% C.I= 2.24- 18.05, p =0.001) while being a non-healthcare worker (AOR= 0.18, 95% C.I= 0.04-0.78, p=0.02) was protective. However, none of the variables assessed predicted in-hospital mortality.

Conclusion

Our findings underscore the contributions of demographic variables in COVID-19 transmission and gender differences in clinical presentation. Underlying comorbidity likewise prior antimicrobial use increased the likelihood of severe COVID-19. The absence of mortality predictors in our study may be related to the relatively small number of deaths. Further studies are recommended to unravel the predominance of severe disease in healthcare workers.

Keywords: COVID-19, Epidemiology, Clinical features, Nigeria, Co-morbidity, Mortality

Introduction

The coronavirus disease 2019 (COVID-19) was discovered in Wuhan, Hubei province of China in December 2019 following a series of events heralded by a cluster of "mysterious" pneumonia cases[1]. It was subsequently declared a pandemic by the World health organization (WHO) on 11th March, 2021[2]. As of 13th August 2021, a total of 205,338,159 confirmed cases and at least 4,333,094 confirmed deaths had been reported globally to the WHO[3]. Several countries have already experienced multiple waves of the pandemic. In Nigeria, COVID-19 was first confirmed on 27th February 2020 following an imported case in an Italian businessman[4]. This was relentlessly followed by widespread community transmission[3]. As of 15th August 2021, Nigeria was experiencing a third wave of the outbreak with a total of 181,962 confirmed cases, including 2,219 deaths since the onset of the pandemic[5,6].

Several studies have been undertaken in various parts of the world to characterize COVID-19[7–11]. So far, the literature from sub-Saharan Africa has been limited partly due to the impact of the pandemic on an already fragile healthcare system[12,13]. It is established that disease severity varies from asymptomatic to critical disease, which may require intensive care and may lead to mortality[14–16]. Older age and pre-existing co-morbidities such as chronic lung disease, hypertension, diabetes, and cardiovascular disease among others have been associated with more severe disease and increased mortality[7,16,17]. Healthcare worker exposure remains a source

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of concern[7,12]. The possible existence of 'super spreaders' has been suggested[18]. Although a slight male preponderance has been widely observed[7,18], gender differences in clinical presentation remain debatable.

Geographical differences in the epidemiology and clinical characteristics of COVID-19 have been apparent, especially during the first wave of the pandemic[19,20]. With the emergence of variants across the world[21], the disease characteristics have continued to evolve. Regional disparities in COVID-19 vaccine deployment and resumption of international travel have further complicated risk assessments in various parts of the world. The majority of sub-Saharan Africa has already experienced multiple waves of the pandemic presumably fueled by variants of concern such as the delta variant and low vaccine availability/uptake. An improved understanding of the epidemiology and clinical characteristics of the disease during the previous waves in the region may be useful in the development of risk mitigation measures and clinical management algorithms during subsequent waves. We described the demographic characteristics, clinical presentation, and in-hospital outcome among patients managed for COVID-19 during the first wave of the pandemic at the isolation centre of the University of Nigeria Teaching Hospital (UNTH), a large referral hospital in South-East Nigeria.

Methodology

Study Design/Study Site

We conducted retrospective cohort analyses of all patients managed for COVID-19 at the UNTH, Ituku/Ozalla, Enugu, South-East Nigeria from 1st May to 30th September 2020. The UNTH is about the largest referral healthcare facility in South-East Nigeria. Before the pandemic, the UNTH had a 5-bed capacity isolation unit for the management of emerging infectious diseases. As part of the COVID-19 response, a purpose-built 16-bed capacity Covid-19 treatment facility was commissioned while another 25-bed capacity ward was repurposed for emergent COVID-19 services in April 2020. In addition, two polymerase chain reaction (PCR) platforms and one GeneXpert equipment were re-purposed for the laboratory diagnosis of SARS-CoV-2 infection. Both the treatment and testing facilities were assessed and accredited by the Nigeria Center for Disease Control (NCDC). The study was approved by the Health Research Ethics Committee of UNTH.

Study Population

The study population comprised adults aged ≥18 years who presented to the UNTH and were confirmed to have SARS-CoV-2 infection irrespective of the symptom profile. The study participants either presented directly to the COVID-19 treatment facility or through other units of the hospital such as the Accident and Emergency Unit and various Outpatient Clinics. SARS-CoV-2 infection was defined as a positive PCR or GeneXpert test result of a nasopharyngeal (NP) or oropharyngeal (OP) swab sample. Individuals with SARS-CoV-2 negative test results were excluded from the analyses irrespective of their clinical features. Based on the physician's assessment of disease severity and need for in-hospital supportive care, a patient was either hospitalized at the COVID-19 treatment facility or reviewed and prescribed medications for home-based care. The performance of laboratory investigations for patients was determined by clinical indication, availability of funds, and infection prevention and control (IPC) considerations.

Data collection and Outcome Measures

Available demographic, exposure, clinical, laboratory, and treatment data were extracted from the medical records of eligible patients. Demographic data included sex, age, marital status, residence/local government area, occupation, and educational level. Exposure data related to contact with a confirmed or suspected COVID-19 case and travel within 14 days of symptom onset were obtained. Clinical information included symptoms, signs, and co-morbidities as assessed/determined and documented by the managing physician. All patients had either a polymerase chain reaction (PCR) or GeneXpert test of NP and OP swab samples for SARS-COV-2 diagnosis per the NCDC guideline[5]. Additional laboratory test results were available for a variable number of participants, including chest radiograph, complete blood count, erythrocyte sedimentation rate (ESR), serum bilirubin, liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and alkaline phosphatase [ALP]), serum creatinine, serum electrolytes, and urinalysis. The primary treatment outcome was in-hospital all-cause mortality. Length of hospital stay (LOS) was defined as the time from admission to discharge or demise.

Statistical analysis

Data was analysed using the statistical package for social sciences (SPSS) version 25 (Chicago, IL, USA). Categorical variables were presented as frequencies and percentages, while continuous variables were presented as mean ± standard deviation when normally distributed and median (interquartile range) if skewed. The chi-square test or Fisher's exact test was used to assess differences between categorical variables. Continuous variables were compared using the Student t-test if normally distributed or the Wilcoxon rank-sum test for skewed data.

Multivariate logistic regression analysis was used to determine factors that independently predicted severe disease. For the survival analysis, the outcome of interest was 'death' which was measured from the time of admission to the time of the demise. The median time to death (survival duration) for independent variables (such as age, sex, oxygen use, and dexamethasone) was compared using a Kaplan -Meier (KM) survival analysis with observed survival differences assessed using log-rank tests. The cox-proportional hazard model was used for the multivariate analysis to determine predictors of in-hospital mortality and to obtain adjusted hazard ratios using variables that had p-value <0.25 on simple regression analysis. A p-value < 0.05 was considered statistically significant.

Results

Demographic characteristics of the patients

Of 172 patients with confirmed COVID-19, 113 (65.7%) were males and 59 (34.4%) were females. The mean age of the patients was 45.2 ± 19.4 years. The majority of the patients, 111 (64.5%) were married, and 124 (72.1%) resided in urban areas.

Trading was the most common occupation (29.7%) while healthcare workers constituted 15.7% of the patients. Only 34 (19.8%) patients gave a history of contact with a suspected or confirmed COVID-19 case while 7 (4.1%) had a history of travel in the last 14 days before the onset of symptoms.

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Table 1: Definition of outcome measures among patients with COVID-19 at the University of Nigeria Teaching Hospital, May – September, 2020

Parameter	Definition
Symptomatic COVID-19	Persons presenting with at least one symptom in addition to a positive SARS-CoV-2 test result.
***Asymptomatic COVID-19*:**	An apparently healthy individual with no clinical symptoms but has a positive SARS-CoV-2 test result.
Severe COVID-19	In line with WHO recommendation, severe COVID-19 disease included patients in respiratory distress and/or tachypnea with respiratory rate > 30 cycles/minute; hypoxemia with $Sp0_2$ < 92% on room air, presence of severe pneumonia, and those with evidence of critical systemic conditions such as septic shock that will require life-sustaining therapy
Non-severe COVID-19	All those who did not meet the criteria definition of severe COVID-19 as stated above
In-hospital Mortality	Death in a patient admitted to the hospital as a confirmed case of COVID-19 irrespective of the cause
Fever	documented body temperature of ≥ 37.5°C
Hypoxaemia	Oxygen saturation (SpO2) < 92% on room air
Anaemia	Hemoglobin level <10g/dl
Leucocytosis	Total white blood cell count >12,000 × 10^9 cells/l
Leucopenia	Total white blood cell count < 4000 × 10^9 cells/l
Thrombocytopenia	Platelet count of <150 000/mm
Markedly elevated ESR	ESR ≥ 100 mm 1st hour Westergreen
Elevated ALT	ALT > 40IU/L
Elevated AST	ALT > 40IU/L
Elevated Creatinine	Serum creatinine >80 µmol/L
Hyperglycaemia	Random blood glucose ≥10mmol/l

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ESR: Erythrocyte sedimentation rate

Table 2: Epidemiological/Demographic Characteristics of Patients with COVID-19 at the University of Nigeria Teaching Hospital,

Characteristics	**Patients** (N=172) n (%)
Gender	
Male	113 (65.7)
Female	59 (34.3)
Age (years)	
Mean ± SD	45.2 ± 19.4
<25	20 (11.6)
25-34	32 (18.6)
35-44	40 (23.3)
45-54	24 (14.0)
55-64	25 (14.5)
≥65	31 (18.0)
Marital Status	
Single	54 (31.4)
Married	111 (64.5)
Widowed	7 (4.1)
Residence	
Urban	124 (72.1)
Rural	48 (27.9)
Location of Residence	
Enugu East	118 (68.4)
Enugu West	27 (15.8)
Enugu North	5 (3.0)
Others†	22 (12.8)
Educational level	
None	35 (20.3)
Primary	37 (21.5)
Secondary	32 (18.6)
Tertiary	68 (39.5)
Occupation	
Health care worker	27 (15.7)
Civil servant	36 (20.9)
Trader	51 (29.7)

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Table 2 Cont....

Artisan	12 (7.0)
Student	18 (10.5)
Retired	16 (9.3)
Unemployed	9 (5.2)
Others	3 (1.7)
History of Contact with COVID-19 Case*	
Yes	34(19.8)
No	138 (80.2)
History of Recent Travel	
Yes	7 (4.1)
No	165 (95.9)
Care Setting	
Hospital-based	82 (47.7)
Home-based	90 (52.3)

*Suspected or confirmed; †Others: Abia State (3), Anambra State (6), Delta State (2), Edo State (1), Imo State (3), Lagos State (2), Rivers State (5)

Table 3: Baseline Clinical Characteristics of Patients Diagnosed with COVID-19 at the University of Nigeria Teaching Hospital, May – September, 2020

Characteristics	**Patients** (N=172)
Symptomatic, n (%)	
Yes	126 (73.3)
No	46 (26.7)
Symptoms Duration at Presentation (days), Mean (IQR)	7.0 (1-14)
Symptoms, n (%)	
Fever	97 (56.4)
Cough	81 (47.1)
Sputum production (N=81)	43 (53.1)
Hemoptysis	11 (6.4)
Breathlessness	81 (47.1)
Sore throat	22 (12.8)
Malaise	54 (31.4)
Anosmia	24 (14.0)
Ageusia	19 (11.0)
Headache	73 (42.4)
Nasal discharge	15 (8.7)
Body aches	56 (32.6)
Fatigue	70 (40.7)
Abdominal pain	27 (15.7)
Diarrhea	22 (12.8)
Nausea/Vomiting	19 (11.0)
Vitals, mean ± SD	
Temperature (°C)	37.0 ± 1.0
<37.5, n (%)	125 (72.7)
≥37.5, n (%)	47(27.3)
Pulse rate (beats/min)	91.0 ± 18.9
Systolic blood pressure (mmHg)	125.0 ± 20.0
Diastolic blood pressure (mmHg)	77.3 ± 14.3
Mean arterial pressure (mmHg)	93.2 ± 15.3
Respiratory rate (Cycles/min)	27.6 ± 10.9
SPO_2 (%)	91.5 ± 11.8
<92, n (%)	56 (32.6)
≥ 92, n (%)	116(67.4)
Systemic Findings, n (%)	
Respiratory	
Normal	114 (66.3)
Abnormal	58 (33.7)
Cardiovascular	
Normal	140 (81.4)
Abnormal	32(18.6)
Neurological	
Normal	154(89.5)
Abnormal	18 (10.5)
Gastrointestinal	
Normal	161 (93.6)
Abnormal	11(6.4)
Urogenital	

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Table 3 Cont....

Normal	168 (97.7)
Abnormal	4(2.3)
Musculoskeletal	
Normal	171 (99.4)
Abnormal	1 (0.6)
Skin	
Normal	164 (97.7)
Abnormal	4(2.3)
Comorbidity	
Yes	68 (39.5)
No	104 (60.5)
Type of Comorbidity	
Cardiovascular disease*	59 (34.3)
Diabetes mellitus	30 (17.4)
Chronic lung disease	18 (10.5)
Cerebrovascular disease	6 (3.5)
Chronic kidney disease	4 (2.3)
HIV	2 (1.2)
Cancers	2 (1.2)

SD: Standard deviation, HIV: Human immunodeficiency virus; *Cardiovascular disease: hypertension/hypertensive heart disease= 54, ischaemic heart disease=5

Table 4: Baseline Laboratory Findings among COVID-19 In-patients at the University of Nigeria Teaching Hospital, May – September, 2020

Parameters	
Haemogbobin (g/dl), Ref. Range = 11-17, N=70	
Mean ± SD	11.8 ± 2.2
<10	14 (20.0)
White Blood Cells- Total, × 10^9/µL, Ref. Range =4.0- 12.0, N=70	
Median (IQR)	10.4(7.7-13.3)
<4.0	2 (2.9)
>12.0	22 (31.4)
White Blood Cells- Differential, %, N=70	
Median (IQR)	
Neutrophils	73.8 (65.7-80.2)
Lymphocytes	20.7 (13.9-26.0)
Monocytes	3.8 (1.0-7.0)
Eosinophils	0.6 (0.0-1.8)
Basophils	0.1 (0.0-0.6)
Platelet Count, × 10^9/µL, Ref. Range =150-400, N=70	
Mean ± SD	254.1 ± 118.0
<150	8 (11.4)
>400	6 (8.6)
Erythrocyte Sedimentation Rate, mm 1st hour Westergren, N=53	
Mean ± SD	91.4 ± 29.6
≥ 100	26 (49.1)
Total Serum Bilirubin, µmol/L, Ref. Range =8.0-17.0umol/L, N= 17	
Median (IQR)	7.0 (2.5-10.0)
>17	1 (5.9)
Conjugated Bilirubin, µmol/L, Ref. Range = <8umol/L, N= 17	
Median (IQR)	1.8 (0.6-3.6)
>8	1 (5.9)
Aspartate Transaminase, IU/L, Ref. Range = <40, N= 18	
Median (IQR)	56.0 (21.1-125.6)
>40	10 (55.6)
Alanine Transaminase, IU/L, Ref. Range = <40, N= 18	
Median (IQR)	51.0 (27.0-82.6)
>40	10 (55.6)
Alkaline Phosphatase, IU/L, Ref. Range =25-92, N= 18	
Median (IQR)	81.0 (50.4-136.3)
>92	7 (38.9)
Random Blood Glucose, mmol/L, Ref. Range = 3.8- 7.8, N= 84	
Median (IQR)	6.9 (5.4-11.1)
≥10	29 (34.5)
Urea, mmol/L, Ref. Range =<8.3mmol/L, N= 47	
Median (IQR)	5.3 (4.6-8.8)
>8.3	12(25.5)
Ceatinine, µmol/L, Ref. Range = < 80umol/L, N= 47	
Median (IQR)	106.0 (70.0-133.9)

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Table 4 Cont....

>80	28 (59.6)
Sodium, mmol/L, Ref. Range = 135-145, N= 48	
Mean ± SD	140 ± 7.5
<135	9 (18.8)
>145	5 (10.4)
Potassium, mmol/L, Ref. Range = 3.5-5.0, N= 48	
Mean ± SD	4.5 ± 0.67
<3.5	6 (12.5)
>5.0	14 (58.3)
Chloride, mmol/L, Ref. Range = 97-108, N= 48	
Mean ± SD	104.9 ± 7.0
<96	8 (16.7)
>108	9 (18.8)
Bicarbonate, mmol/L, Ref. Range =24-28 , N= 48	
Mean ± SD	20.3 ± 4.4
<24	38 (79.2)
>28	2 (4.2)
Proteinuria, N= 23	
Yes	18 (78.3)
No	5 (21.7)
Haematuria, N= 22	
Yes	5 (22.7)
No	17 (77.3)
Chest Radiograph, N= 13	
Abnormal	12 (92.3)
Ground-glass opacities/bilateral	4 (30.8)
Patchy opacities/bilateral	3 (23.1)
Lacy opacities/bilateral	2 (15.4)
Homogenous opacity (consolidation)/unilateral	2 (15.4)
Homogenous opacity (consolidation)/bilateral	1 (7.7)
Normal	1 (7.7)
BSTI Grading	
Mild	5 (21.7)
Moderate/Severe	7 (53.8)

SD: Standard deviation, HIV: Human immunodeficiency virus; *Cardiovascular disease: hypertension/hypertensive heart disease= 54, ischaemic heart disease=5

Table 5: Gender differences in clinical characteristics of patients with COVID-19 at the University of Nigeria Teaching Hospital, May – September 2020

Characteristics	Male (N=113)	Female (N=59)	OR (95% C.I)	p-value
Symptomatic, yes	87(77.0)	39(66.1)	1.72 (0.86-3.43)	0.13
Symptom duration at presentation (days), Median (IQR)	7.0 (1-14)	3.0 (1-7)	**N/A**	**<0.01***
Fever	71(62.8)	26(44.1)	**2.42 (1.13-4.07)**	**0.02***
Cough	57(50.4)	24(40.7)	1.48 (0.79-2.81)	0.22
Sputum production	40(52.6)	13(54.2)		0.90
Hemoptysis	9(8.0)	2(3.4)	2.47 (0.52-11.81)	0.24
Breathlessness	60(53.1)	21(35.6)	**2.05 (1.07-3.92)**	**0.03***
Sore throat	16(14.2)	6(10.2)	1.46 (0.54-3.95)	0.46
Malaise	36(31.9)	18(30.5)	1.07 (0.54- 2.10)	0.86
Anosmia	15(13.3)	9()15.3	0.85 (0.35- 2.08)	0.72
Ageusia	11(9.7)	8(13.6)	0.69 (0.26-1.82)	0.45
Headache	51(45.1)	22(37.3)	1.38(0.73-2.64)	0.32
Nasal discharge	12(10.6)	3(5.1)	2.22 (0.60- 8.19)	0.22
Body aches	38(33.6)	18(30.5)	1.15 (0.59-2.27)	0.68
Fatigue	50(44.2)	20(33.9)	1.55 (0.80-2.98)	0.19
Abdominal pain	21(18.6)	6(10.2)	2.02 (0.77-5.31)	0.15
Diarrhea	8(7.1)	14(23.7)	0.25 (0.10-0.63)	**<0.01***
Nausea/Vomiting	9(8.0)	10(16.9)	0.42 (0.16-1.11)	0.07
Temperature (°C), Mean ± SD	37.1 ± 1.0	36.7 ± 0.9	N/A	**0.03***
Pulse rate (beats/min), Mean ± SD	93.45 ± 19.2	86.3 ± 17.4	N/A	**0.02***
Systolic blood pressure (mmHg), Mean ± SD	128.0 ± 21.7	119.1 ± 14.7	N/A	**<0.01***
Diastolic blood pressure (mmHg), Mean ± SD	79.1 ± 14.6	73.9 ± 13.1	N/A	**0.02***
Mean arterial pressure (mmHg), Mean ± SD	95.4 ± 15.9	88. 9 ±13.2	N/A	**<0.01***
Respiratory rate (Cycles/min), Mean ± SD	28.7 ± 11.8	25.4 ± 8.5	N/A	0.06
SPO_2 (%), Mean ± SD	91.1 ± 11.4	92.2 ± 12.5	N/A	0.58
Comorbidity, yes	48 (42.5)	20(33.9)	1.44 (0.75-2.78)	0.28

Table 6: Univariate and Multivariate Analysis of Predictors of Severe COVID-19 among Patients at the University of Nigeria Teaching Hospital, May – September 2020

Characteristics	All Patients (N=172) n (%)	Severe (N=72) n (%)	Non-Severe (N=100) n (%)	Univariate Analysis		Multivariate Analysis	
				OR (95% C.I)	p=value	AOR (95% C.I)	p- Value
Age (years)							
> 40	91 (52.9)	13 (16.0)	68 (84.0)	9.64 (4.63-20.07)	<0.001**	2.26 (0.69-7.45)	0.18
≤ 40	81 (47.1)	59 (64.8)	32 (35.2)				
Gender							
Male	113 (65.7)	52 (46.0)	61 (54.0)	1.66 (0.87-3.20)	0.13**	1.50 (0.54-4.12)	0.44
Female	59 (34.3)	20 (33.9)	39 (66.1)				
Educational Status							
≥ Secondary	100 (58.1)	43 (43.0)	57 (57.0)	1.12 (0.61-2.07)	0.72	N/A	N/A
≤ Primary	72 (41.9)	29 (40.3)	43 (59.7)				
Occupation							
Non-HCW	145 (84.3)	67 (46.2)	78 (53.8)	3.38 (1.36-10.53)	0.01**	0.18 (0.04-0.78)	0.02*
HCW	27 (15.7)	5 (18.5)	22 (81.5)				
Marital Status							
Married	111 (64.5)	57 (51.4)	54 (48.6)	3.24 (1.62-6.46)	0.001**	0.65 (0.20-2.15)	0.48
Single	61 (35.5)	15 (24.6)	46 (75.4)				
Residence							
Rural	48 (27.9)	27 (37.5)	21 (21.0)	2.26 (1.15-4.45)	0.02**	1.96 (0.70-5.47)	0.20
Urban	124 (72.1)	45 (62.5)	79 (79.0)				
Symptoms Duration at Presentation (days)							
> 7	63 (36.6)	43 (68.3)	20 (31.7)	5.93 (3.01-11.70)	<0.001**	0.44 (0.16-1.18)	0.10
≤ 7	109 (63.4)	29 (26.6)	80 (73.4)				
Comorbidity							
Yes	68 (39.5)	56 (82.4)	12 (17.6)	25.67 (11.30-58.28)	<0.001**	14.44 (4.79-43.58)	<0.001*
No	104 (60.5)	16 (15.4)	88 (84.6)				
Prior antibiotic /antimalarial use							
Yes	91 (52.9)	51 (56.0)	40 (44.0)	3.64 (1.91 -6.96)	<0.001**	6.35 (2.24-18.05)	0.001*
No	81 (47.1)	21 (25.9)	60 (74.1)				

**Met the set condition for inclusion in the multivariate model at p< 0.25, *Statistically significant at p<0.05, -Fisher's Exact test, OR= Odds ratio, AOR= Adjusted odds ratio, C.I= Confidence interval, HCW= Health care worker, N/A: Not applicable

Table 7: Simple Regression Analysis and Multivariate Cox-proportional Hazard Model of Predictors of In-hospital Mortality among Patients with COVID-19 at the University of Nigeria Teaching Hospital, May – September 2020

Characteristics	Dead N= 19 n (%)	Alive N= 63 n (%)	Simple Regression Analysis		Multivariate Cox Proportion Analysis	
			CHR (95% CI)	P-value	AHR (95% C.I)	p-Value
Age (years)						
< 60	7 (17.5)	33 (82.5)	0.53 (0.19 – 1.52)	0.24**	1.35 (0.12 – 15.03)	0.81
≥ 60	12 (28.6)	30 (71.4)				
Gender						
Male	15 (25.4)	44 (74.6)	0.62 (0.18-2.11)	0.44	N/A	N/A
Female	4 (17.4)	19 (82.6)				
Educational Status						
≤ Primary	7 (20.6)	27 (79.4)	0.64 (0.45-3.70)	0.64	N/A	N/A
≥ Secondary	12 (25.0)	36 (75.0)				
Occupation						
HCW	1 (20.0)	4 (80.0)	1.22 (0.13-11.62)	1.00↑	N/A	N/A
Non-HCW	18 (23.4)	59 (76.6)				
Marital Status						
Single	4 (21.1)	15 (78.9)	1.17 (0.34-4.07)	0.80	N/A	N/A
Married	15 (23.8)	48 (76.2)				
Residence						
Urban	11 (22.0)	39 (78.0)	1.18 (0.42-3.35)	0.75	N/A	N/A
Rural	8 (25.0)	24 (75.0)				
Comorbidity						
Yes	17 (27.9)	44 (72.1)	0.27 (0.06-1.30)	0.09**	1.32 (0.05 – 32.79)	0.87
No	2 (9.5)	19 (90.5)				
SPO_2 on admission (%)						
< 92	17 (30.9)	37 (69.1)	5.59 (1.19-26.34)	0.02*	1.23 (0.22 – 7.00)	0.82
≥ 92	2 (7.4)	25 (92.6)				
RBG on admission (mmol/l)						
< 10	10 (18.9)	43 (81.1)	0.52	0.21**	0.46	0.42
			(0.18 – 1.47)		(0.07 – 2.94)	
≥10	9 (31.0)	20 (69.0)				
CRB 65						
< 2	8 (33.3)	16 (66.7)	2.13 (0.73-6.25)	0.16**	0.31 (0.07 – 1.41)	0.130
≥ 2	11 (19.0)	47 (81.0)				
Received supplemental oxygen therapy						
Yes	18 (25.7)	52 (74.3)	0.26 (0.03-2.18)	0.19**	9.15 (0.45 – 185.22)	0.15
No	1 (8.3)	11 (91.7)				

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Table 7 Cont...

Symptom duration at presentation						
≤ 7	5 (15.2)	28 (84.8)	0.45 (0.14 – 1.39)	0.16**	1.39 (0.27 – 7.07)	0.69
>7	14 (28.6)	35 (71.4)				
Prior antibiotic/ antimalarial use						
Yes	14 (26.4)	39 (73.6)	1.72 (0.55-5.39)	0.35	N/A	N/A
No	5 (17.2)	24 (82.8)				
Received dexamethasone therapy						
Yes	13 (19.1)	55 (80.9)	0.32 (0.09-1.07)	0.06**	1.33 (0.17 – 10.34)	0.78
No	6 (42.9)	8 (57.1)				

**Met the set condition for inclusion in the multivariate model at p< 0.25, *Statistically significant at p < 0.05, -Fisher's Exact test, CHR= Crude hazard ratio, AHR= Adjusted hazard ratio, C.I= Confidence interval, HCW= health care worker, RBG= Random blood glucose, N/A: Not applicable N/A

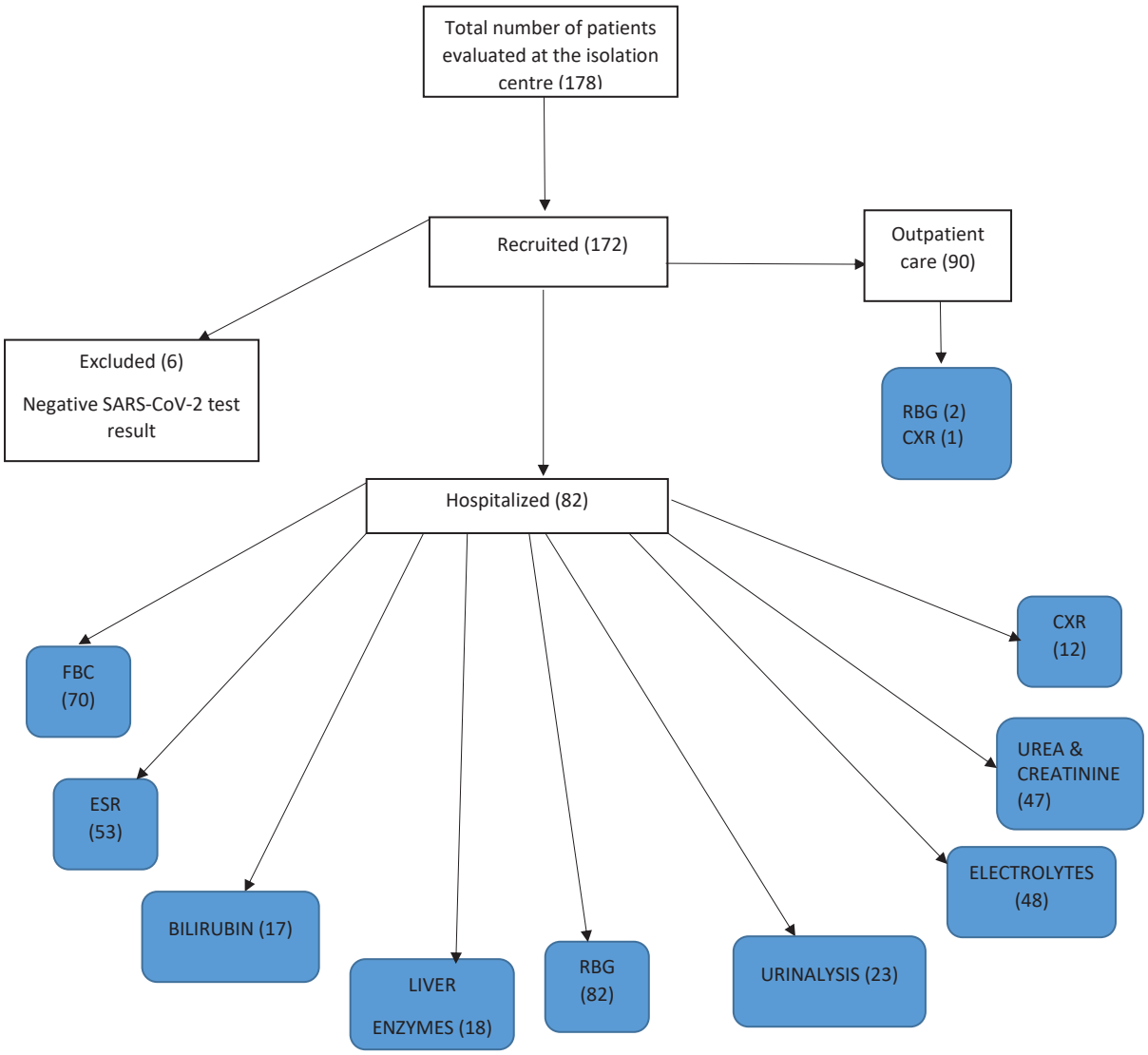

Fig 1: Flow chart showing COVID-19 patient selection, clinical care setting and availability of laboratory investigations. CXR: Chest X-ray, ESR: Erthrocyte Sedimentantion Rate, FBC: Full Blood Count, RBG: Random Blood Glucose

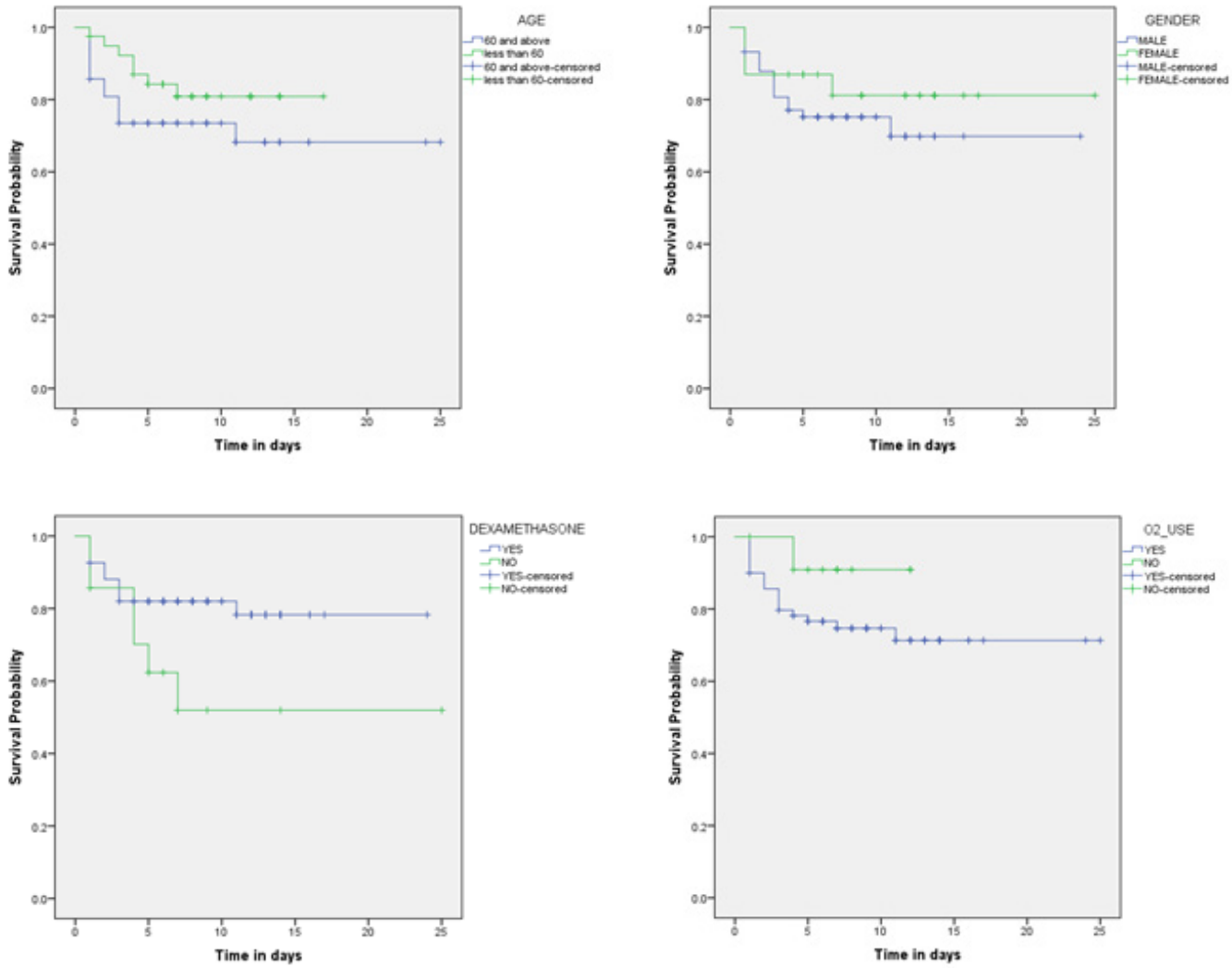

Fig 2: Kaplan-Meier curve comparing survival probability in hospitalized COVID-19 patients based on various predictor variables, including A) Age (≥60 yrs vs. <60 yrs), B) Gender (Male vs. female), C) Dexamethasone use (Yes vs. No), and D) Supplemental oxygen administration (Yes vs. No). Although female patients, those who received dexamethasone and supplemental oxygen were more likely to live longer in days ie 20.83(1.89) vs. 17.98(1.36), log rank=0.62, p =0.41; 19.55(1.12) vs. 14.87(3.06), log rank=3.75, p =0.05 and 18.84(1.25) vs. 11.27(0.69), log rank=1.48, p =0.22 respectively, there was no significant difference in the probability of mortality accordingly in the dichotomous groups for each of the four variables assessed.

The demographic characteristics of the participants are summarized in Table 2.

Baseline clinical and laboratory characteristics of the patients

The baseline clinical characteristics of the patients are shown in Table 3. At presentation, 126 (73.3%) were found to be symptomatic with the median duration of symptoms before presentation being 7.0 (1-14) days. The five most commonly reported symptoms were fever, 97 (56.4%); cough, 81 (47.1%); breathlessness, 81 (47.1%); headache, 73 (42.4%); and fatigue, 70 (40.7%). Pre-existing co-morbidity was seen in 68 (39.5%) patients, with cardiovascular disease 59 (34.3%), diabetes mellitus 30 (17.4%), and chronic lung disease 18 (10.5%) as the most frequently reported conditions. The mean body temperature at presentation was 37.0 ± 1.0 °C with 47 (27.3%) of patients presenting with physician-documented fever. Hypoxaemia was documented in 56 (32.6%) patients. Abnormalities of body systems were mostly observed in the respiratory 58 (33.7%), cardiovascular 32 (18.6%), and neurological 18 (10.5%) systems.

As shown in Table 4, baseline laboratory investigations were available for a variable number of patients. The observed haematological abnormalities included anaemia 14/70 (20%), leucocytosis 22/70 (31.4%), leucopenia 2/70 (2.9%), thrombocytopenia 8/70 (11.4%) and a markedly elevated ESR 26/53 (49.1%). Proteinuria was seen in 18 out of 23 patients (78.3%) while 5/23 (22.7%) had hematuria. Among biochemical abnormalities, hyperbilirubinemia was uncommon in 1/17 (5.9%) while elevated AST, ALT, and ALP were found in 10/18 (55.6%), 10/18 (55.6%) and 7/18 (38.9%) patients, respectively. Hyperglycaemia was observed in 29/84 (34.5%) patients. Urea and creatinine were raised in 12/47 (25.5%) and 28/47 (59.6%) patients, respectively. All but 1 of the 13 patients with an available report of a chest radiograph had varying degrees of radiological abnormalities, with 7 (53.8%) of them demonstrating moderate to severe disease according to the British Society of Thoracic Imaging (BSTI) classification.

Gender differences in clinical characteristics

As shown in Table 5, women presented to the hospital earlier than men (median [IQR], 3.0 [1-7] days vs. 7.0 [1-14] days, p<0.01). Also, male patients were more likely to have fever (62.8% vs. 44.1%, OR=2.4, 95% CI 1.1-4.1, p=0.02) and breathlessness (53.1% vs. 35.6%, OR=4.08, 95% CI 1.1-4.0,

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p=0.03), while diarrhoea was predominant among women (23.7% vs. 7.1%, OR=0.3, 95% CI 0.1-0.6 p<0.01). Women were found to have significantly lower systolic and diastolic blood pressure [BP] (119mmHg vs. 128mmHg, p<0.01 and 74 mmHg vs. 79 mmHg, p=0.02 respectively) likewise a lower mean arterial BP (89 mmHg vs. 95 mmHg, p<0.01).

COVID-19 severity

Of the 172 patients, 72 (41.9%) had severe COVID-19 while the remaining 100 (58.1%) did not meet the criteria definition of severe disease. The univariate and multivariate analyses of factors associated with severe COVID-19 are presented in Table 6. On univariate analysis, severe COVID-19 was associated with age >40 years (Odds ratio [OR]= 9.64, 95% C.I= 4.63-20.07, p <0.001), being a non-healthcare worker (OR= 3.38, 95% C.I= 1.36-10.53, p=0.01), being married (OR= 3.24, 95% C.I= 1.62-6.46, p=0.001), rural residence (OR=2.26, 95% C.I= 1.15-4.45, p=0.02), delayed presentation >7days from illness onset OR=5.95, 95% C.I= 3.01-11.70, p <0.001), presence of co-morbidity (OR= 25.67, 95% C.I= 11.30- 58.28, p <0.001) and prior antibiotic/ antimalarial use (OR= 3.64, 95% C.I= 1.90- 6.96, p <0.001). After adjusting for potential confounding variables, severe COVID-19 was independently predicted by the presence of co-morbidity (AOR= 14.44, 95% C.I= 4.79- 43.58, p <0.001) and prior antibiotic/antimalarial use (AOR= 6.35, 95% C.I= 2.24- 18.05, p =0.001) while being a non-healthcare worker was protective (AOR= 0.18, 95% C.I= 0.04-0.78, p=0.02).

In-hospital Care and Outcome

Of 172 patients diagnosed with COVID-19, only 82 (47.7%) were admitted to the hospital per physician assessment (Fig. 1). The median (IQR) length of stay (LOS) in the hospital was 7.0 days (4- 12 days). In terms of antimicrobial drugs administered as COVID-19 treatment, the regimens used included hydroxychloroquine 79 (96.3%) and chloroquine 3 (3.7%). Dexamethasone therapy was administered to 68 patients (82.9 %) while supplemental oxygen therapy was provided to 70 patients (85.4%)

Of 82 patients with COVID-19 admitted to the hospital, 19 died giving an in-hospital mortality rate of 23.2%. The simple regression analysis and multivariate cox-proportional hazard model of factors associated with in-hospital mortality are presented in Table 7. On simple regression analysis, in-hospital mortality was associated with SpO2 <92 (OR= 5.59, 95% C.I= 1.19-26.34, p=0.02) while dexamethasone use showed a trend towards protection from in-hospital mortality (OR=0.32, 95% C.I= 0.09-1.07, p=0.06). Despite participants aged > 60 years, those with hyperglycemia >10mmol/l, and those with late presentation >7 days showing more likelihood to die, the difference was not statistically significant. Also, individuals who received supplemental oxygen therapy were more likely to survive but the difference was not statistically significant. After adjusting for potential confounding variables, no variable independently predicted in-hospital mortality.

Discussion

Globally, the epidemiology and clinical manifestation of COVID-19 have evolved. In this study, we found that Nigerian patients with confirmed COVID-19 during the first wave were predominantly males, young or of middle age, resided mostly in urban areas, and had an infrequent history of travel or contact with a suspected/confirmed Covid-19 case. Healthcare worker exposure and pre-existing co-morbidities were common. The clinical presentation of COVID-19 in our study population was typical of those reported in the literature. Interestingly, we found a few gender differences in COVID-19 clinical presentation. Notable laboratory abnormalities were observed. Underlying co-morbidity, prior antimicrobial use, and being a healthcare worker increased the likelihood of severe COVID-19.

The average age of presentation in our participants is similar to previous studies that reported an average age of 42 to 49 years among patients with COVID-19[1,10,15,22–25]. Contrarily, previous studies in Uganda[11] and Chile[26] observed an average age of 34 years and 39 years, respectively, while studies in Libya and the United States reported 56 years and 65 years respectively as the average age of their cohorts[27]. These findings show that COVID-19 can affect various age groups though patients in some regions such as Africa may be relatively younger possibly due to their population dynamics. Moreover, young persons tend to readily move about hence increasing the risk of SARS-CoV-2 exposure. As documented in this study, an overwhelming majority of the previous literature has reported a male preponderance among COVID-19 patients globally[1,8,10,11,22,24,25,27–29]. A few others showed marginal female preponderance or no gender predilection[15,23,26]. There are suggestions that biological factors such as sex/steroid hormones, an abundance of the angiotensin-converting enzyme (ACE 2) receptors, and immune response in males may influence susceptibility and severity of infection[30,31]. The contribution of behavioural factors commoner in males such as cigarette smoking has been speculated[27]. The predominance of urban residence among our patients is in tandem with other studies in the tropics[32,33]. Moreover, the proximity of our teaching hospital to Enugu town and the barriers experienced by rural dwellers in accessing testing, care, and treatment in tertiary facilities could have contributed to the dominance of urban dwellers in our study population. Overcrowding and dynamic human movements are quite common in urban settlements, partly explaining our findings.

Healthcare workers represented one-sixth of COVID-19 cases in this study which underscores the high rate of healthcare worker exposure during the pandemic. Globally, various studies have reported relatively high proportions of SARS-CoV-2 infection among healthcare workers ranging from 5.6% to 19%[7,23,24,29]. Factors that may contribute to the relatively high representation of healthcare workers in the Covid-19 cohort include inadequate IPC strategies and easy access to testing and treatment. The high burden of COVID-19 among healthcare workers is of grave concern, especially in resource-limited settings such as Nigeria, where the healthcare workforce and infrastructure are sub-optimal. Traders comprised the most frequent occupation group, an observation that has previously been documented[11]. Other occupation groups that have been frequently reported among patients with COVID-19 in Sub-Saharan Africa include prisoners and students[11,24]. The inherent overcrowding and non-compliance with non-pharmacological measures in typical Nigerian marketplaces and the attendant risk of increased viral transmission makes our finding unsurprising. History of contact with suspected/confirmed COVID-19 cases and travel history were respectively documented in only 20% and 4.1% of patients, which suggests that most of the patients might have been exposed through ongoing community transmission. Similar observations have been previously reported[7,23,34].

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Pre-existing co-morbidity was seen in nearly 40% of the patients with cardiovascular disease as the commonest, followed by diabetes mellitus and chronic lung disease. Pre-existing co-morbidity has been reported in 26.8% to 94% of patients with COVID-19[11,17,24,25,27,34]. Our finding is comparable with a previous study in Lagos, Nigeria where half of the patients had co-morbidities[10]. However, another study in China reported co-morbidities in only a quarter of their cohort[35]. In line with our findings, previous studies in Sub-Saharan Africa and the US found cardiovascular disease and diabetes as the commonest co-morbidities in their COVID-19 patients[11,24,34]. Unlike our study, other co-morbidities that were frequently reported among patients with COVID-19 in the US include obesity, chronic kidney disease, and dyslipidemia[8,34,36]. Subtle differences in the various studies may be a reflection of the burden of chronic diseases in their populations. In addition, the limited number of patients with laboratory investigations also impacted our ability to assess for some co-morbidities such as kidney disease and dyslipidemia in our cohort.

The clinical presentation of COVID-19 is varied, ranging from asymptomatic to severe disease. About three-quarters of our patients were symptomatic, similar to other hospital-based studies[10,16,23,27,37]. National epidemiological reports suggest that the proportion of symptomatic individuals among COVID-19 cases is generally less than 20% in sub-Saharan Africa[38]. The predominance of symptomatic individuals in this study is understandable since ill persons are more likely to seek care, unlike asymptomatic cases that may remain unaware of their COVID-19 unless tested. Fever, cough, sputum production, breathlessness, headache, and fatigue were the most frequently reported symptoms. This is in tandem with the clinical presentation of COVID-19 reported in most previous studies[1,7,8,10,11,35,39]. Kirenga et al however did not report breathlessness among the 56 patients with COVID-19 evaluated in a COVID-19 treatment facility in Uganda[11]. Also, a previous study among 32 patients in Lagos, Nigeria reported breathlessness in only 9.4% of its participants[37]. The disparity between these studies and ours may be because of their cohorts' small sample sizes and the milder disease severity. Some of the less commonly reported symptoms in our patients include nasal discharge, sore throat, diarrhoea, nausea, and vomiting, similar to the observations of several previous studies[1,9,10,35]. About 11% and 14% of patients respectively reported ageusia and anosmia in our cohort, which is slightly lower than the 19% reported for each of these symptoms in the US[8]. Due to the non-specific clinical profile of COVID-19, the presence of ageusia and anosmia has been used by some clinicians to empirically strengthen the clinical suspicion of COVID-19 among patients with respiratory symptoms during the pandemic. However, their relatively low frequency among patients with COVID-19 continues to undermine their utility in presumptive diagnosis.

We documented hypoxaemia at presentation in one-third of our study patients which is similar to the report of 28.9% seen in COVID-19 cohorts in a previous study in Katsina, North-West Nigeria[22]. Several studies in other populations have reported variable proportions of hypoxaemia ranging from 36% to 65.4% among Covid-19 patients[39,40]. COVID-19 cases with hypoxaemia represent cohorts with severe disease that require supplemental oxygen therapy, more aggressive monitoring, and in some cases intensive care. The pandemic generally exposed the fragile healthcare systems of resource-constrained settings with limited availability of supplemental oxygen systems, ventilators, and other respiratory support which partly impacted Covid-related mortality in affected populations[12,13].

Despite the relatively small number of patients with available laboratory results, we documented several laboratory abnormalities suggestive of the multi-system complications of COVID-19. Half of our patients had markedly elevated ESR while leucocytosis and anaemia were documented in one-third and one-fifth of patients, respectively. Thrombocytopenia and leucopenia were much less common. Similarly, Ibrahim et al in a previous study in Nigeria documented leucopenia in 2.9% of COVID-19 cases while leukocytosis occurred in 14.3% of them[22]. Contrarily, previous studies in other parts of the world reported slightly higher occurrences of leucopenia ranging from 8.6% in Libya to 33.7% in China[27,35]. Varied reports of thrombocytopenia ranging from 14.3% to 36.2%[11,22,27,35,39] were seen among individuals with COVID-19 and this closely relates to 11.4% found among our participants but higher than 2.7% seen in participants in Chile, South America[26]. Anaemia has been documented in 5.7% to 39.47% of participants with COVID-19[11,15,22,32]. The differences in haematological profile may be accounted for by the clinical phase of the infection, disease severity, co-morbidities, and methodological issues such as sample size and the definition of anaemia. Biochemical derangements were common among patients with available results, including liver enzyme derangement, azotaemia, and hyperglycaemia. Liver enzyme derangement and azotaemia in patients with COVID-19 have been previously reported in other parts of the world[11,27,35,39]. Aggarwal and colleagues[8] found a high frequency of elevated transaminase (38.0%) and elevated creatinine (33.0%) in their COVID-19 cohort which is comparable to ours, while Ibrahim et al and Kirenga observed that most of their patients with COVID-19 had normal liver enzymes and normal creatinine level[11,22]. About three-quarters of our patients with available urinalysis results had proteinuria while a quarter had hematuria. This was relatively higher than that observed in India, where proteinuria and hematuria were seen in 58.2% and 17.3% of COVID-19 patients respectively[41]. Our finding of proteinuria was comparable to that reported in Italy (89.8%)[42]. The study in Italy however observed a higher frequency of hematuria (72.1%) compared to ours[42]. Although urinalysis findings have not been commonly reported in studies involving COVID-19 patients, available observations have shown their importance in accessing acute kidney injury and the severity of COVID-19[41,42]. In resource-limited settings, urinalysis may serve as a readily available cost-effective test for renal complications in patients with COVID-19. The proportion of patients with hyperglycemia in our cohort was twice the proportion of those reporting pre-existing diabetes, suggesting either a fairly high magnitude of undiagnosed diabetes or a COVID-related metabolic complication in our patients. Despite the subtle differences in the spectrum of biochemical abnormalities in various studies, these observations buttress the need to monitor various organ functions in Covid-19 patients and proactively intervene to avoid organ dysfunction with its attendant impact on disease outcome. Although requested laboratory investigations were partly determined by clinical indication, the unavailability of ancillary investigations for most of our patients highlights an important gap in the comprehensive management of COVID-19 cases in resource-limited settings.

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As part of our management protocol, most of the patients in whom chest radiograph was available comprised those with severe disease and others with a strong suspicion of alternative diagnosis or co-morbidities which partly explains why nearly all our patients had an abnormal chest radiograph. High frequency of chest radiographic abnormalities among COVID-19 patients had been reported in other studies in China, the US, Europe, and Northern Nigeria[17,22,34,35]. This is contrary to the study in Uganda where only 14% of patients with chest radiographs demonstrated abnormalities[11]. The disparity may be related to differences in disease severity and sample size. Furthermore, the most frequent chest radiographic findings in our study were bilateral ground-glass opacities (30.8%), bilateral patchy opacities (23.1%), bilateral lacy opacities (15.4%), and unilateral homogenous opacity (15.4%). This closely relates to the study by Ibrahim et al that reported ground-glass opacity in 45.5% of their participants while patchy opacities were seen in 27.3%[22]. The varying degrees of opacities seen in the majority of our patients are largely suggestive of pneumonia and compare favourably with findings in Chile[26].

We also explored gender differences in clinical characteristics among patients with COVID-19, which showed that fever and breathlessness were predominant in men while women presented to the hospital earlier and were more likely to have diarrhoea. In addition, women had significantly lower levels of BP readings, though this may have physiological bases. Though there is limited literature on gender differences in the clinical presentation of COVID-19, available literature has shown mixed findings. Elhadi and colleagues likewise Boddington et al did not find any statistically significant gender differences in clinical characteristics of their COVID-19 cohorts[25,27]. However, Boddington and colleagues observed a higher frequency of diarrhoea in female patients though not statistically significant[25]. Among other findings observed more frequently in females by Boddington et al were headache, sore throat, joint pain, and nausea[25]. These findings were not corroborated by Jin et al [43].

Our study identified pre-existing comorbidity, prior use of antibiotics/antimalarials, and being a healthcare worker as independent predictors of severe COVID-19. Popov et al in Bulgaria, likewise Wang et al in China demonstrated the association of co-morbidity with severe disease[17,44]. Other factors previously identified as predictors of severity include increasing age, male gender, and deranged laboratory markers[15,45]. Although older age and late presentation to the hospital were associated with severe disease on univariate analysis, the association did not show statistical significance after controlling for potential confounders. Nevertheless, these two factors are socio-demographic determinants of health that cannot be ignored. Though the association of COVID-19 severity with prior use of antibiotics/antimalarial and occupation has been poorly explored, this finding may buttress common knowledge that antimicrobials are frequently taken prophylactically or presumptively in our environment before seeking care in the hospital. This further highlights the huge public health risk of self-medication and over-the-counter use of antimicrobials during the pandemic. The increased likelihood of severe disease in healthcare workers could have been contributed by poorly understood factors possibly virulent strains acquired nosocomially but this cannot be substantiated in the absence of genomic sequencing.

Following multivariate analysis, none of the variables predicted mortality amongst hospitalized patients. Although hypoxemia on simple regression analysis was associated with a five-fold higher risk of death, the association was not statistically significant after controlling for potential confounding variables however a marginally increased risk of death was still seen in this subset of patients. It is possible that the tendency to intensify supplemental oxygen therapy in hypoxemic patients could have improved the chances of survival in this group hence the lack of association with mortality on multivariate analysis.

The findings of our study should be interpreted in light of its limitations. The study design was retrospective which meant that only information available in patients' medical records was available for analysis. Unfortunately, the data collected in this study is focused on patients with confirmed SARS-CoV-2 infection so we are unable to predict individuals who are at higher risk of returning a positive SARS-CoV-2 PCR or GeneXpert test result, which could have potentially improved our knowledge of the epidemiology of the disease in Africa. Since the study setting was a referral hospital, it is possible that individuals with severe diseases were slightly overrepresented in our cohort; hence caution should be exercised while generalizing our findings. Due to the non-availability of laboratory tests in most of our patients, the high frequency of abnormal laboratory parameters should be interpreted cautiously since most of them are based on small sample sizes.

The epidemiology of COVID-19 in our patients underscores the contributions of the male gender, urban residence, healthcare worker exposure, co-morbidities, and community transmission. The clinical presentation of COVID-19 in our study population is similar to what is widely reported in the literature. Interestingly, we found a few gender differences in the clinical presentation of COVID-19. Several haematological and biochemical abnormalities suggestive of organ dysfunction were observed. Underlying comorbidity likewise prior antimicrobial use and being a healthcare worker increased the likelihood of severe COVID-19. Fieldworkers and clinicians involved in COVID-19 response and patient management in sub-Africa during the subsequent waves of the pandemic should consider these observations for improved health education, risk mitigation, surveillance, and clinical management. While the relatively small number of hospital admissions and death might be reflective of COVID-19 epidemiology in sub-Saharan Africa, it is possible that this contributed to the absence of independent predictors of in-hospital mortality in our cohort. Despite the relatively small number of patients with available laboratory results, our cohort's high-frequency laboratory indicators of multi-system complications argue for improved monitoring and support of organ function among individuals with COVID-19. Large population-based prospective cohort studies are recommended to further characterize COVID-19 in Africa.

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Competing interests

None declared.

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Ethical approval

This was obtained from the Health Research Ethics Committee of the University of Nigeria Teaching Hospital (UNTH), Ituku/Ozalla, Enugu. Participants' consent was not required as the study involved retrospective data collection and analyses.

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