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Clinical Characteristics and Outcome of COVID-19 among People Living with Diabetes in Nigeria

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Abstract

Introduction: The novel coronavirus disease 2019 (COVID-19) has affected millions of people globally with over 3 million deaths. People with underlying comorbidities are at a risk of having severe disease with increased fatality. This study aimed at describing the clinical characteristics and outcome of COVID-19 among people living with diabetes mellitus (DM) in Nigeria.

Methodology: This was a retrospective study that analyzed the data of adult patients who were admitted into the isolation and treatment center at the University of Abuja Teaching Hospital (UATH) in Nigeria, with a diagnosis of COVID-19 from March 2020 to March 2021. Data on demographic and clinical features as well as outcome was extracted and analyzed using the Statistical Package for Social Sciences (SPSS) version 20.0.

Results: A total of 588 adult patients were hospitalized with COVID-19 during the study period; 364 (61.9%) of who were males with a male: female ratio of 1.81:1. The commonest symptoms at presentation were fever (56.3%), cough (54.3%), shortness of breath (37.6%), headache (14.5%), sore throat (9.2%), anosmia (6.5%), rhinorrhea (5.6%) and diarrhea (5.3%). Of the 588 patients, 169 (28.7%) had diabetes; 109 (64.5%) of whom were males. Patients with DM were older than those without DM ($p < 0.0001$), and had a high proportion of symptoms of fever, cough and shortness of breath ($p = 0.001$). They had more severe disease ($p = 0.0001$) with a higher mortality rate (22.5%) when compared to those without DM (12.5%) ($p = 0.003$).

Conclusion: DM is among the most frequently reported comorbidities in patients infected with COVID-19 and is associated with a higher risk of severe and fatal forms of the disease. People living with DM in Nigeria are 1.8 times more likely to die from COVID-19 than people who do not have DM.

Keywords

COVID-19, Diabetes, Clinical characteristics, Outcome, Nigeria

Abbreviations

COVID-19: Coronavirus Disease 2019; UATH: University of Abuja Teaching Hospital; WHO: World Health Organization; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; DM: Diabetes Mellitus; FCT: Federal Capital Territory; RNA: Ribonucleic Acid; IFN: Interferon; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SPO2: Oxygen Saturation; WBC: White Blood Count; RBS: Random Blood Sugar; CRP: C-Reactive Protein; LDH: Lactate Dehydrogenase

Introduction

In December 2019, a new beta coronavirus causing pneumonia emerged in Wuhan, Hubei Province of China. This virus was later identified and called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. The disease was given the name Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) in February 2020. It rapidly spread to the rest of the World and was declared a global pandemic by the WHO on the 11th of March 2020 [2]. As of 22nd June 2021, there have been confirmed 178,360,849 cases of

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COVID-19, including 3,869,384 deaths, reported to the WHO [3].

Coronaviruses are single stranded RNA viruses, named for the crown-like spikes on their surface. There are four main sub-groupings of coronaviruses, known as alpha, beta, gamma, and delta [4]. Human coronaviruses were first identified in the mid-1960s. The seven coronaviruses that can infect man are: 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (beta coronavirus), SARS-CoV (the beta coronavirus), and SARS-CoV-2 (the novel beta coronavirus that causes COVID-19).

Traditionally, coronaviruses cause a mild respiratory illness. However, it has become apparent that coronaviruses can also cause severe disease; first the SARS-CoV caused an outbreak of respiratory disease originally in China in 2003 and MERS-CoV caused an outbreak in Saudi Arabia in 2012. Since the outbreak of COVID-19, emerging data has shown that people with underlying comorbidities like diabetes mellitus, hypertension, chronic kidney disease, Human Immunodeficiency Virus, chronic obstructive pulmonary disease as well as the elderly are at a risk of developing severe disease with a higher mortality rate [5,6].

Diabetes mellitus (DM) is a metabolic disorder of chronic hyperglycemia characterized by disturbances to carbohydrate, protein, and fat metabolism resulting from absolute or relative insulin deficiency with dysfunction in organ systems [7]. Data published by the International Diabetes Federation (IDF) in 2017 showed that 425 million persons were living with DM worldwide, with nearly 50% of these undiagnosed [8]. The prevalence of DM in Nigeria is estimated at 5.77%; with a population of about 200 million, this suggests that about 11.5 million Nigerians are living with the disease [9].

Early in the pandemic, DM emerged as a medical condition that is associated with severe COVID-19. Many pathophysiological abnormalities occur in patients with DM that make them more susceptible to infections. Patients with DM have a deficiency of complement C4 protein [10]. The complement proteins promote the opsonization and phagocytosis of microorganisms through macrophages and neutrophils and induce the lysis of these microorganisms. A deficiency of a complement protein will ultimately lead to a defect in the opsonization and phagocytosis of microorganisms. Secondly, the hyperglycemic environment in DM increases apoptosis of polymorphonuclear leukocytes, and reduces their ability to transmigrate through the endothelium [11]. Also, there is dysregulation of nitric oxide (NO) production in response to bradykinin leading to vasoconstriction, which could attenuate the ability of phagocytes to reach their targets [12]. Thirdly, glycation of immunoglobulins also occur in patients with DM, leading to a decrease in the function of the immunoglobulins [13]. Fourthly, it has also been shown that patients with DM have a decreased antiviral response demonstrated by a diminished production of IFN-α and IFN-1 [14]. These processes lead to a defective immune function in patients with DM, making them susceptible to bacterial and viral infections.

Angiotensin converting enzyme-2 (ACE-2) is a plasma membrane protein expressed largely in the lungs as well as in many other tissues and endothelial cells including the heart, kidneys, and importantly in insulin producing β-cells. SARS-CoV-2 virus has a high affinity towards ACE-2 which acts as the "receptor" for SARS-CoV-2 and is the dominant pathway through which the virus gains entry into the lungs and other cells in the body [15,16]. Using a Mendelian randomization analyses, Rao, et al. identified the association between diabetes and higher lung ACE-2 expression which may predispose DM patients to increase susceptibility to SARS-CoV-2 infection [17]. Also, the use of ACE-2 inhibitors and Angiotensin Receptor Blockers (ARBs) in the treatment of DM and hypertension can up regulate the expression of the ACE-2 receptors as an adaptive response to counteract the elevated levels of angiotensin-II, thereby leading to increased susceptibility to SARS-CoV-2 infection [18]. Furthermore, Furin, a type 1 membrane-bound protease expressed in high levels in DM patients activates the spike protein S on the SARS-CoV-2 to bind to the ACE-2 receptors; thereby increasing their susceptibility to COVID-19 [19]. It is therefore not surprising that people living with DM may have an increased susceptibility to COVID-19.

Nigeria was not left out of the pandemic as the Country recorded the first case of COVID-19 on the 27th of February 2020. So far over 167 thousand people have been infected with over two thousand deaths. With a large number of the population living with DM it becomes imperative that we understand how COVID-19 affects them. This study therefore aimed at describing the clinical characteristics and outcome of COVID-19 among people living with DM in Nigeria.

Methodology

Study site

The study was conducted at the University of Abuja Teaching Hospital (UATH), which is located in the capital city of Abuja, Nigeria. The hospital is a 520 bedded tertiary healthcare facility that was assigned the responsibility for the treatment of moderate to severe cases of COVID-19 patients by the Federal Ministry of Health.

Study design

The study was a single-centered retrospective study that analyzed the data of adult patients who were admitted into the isolation and treatment center at

UATH with a diagnosis of COVID-19 from March 2020 to March 2021. The diagnosis of COVID-19 was done by real-time polymerase chain reaction (RT-PCR) using nasopharyngeal and oropharyngeal swabs according to the Nigerian Center for Disease Control guideline. A patient was defined as having moderate COVID-19 if they were breathless but oxygen saturation at room air was greater than 90%; while severe COVID-19 was defined as breathlessness plus oxygen saturation at room air less than 90%. Diabetes was defined as self-reported medical history of diabetes, and the use of anti-diabetic drugs. We reviewed the clinical records of the patients and extracted data on demographic characteristics, clinical symptoms, underlying comorbidities, essential examination findings including pulse rate, blood pressure on admission, oxygen saturation (at room air), investigation findings and clinical outcomes. The primary outcome of interest was either discharged or death.

Data analysis

Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 20. Continuous variables were expressed as mean and standard deviation. Categorical variables were analyzed as counts and percentages. Chi-square analysis was used to determine the significance of difference between categorical variables. A value of $p < 0.05$ was considered statistically significant.

Ethical approval

Data used for this study was based on secondary data analysis and ethical approval is not required. The UATH hospital management gave the approval for the release and use of the data which was de-identified to ensure anonymity.

Results

Clinical features of the general population

The baseline characteristics of the study subjects are provided in Table 1 and Table 2. A total of 588 adult patients were hospitalized with COVID-19 during the study period; 364 (61.9%) of who were males with a male:female ratio of 1.81:1. The age range was from 18 years to 103 years with a mean age of 51 (± 16.8) years. The commonest symptoms at presentation were fever (56.3%), cough (54.3%), shortness of breath (37.6%), headache (14.5%), sore throat (9.2%), anosmia (6.5%), rhinorrhea (5.6%) and diarrhea (5.3%). Other symptoms such as abdominal pain (1.9%) and myalgia (1.7%) were less common. Based on the definition of disease

Table 1: Demographic and clinical symptoms.

	Overall (%)	DM (%)	NO DM (%)	P value
Mean Age (years)	51 ± 16.8	59.7 ± 11.1	47.4 ± 17.3	0.0001
Gender				
Female	223 (37.9)	60 (35.5)	163 (38.9)	0.37
Male	365 (62.1)	109 (64.5)	256 (61.1)	
Clinical Features				
Fever	331 (56.3)	115 (68.0)	216 (51.6)	0.0001
Cough	319 (54.3)	115 (68.0)	204 (48.7)	0.0001
Shortness of breath	221 (37.6)	84 (49.7)	137 (32.7)	0.0001
Headache	85 (14.5)	27 (16.0)	58 (13.8)	0.477
Sore throat	54 (9.2)	17 (10.1)	37 (8.8)	0.616
Vomiting	44 (7.5)	16 (9.5)	28 (6.7)	0.233
Anosmia	38 (6.5)	9 (5.3)	29 (6.9)	0.492
Diarrhea	31 (5.3)	13 (7.7)	18 (4.3)	0.09
Loss of appetite	24 (4.1)	9 (5.3)	15 (3.6)	0.321

Table 2: Vital signs and laboratory parameters.

	Diabetes			
vital signs/Lab parameter	**Total**	**Yes**	**No**	**P Value**
SPO2 (%)	93.93 ± 9.92	89.79 ± 12.44	94.85 ± 8.28	< 0.0001
TEMP (°C)	36.51 ± 0.59	36.5 ± 0.5	36.52 ± 0.63	0.7193
Heart rate (b/min)	93.67 ± 16.99	95.72 ± 17.97	92.84 ± 16.52	0.0638
SBP (mmHg)	133.33 ± 21.38	136.55 ± 23.09	132 ± 20.52	0.0203
DBP (mmHg)	84.28 ± 14.11	84.4 ± 14.46	84.22 ± 13.98	0.888
WBC (10^9/L)	10.44 ± 8.25	11.08 ± 8.66	10.17 ± 8.07	0.2708
RBS (mmol/L)	9.22 ± 5.46	9.54 ± 5.28	9.08 ± 5.55	0.5364

severity, 103 (17.5%) patients had severe disease while 485 (82.5%) patients had mild to moderate disease. Disease severity was higher among those with DM (31.4%) compared to those without DM (11.9%) (P < 0.0001). A total of 140 (23.8%) patients had underlying comorbidities; the commonest being hypertension (51.4%), diabetes (28.7%), asthma (3.4%) and HIV (3.4%).

COVID-19 in people living with DM

Out of the 588 patients hospitalized with COVID-19 during the study period, 169 (28.7%) had diabetes; 109 (64.5%) of whom were males. The age range of those with DM was 27-88 years, with a mean age of 59.7 (± 11.1) years. The patients with DM were older (mean age 59.7 years) compared to the patients without DM who had a mean age of 47.4 (± 17.3) years (p < 0.0001). The clinical symptoms were the same for both the DM and the non DM patients. However, patients with DM had more symptoms of Fever (68% versus 51.6%), cough (68% versus 48.7%) and shortness of breath (49.7% versus 32.7%) when compared to patients without DM (p < 0.001).

Patients with DM presented with lower oxygen saturation (89.7 ± 12.4) compared to those without DM (94.85 ± 8.28) (p < 0.0001). The mean systolic blood pressure was higher among the DM group compared to the non DM group (136.55 mmHg versus 132.0 mmHg) (p = 0.02). There was no difference in the mean diastolic blood pressure, temperature and mean random blood sugar at presentation between the DM patients and the non DM patients (Table 2).

Outcome

The primary outcome of interest was either discharged or death (Table 3). A total of 497 (84.5%) patients were successfully treated and discharged home in a stable condition; while 91 (15.5%) patients died. Out of the 169 patients who had DM, 38 (22.5%) died. Mortality rate was higher among the DM group (22.5%) when compared to the mortality rate among those without DM (12.6%) (p = 0.003). The patients spent between 0 days to 43 days on hospitalization; the average length of hospital stay was 10 (± 5.7) days. Those with DM had a mean hospital stay of 9.3 (± 5) days; while those without DM had a mean hospital stay of 10.3 (± 5.9) days. The difference was however not statistically significant (p = 0.104).

Discussion

Diabetes is among the most frequently reported comorbidities in patients infected with COVID-19 [20-22]. In this retrospective study of 588 patients hospitalized with COVID-19 at UATH, 28.7% were patients living with DM. This is about 5 times the prevalence of DM in the general population in Nigeria which is estimated at 5.77%. Orioli, et al. reporting from Belgium found a prevalence of 21.1%, which was 3-fold higher than the prevalence of DM in the general adult population [23]. Yan, et al. in a similar study in China reported that 24.9% of the patients with severe COVID-19 had diabetes; the prevalence of DM in the Chinese population has been estimated at 11.6% [24]. These epidemiologic evidences show that people living with DM are not only susceptible to bacterial infections but also to SARS-CoV-2.

This study showed that patients with DM were older when compared to those without DM (p = 0.0001). Older adults are at high risk for the development of type 2 DM due to the combined effects of increasing insulin resistance and impaired pancreatic islet function with aging. A decline in lean body mass and an increase in body fat that often accompanies aging may contribute to the development of insulin resistance [25]. Age-related insulin resistance is associated with physical inactivity in the elderly. Zhou, et al. from China in a similar study also showed that COVID-19 patients with DM were older than those without DM [26]. With improvement in healthcare in most parts of the World, people are living longer and this unprecedented aging of the world's population is a major contributor to the diabetes epidemic [27].

We also observed that patients with DM had a similar pattern of clinical characteristics of COVID-19 compared to patients without DM. Patients with DM however had a high proportion of symptoms of fever (68% versus 51.6%), cough (68% versus 48.7%) and shortness of breath (49.7% versus 32.7%) (p = 0.001). Yan, et al. reporting from China also showed that the clinical characteristics of COVID-19 were similar in both the patients with DM and those without DM [24]. Disease severity was higher among the patients with

Table 3: Disease severity and outcome.

	Overall (%)	**DM** (%)	**No DM** (%)	**P-Value**
Disease Severity				
Severe	103 (17.5)	53 (31.4)	50 (11.9)	**0.0001**
Mild-Moderate	485 (82.5)	116 (68.6)	369 (88.1)	
Outcome				
Dead	91 (15.5)	38 (22.5)	53 (12.6)	**0.003**
Discharged	497 (84.5)	128 (75.7)	369 (88.1)	
Length Of Hospital Stay (Days)	10 ± 5	9.3 ± 5	10.3 ± 5.9	**0.104**

DM (31.4%) compared to those without DM (11.9%) ($p < 0.001$). Earlier reports from China, US and Italy showed that COVID-19 patients with DM often have severe disease with poor outcome [28-30]. A meta-analysis by Kumar, et al. showed that Diabetes was associated with severe COVID-19 with a pooled odds ratio of 2.75 (95% CI: 2.09-3.62) [31]. de Almeida-Pititto, et al. in another meta-analysis also identified a 2.3-fold increase in the risk of severity and a 2.5-fold increase for mortality associated with COVID-19 in patients with DM [32]. Diabetes is associated with a low grade chronic inflammation induced by the excessive visceral adipose tissue; C-reactive protein (CRP), IL-1β, IL-6 and other cytokines are elevated in patients with DM [33]. When a person living with DM gets infected with SARS-CoV-2, the pre-existing chronic inflammation is further increased and plays a critical role in disease progression. Hyperglycemia also increases the formation of advanced glycation end products (AGEs) that stimulate the production of reactive oxygen species, leading to increased oxidative stress and activation of immune response [34]. These processes lead to severe COVID-19 with a poor outcome in people living with DM. Guo, et al. reported that DM patients with COVID-19 had higher levels of C-reactive protein (32.8 [IQR, 11.3-93] vs. 16.3 [IQR, 7.17-43.9]), Erythrocyte sedimentation rate (67 [47.5-81] vs. 23 [10-49]), as well as D-dimer (1.15 [IQR, 0.83-2.11] vs. 0.54 [0.25-1.1]) [35]. In another report by Zhu, et al. they observed that DM patients with COVID-19 had greater incidences of decreased lymphocyte counts and increased neutrophil counts, as well as higher levels of serum interleukin-6 (IL-6), C-reactive protein (CRP), and lactate dehydrogenase (LDH) [36]. These reports show that patients with diabetes are at higher risk of excessive uncontrolled inflammatory responses and hypercoagulable state, which may contribute to a poorer prognosis of COVID-19. In addition, people living with DM are characterized by pulmonary dysfunction due to decreased lung volume, reduced pulmonary diffusing capacity, as well as ventilation control, bronchomotor tone and noradrenergic innervation impairment [37]. These pulmonary changes contribute to a poor outcome when DM patients get infected with SARS-CoV-2.

The mortality rate in this study was 22.5% among the patients with DM as compared to 12.6% in the non DM group. This difference was statistically significant ($P = 0.003$). Patients with DM were 1.8 times more likely to die from COVID-19. Acharya, et al. reported a mortality rate of 20.0% among COVID-19 patients with DM in Korea; which was 4.2 times higher than the mortality rate among non DM patients with COVID-19 [38]. In a meta-analysis by Corona, et al. that studied 87 articles with 35,486 patients, mortality was higher in COVID-19 patients with DM in the USA and in Europe [39]. Zhu, et al. found a mortality rate of 7.8% versus 2.7% ($p < 0.001$) for DM and non-DM patients respectively, with COVID-19 in a similar study in China [36]. They went further to categorize the DM patients into those with well controlled blood glucose and those with poor glycemic controlled and observed that those with well-controlled blood glucose had higher lymphocyte counts, lower neutrophil counts, and lower serum levels of IL-6, CRP, and LDH. They further noticed that the in-hospital death rate was significantly lower (1.1% versus 11.0%) in the well-controlled group relative to the poorly controlled group. This report shows the benefit of a good blood glucose control in the management of DM patients with COVID-19.

Conclusion

Though infection by SARS-CoV-2 causes mild disease in a majority of people, severe disease is seen in people with underlying comorbidities. DM is among the most frequently reported comorbidities in patients infected with COVID-19. This study showed that 28.7% of COVID-19 patients hospitalized in a tertiary hospital in Nigeria were people living with DM. The study also showed that DM was associated with a higher risk of severe and fatal forms of COVID-19. People living with DM were 1.8 times more likely to die from COVID-19 than people who do not have DM. More intensive attention should be paid to DM patients with COVID-19 in order to prevent a poor outcome.

Limitations

This study was a single-centered retrospective study. Diabetes was defined as self-reported medical history of diabetes; some patients with DM who were unaware of their status before they became infected may have been missed. Also, information on the pre-hospitalization glycemic control was not available.

Competing Interests

The authors declare no competing interest.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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