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Haemoglobin (Hb) Genotype Profile in COVID-19 Disease Susceptibility and Severity in Lagos State Nigeria

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ABSTRACT

COVID-19 pandemic has posed unique challenges to the health providers involved with chronic diseases like Haemoglobin disorders (sickle cell disease). Therefore, this study highlights the susceptibility and severity of COVID-19 associated with normal and haemoglobin variants.

This study is a case series that includes patients evaluated between June and August 30, 2020, and diagnosed with COVID-19 by the Quantitative Polymerase Chain Reaction method. Alkaline haemoglobin electrophoresis was used to identify types of Haemoglobin genotype associated with mild-to-severe cases of COVID-19. A total of 697 COVID-19 patients were included in this study, with a mean age of 41.32 (12.917). There were more males (66.1%) than females. The most frequently detected genotype was AA (75.8%), followed by AS (22%). Severe conditions of COVID-19 were present in patients with HBAC 2(14.28%) and HBAS 13 (8.5%). Co-morbidities were present in (24.0%) of the patients, with a mortality rate of 1.3%. Patients with pneumonia in association with other co-morbidities are 26 times more likely to have severe SARS CoV-2 than those with only pneumonia, irrespective of their haemoglobin genotype profile. The clinical course is seen in normal haemoglobin, and the variant with COVID-19 was the same. It is suggested that people with haemoglobin variant are not at increased risk during COVID-19 infection or risk of a sickle cell crisis.

Keywords: COVID-19, SARS-CoV-2, Haemoglobin Genotype, Lagos, Nigeria.

INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has swept the globe. It has become a major public health crisis causing severe respiratory illness that puts patients with chronic medical illnesses at risk of increased morbidity and mortality [1,2]. A recent study [3] reported that the virus isolation and nucleic acid sequencing showed that the novel coronavirus is a positive-stranded RNA8, and the virus acts through ACE2, CD147, and CD26 receptors on the erythrocytes, resulting in a haemoglobinopathy interaction with the haemoglobin molecule; viral ORF8 surface glycoproteins combine with porphyrin to form a complex with 1-beta chain of haemoglobin,

with or without haemolysis forming dysfunctional haemoglobin. This decreases haem-oxygen-carrying capacity as reported [4, 5, and 6]. Patients with chronic hereditary (HBSS, HBSC, and HBCC) and acquired haematological diseases are immunocompromised due to their chromosomal structural defect and/or treatment [7]. Getting infected with SARS-CoV-2 puts them at the risk of severe respiratory complications such as pneumonia, acute respiratory distress syndrome, and secondary bacterial infections [8, 9]. The recurrent sickling process in Sickle cell disease (SCD/HB-CC/HB-SC) causes tissue hypoxemia and micro-infarcts, resulting in end-organ damage. Several reports have suggested worse COVID-19 complications in SCD [10, 11, and 12]. Some literature indicated that SARS-CoV-2 infection and SCD should be considered to be an important eliciting factor of sickle cell crisis. A review journal reported that sickle cell trait has potentially increased the risk(s) of hypercoagulability [13, 14, and 9]. Another recent study [15] concluded that vaso-occlusive crisis could complicate COVID-19 infection, occurring in half of the inpatients with sickle cell disease.

Haemoglobin (HB) is the protein present in red blood cells that transport oxygen to the body's tissues and organs and give blood its red color [16]. There is one normal haemoglobin (HB-AA) and five variants: HB-AS, HB-SS, HB-SC, HB-AC, and HB-CC [16]. The inheritance of HB-S from both parents results in a homozygous state (HB-SS) known as sickle cell anaemia/disease (SCA/SCD). In contrast, the inheritance of HB-S from one parent and HB-A from the other leads to a heterozygous state (HB-AS) which is known as sickle cell trait (SCT) [17].

One of the variants, HB-C, is formed by replacing glutamic acid with lysine at the 6th position of the β-globin chain of the molecule and causes a mild chronic haemolytic anaemia. The inheritance of HB-C from both parents results in a homozygous state (HB-CC). HB-C can also combine with HB-A and HB-S at the point of inheritance to form HB-AC and HB-SC, respectively [18,19].

The clinical features of HB-SS include haemolytic anaemia, jaundice, fever, joint ache, skeletal changes due to erythroid hyperplasia, painful infarcts, pulmonary complications, kidney damage, haemolytic, and aplastic anaemia, among others, and they often require specialized medical care and other forms of support [19].

Nigeria has the highest disease incidence globally, with approximately 91,011 children born with sickle cell disease and complications. The rate accounts for almost 2% of all newborns annually, followed by the Democratic Republic of Congo with 39,743 sickle cell births per year [20]. There is also a high incidence of the HB-S gene among Africans, associated with some kind of protection against P falciparum infection [21].

There presently seemed to be little data on the outcomes of patients with sickle cell disease and/or other haemoglobin genotype profiles and COVID-19 clinical presentations in association with SARS-CoV-2 infection and management in Nigeria.

Therefore, this study examined the role of the haemoglobin genotype profile and its variants in COVID-19 diseases susceptibility and severity.

METHODS

Study Design and Participants

With ethical approval obtained from the Institutional Review Board (IRB) at the Nigerian Institute of Medical Research (NIMR), Yaba, Lagos, Nigeria, patient data were obtained and reviewed at the Mainland Infectious Disease Hospital, Yaba. Informed consent was also obtained from the study participants before their health records were obtained. This study is a case series that includes patients that are evaluated between June and August 30, 2020, and diagnosed with COVID-19. The Infectious Disease and Isolation Centre (IDIC), Mainland, Yaba, Lagos is a central, comprehensive, and integrated healthcare organization attending to COVID-19 patients in Lagos, the epicenter of the epidemic in Nigeria. All the patients included in this study were confirmed to have been infected with SARS-CoV-2 by a positive reverse transcriptase-polymerase chain reaction test of nasopharyngeal, throat, and blood samples. Clinical outcomes were also monitored and recorded.

Data Collection and Statistical Analysis

Clinicians and trained research assistants reviewed patient health records retrospectively and copied them to a standardized data collection form. Health records included demographic information, signs and symptoms presented with, co-morbidities, and patient outcome. Records were double entered into the forms before merging to reduce errors during data entry. A total of 697 blood samples were collected. A purposive sampling technique was used for all patients who met the eligibility criteria during the study period. During the study period, there was no prevalence rate for the COVID-19 study hence this method was used. The Patients' haemoglobin genotype profile was done for those with enough information in

their health records. Descriptive analyses were performed using Statistical Package for the Social Science (SPSS) version 25 (IBM, USA).

RESULTS

A total of 697 COVID-19 patients were included in this study. The mean age of the study participants was 41.32 (12.917). COVID-19 was more common in males than in females (461 (66.1%) and 236 (33.9%), respectively). Out of the 697 participants, 56.4% were symptomatic.

The clinical characteristics and outcomes of 697 patients included in the study according to their genotypes are presented in Table 1. The patients demonstrated breathing difficulty, fever, dry cough, malaise, and sore throat, which were the most frequent symptoms. There was a history of hypertension[A1] in 14.2% of patients and diabetes mellitus in 5.9% of patients.

The most frequently detected haemoglobin genotype was AA 528 (75.8%) followed by AS 153 (21.9%), AC 14 (2.0%) and the least SS 1 and SC 1 of each: 2 (0.3%) amongst the COVID-19 patients. This is shown in Figure 1.

Figure 2 shows the frequency of detected haemoglobin genotypes among male and female patients. Male patients seem to have more HB-AA 365 (67.42%) followed by HB-AS 92 (60.13%), HB-AC 13(81.25%), and the least HB-SC 1(100%).

The frequency of detected haemoglobin genotype among the female patients shows that HB-AA 172(32.58%) followed by HB-AS 61(39.87%), HB-AC 3 (18.79), and the least HB-SC1 (100%).

Table 3 shows the HB genotype profile and severe conditions of COVID-19 diseases. The patients that have HB-AC 2(14.28%) followed by HB-AA 46 (8.71%) and HB-AS 13(8.5%). HBSC and HBSS were just one case each and were found in patients with mild COVID -19 diseases. Severe conditions of COVID-19 were found to be more in patients with HB-AC 2(14.28%) than any other haemoglobin genotypes. HB-SC and HB-SS were one case each and were found in patients who had mild COVID -19 diseases

Table 4 shows the HB Genotype of the Deceased COVID -19 Patients and comorbidities. These include TB, asthma, diabetes, hypertension, pneumonia, and others present in (24.0%) of the patients. Seven 7(77.77%) deceased patients had HB-AA followed by three HB-AS (33.33%). It is noteworthy that 3(33.33%) mild cases also died of COVID-19, out of which 2(22.22%) patients are HB-AS.

Patients with comorbidities such as pneumonia were 15 times more likely to have severe SARS CoV-2 than those who do not have pneumonia OR= 14.8 95% CI lower 3.234 and upper 67.788 p-values = 0.01.

Furthermore, in association with other comorbidities such as TB and hypertension, pneumonia shows it can significantly contribute to SARS CoV-2 severity. Patients who had pneumonia in association with other comorbidities are 26 times more likely to have severe SARS CoV-2 than those with only pneumonia, OR= 26.810 95% CI lower 5.723 and upper 125.595 p-value = 0.00 as shown in table 5

Also, hypertension patients are 0.9 times less likely to have severe SARS CoV-2 than others OR= 0.136 95% CI lower 0.78 and upper 0.239 p-values = 0.000. The odds remain the same irrespective of the genotype of the patient.

Tuberculosis (TB) alone did not contribute significantly to SARS-CoV-2 severity irrespective of the HB genotype profile of the patient's OR= 10.583, CI: lower .654 and upper 171.349 p-value = 0.97. Similarly, TB in association with other comorbidities such as pneumonia and hypertension showed significant association (p-value = 0.034) to SARS CoV-2 severity with a high odd ratio, as shown in Table 5

Other comorbidities: Malaria, Cancer, Asthma, Chronic Obstructive Pulmonary Disease (COPD), Diabetes, Congestive Cardiac Failure, and Lower Respiratory Tract Infection (LRTI) did not show any statistical significance in contributing to SARS CoV-2 severity irrespective of the HB genotype profile of the patient (p value=0.948).

DISCUSSION

In this preliminary report, there are 16 (2.3%) who have HB-AC/SS/SC compared to those who have HB-AA 528 (75.5%) and HB-AS 153(22.0%) amongst the COVID-19 patients who participated in the study. Furthermore, none of the HB- SS and HB-SC patients were among the diseased or moderate to severe COVID 19 cases. Also, our record shows no HB-SS/SC patient suffered sickle cell crisis as it had been hypothesized that the SARS-CoV-2 virus might affect the haemoglobin beta chain that could precipitate crisis [9, 10, and 11]. Our study is consistent with another case series that reported four SCD patients who demonstrated a milder COVID-19 course and seemed to have benefited from early risk stratification and initiation of treatment [18]. Another recent study reported 10 SCD patients,

Table 1. Baseline Characteristics and Symptoms of COVID-19 among the Patients.

Baseline Characteristics and Symptoms	Frequency(%) n=697 (100)
Mean (S.D)	41.32 (12.917)
Range (minimum -Maximum)	1-83
Gender	
Male	461 (66.1)
Female	236 (33.9)
Symptomatology	
Asymptomatic	304 (43.6)
Symptomatic	393 (56.4)
Patient Outcome	
Dead	9 (1.3)
Survived	688 (98.7)
Breathing Difficulty	
Yes	129 (18.5)
No	568 (81.5)
Fever	
Yes	185 (26.5)
No	512 (73.5)
Nasal Congestion	
Yes	22 (3.2)
No	675 (96.8)
Dry Cough	
Yes	192 (27.5)
No	505 (72.5)
Running Nose	
Yes	28 (4.0)
No	669 (96.0)
Diarrhoea	
Yes	44 (6.3)
No	653 (93.7)
Abdominal Pain	
Yes	36 (5.2)
No	661 (94.8)
Malaise	
Yes	123 (17.6)
No	574 (82.4)
Sore Throat	
Yes	72 (10.3)
No	635 (89.7)
Joint Pain	
Yes	38 (5.5)
No	659 (94.5)
Loss of Appetite	
Yes	57 (8.2)
No	640 (91.8)
Chest Pain	
Yes	81 (11.6)
No	616 (88.4)
Loss of Smell	
Yes	77 (11.0)
No	620 (89.0)
Loss of Taste	
Yes	48 (6.9)
No	649 (93.1)
Headache	
Yes	45 (6.5)
No	652 (93.5)

Symptomatic patients (56.4%). The most common symptoms were: dry cough (27.5%), Fever 185 (26.5) and breathing difficulty (18.5%).

of which six were confirmed COVID-19 cases, and one was fatal [9]. However, this report is not consistent with our preliminary result. Another two independent case reports consistent with our result showed how SCD patients with severe COVID-19 responded well to tocilizumab. Therefore, the dataset on COVID-19 in SCD patients will continue to evolve [20].

In this report, seven (7) patients out of fourteen (14) HB-AC had mild COVID-19 infection, five (5) moderate, and only two (2) had severe cases. However, none was among the diseased cases. The time of clinical cause in HB-AC was not different between patients who have HB –AA, HB-AS, and HB-SS/AC/SC in a similar hospital stay. The two (2) patients with genotype HB-SS/SC experienced a mild form of COVID-19. Another report [21] showed six patients with SCD had COVID-19. Three (3) remained asymptomatic. Two had mild symptoms, and one required oxygen therapy. The SCD patients had a similar average length of stay compared with non-SCD COVID-19 patients, which is consistent with our report.

At the time of this report, 7 (77.77%) males (age range 37- 57 years) out of the 9 COVID-19 patients who were diseased had HB–AA, and 2 (22.22%) Female (aged 66 and 75) had – HB-AS. The majority (1.29 %) of the diseased patients had co-morbidities – hypertension,

Table 2: Co- morbidities Among COVID -19 Patients.

Co-Morbidities	Frequency (%) n=697(100)
Malaria	
Yes	5 (0.7)
No	692 (99.3)
Pneumonia	
Yes	7 (1.0)
No	690 (99.0)
Hypertension	
Yes	99 (14.2)
No	598 (85.8)
Cancer	
Yes	3 (0.4)
No	694 (99.6)
Chronic Obstructive Pulmonary Disease (COPD)	
Yes	2 (0.3)
No	695 (99.7)
Diabetes	
Yes	41 (5.9)
No	656 (94.1)
Asthma	
Yes	6 (0.9)
No	691 (99.1)
Congestive Cardiac Failure	
Yes	5 (0.7)
No	692 (99.3)
Lower Respiratory Tract Infection (LRTI)	
Yes	5 (0.7)
No	692 (99.3)
Tuberculosis	
Yes	2 (0.3)
No	695 (99.7)

diabetes, Lower Respiratory Tract Infection (LRTI), and pneumonia that further complicated their health conditions. Furthermore, patients with pneumonia are 14.8 times more likely to have severe SARS CoV-2 than those who do not have pneumonia (p value= 0.01). Also, patients with hypertension were 0.9 times less likely to have severe SARS CoV-2 than other chronic conditions. The odds remain the same irrespective of the genotype of the patient OR= 14.803 95% CI lower 3.234 and upper 67.786 p-values = 0.001.

However, all the diseased cases were admitted to either an isolated COVID-19 ICU, hospital, or isolation facility, depending on the patients' medical requirements. This result is consistent with the reports from these authors [22, 23, and 24]. Their studies showed that the risk of death from COVID-19 strongly depends on age and previous health conditions. Older patients and those with chronic comorbidities, such as cardiovascular disease, hypertension,

diabetes, and pulmonary disease, were more prone to critical and fatal disease outcomes. An American study further documented that SC disease and trait in combination with pneumonia may benefit from individualized or personalized medical care in other to improve the prognosis of SARS CoV-2 [25].

In view of the haemoglobin variants with COVID 19 severity in this report, HB-AS (8.5%) and HB-AC (14.28%) patients with sickle cell trait may be at an increased risk of unrecognized COVID-19 induced sickle-cell related complications. The potential complications in HB variants or features may help healthcare providers include sickling complications in their differential diagnosis as they assess individuals from ethnicities as seen in Nigeria with a high prevalence of sickle cell trait. This is further buttressed in a mini-review done among African Americans, which reported that the carrier frequency of SCD is high among Africans [25].

The distribution of haemoglobin genotype has been repeatedly investigated in various populations worldwide, and their frequencies exhibited considerable variation in different geographic locations, reflecting the underlying genetic and ethnic diversity of human populations. In Southwestern Nigeria, a report from a retrospective study [26] showed that HB-AA dominates by 88.11%, followed by HB-AS 10.23%, HB-AC 0.78%, HB-SS 0.72%, and HB-CC0.01%. Therefore, the percentage of all the haemoglobin genotype profiles identified in this study reflected the overall population within Lagos State, Southwest Nigeria, suggesting no increased infection rate in those with normal and haemoglobin variants. However, the main limitation of our preliminary report was the low number of HB-SS, HB-SC, and HBAC who had COVID-19. Future studies with a larger sample size may highlight any association between haemoglobin variants and COVID 19 disease.

Table 3: Haemoglobin Genotype and COVID-19 Diseases Conditions.

Disease Condition COVID -19	AA	AS	AC	SC	SS	Chi square	P value
Mild	302(57.19)	82(53.6)	7(50.0)	1(100)	1(100)	2.924	0.939
Moderate	180(34.1)	58(37.9)	5(35.72)	0	0		
Severe	46 (8.71)	13(8.5)	2(14.28)	0	0		
Total	528(100)	153(100)	14(100)	1(100)	1(100)		

Table 4: HB Genotype of the Deceased COVID -19 Patients.

S/No	Age	Gender	Genotype	Symptoms	Co-morbidities	Disease Condition
1	75	F	AS	Asymptomatic	None	Mild
2	67	F	AA	Weakness	Pneumonia, Diabetes	Severe
3	37	M	AA	Weakness, Dry Cough, Breathing Difficulty	None	Severe
4	60	M	AA	Asymptomatic	LRTI, Hypertension	Severe
5	62	M	AA	Breathing Difficulty	Hypertension, Diabetes	Severe
6	53	F	AA	Asymptomatic	None	Mild
7	61	M	AA	Breathing Difficulty	Hypertension	Severe
8	65	M	AA	Breathing Difficulty, Fever, Dry Cough	Hypertension, Diabetes	Severe
9	66	F	AS	Breathing Difficulty, Weakness	LRTI	Mild

Seven 7(77.77%) deceased patients had HB-AA followed by three HB-AS (33.33%). It is noteworthy that 3(33.33%) mild cases also died of COVID-19 out of which 2(22.22%) patients were HB-AS.

Table 5: Multivariate Analysis of Co-morbidities and SARS CoV-2.

Steps	Variables	p. value	Odds	95% CI	
				Lower	Upper
Step 1	Hypertension	0.00	.136.078	.078	.239
Step 2	Hypertension	0.00	.120	.068	.213
	Pneumonia	.000	26.810	5.723	125.595
Step 3	Hypertension	0.00	.116	0.65	.207
	Pneumonia	0.00	27.753	5.914	130.229
	TB	0.034	20.815	1.268	341.805

CONCLUSION

In conclusion, the clinical course is seen in normal haemoglobin, and the variant with COVID-19 was the same. No significant statistical difference was observed between COVID-19 and normal haemoglobin and the variants (0.939). Therefore, it is suggestive that people with haemoglobin variants are not at increased risk during COVID-19 infection or risk of a sickle cell crisis. However, SARS CoV-2 is worsened by the presence and increasing frequency of comorbidities. Our study may suggest that co-morbid states associated with SARS CoV-2 may require precision medicine.

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