Original Article

Pulmonary dysfunction among adolescents and adults with sickle cell disease in Nigeria: Implications for monitoring

Obianuju B. Ozoh[1,2], Olufunto O. Kalejaiye[1,2], Ojiebun E. Eromesele[2], Yusuf A. Adelabu[2], Sandra K. Dede[2], Folasade O. Ogunlesi[3,4]

[1]Department of Medicine, College of Medicine, University of Lagos, [2]Department of Medicine, Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria, [3]Division of Pulmonary and Sleep Medicine, Children's National Health Systems, [4]Department of Pediatrics, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA

Address for correspondence:
Dr. Obianuju B. Ozoh, Department of Medicine, College of Medicine, University of Lagos, Lagos, Nigeria.
E-mail: ujuozoh@yahoo.com

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Abstract:

BACKGROUND: Pulmonary complications of sickle cell disease (SCD) contribute to excess morbidity and mortality. The burden of pulmonary dysfunction among Nigerians with SCD has not been well elucidated.

OBJECTIVES: The objectives of this study are to describe the frequency and pattern of spirometry abnormalities in SCD and to explore the association between pulmonary dysfunction and selected parameters.

METHODS: A cross-sectional study among adolescents and adults with SCD attending a University Teaching Hospital and healthy age- and gender-matched controls. Respiratory symptoms, oxygen saturation, spirometry, complete blood counts, and fetal hemoglobin (Hb) were measured.

RESULTS: A total of 245 participants with SCD and 216 controls were included in the study. Frequency of respiratory symptoms was similar between the two groups. The median forced expiratory volume 1 (FEV1), forced vital capacity (FVC), and the FEV1/FVC were significantly lower in SCD as compared to controls (P = 0.000 in all instances). The frequency of abnormal pulmonary patterns was higher in SCD as compared to controls with abnormal spirometry pattern in 174 (71%) and 68 (31.5%) of participants with SCD and controls, respectively (P = 0.000). The suggestive of restrictive pattern was predominant (48% vs. 23%), but obstructive (11.8% vs. 7.4%) and mixed patterns (11% vs. 0.9%) were also found among SCD versus controls. Hb concentration was positively associated with FEV1 and FVC, whereas white cell count and age were negatively associated with FVC and FEV1, respectively.

CONCLUSION: There is a high burden of pulmonary dysfunction in SCD among Nigerians which may be related to the severity of disease. There is a need for further research to explore the effectiveness of potential interventions so as to harness the benefits from monitoring and early detection.

Keywords:

Nigeria, pulmonary function, sickle cell disease

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Improvement in the care and management of sickle cell disease (SCD) has enhanced survival leading to increase complications from organ damage.[1,2] The lungs are one of the major organs affected and pulmonary involvement manifests as the acute chest syndrome (ACS) and chronically as pulmonary fibrosis, pulmonary hypertension, hypoxia, and ultimately respiratory failure.[3,4] Fatal pulmonary complications occur in 20%–30% of adults with SCD and contributes to excess mortality.[3,5-7] SCD is caused by genetic substitution in the hemoglobin (Hb) molecule which makes the mutant Hb S susceptible to reduced oxygen tension leading to polymerization and sickling of

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red blood cells (RBC).[8] The reduced deformability of the RBC is a major cause of the hemolytic and vaso-occlusive component of the disease. In addition, states of hypoxia during vaso-occlusive crises increases the expression of chemokines that may ultimately promote pulmonary fibrosis.[9]

Sickle cell chronic lung disease (SCCLD) has been demonstrated to begin at a young age in the course of SCD and progresses with increasing age.[10] Pulmonary dysfunction may be the earliest manifestation of SCCLD and dyspnea and hypoxia late manifestations.[3] Timely detection by pulmonary function testing may provide opportunity for prompt intervention to improve outcome. The patterns of pulmonary dysfunction reported in adults with SCD have varied and the associations with clinical or laboratory parameters have been inconsistent.[11-13]

SCD is the most common inherited disorder worldwide and about three-quarters of cases occur in Africa[14] In Nigeria, about 2% of live births have the HbSS genotype translating to about 150,000 births each year.[15] A population-based survey in Nigeria reported a prevalence of SCD of 12% which is among the highest worldwide.[16] The burden of pulmonary dysfunction and its associated factors in Nigeria has not been extensively evaluated. Previous studies were limited by small sample sizes and the narrow age range of the participants.[11,12] Furthermore, pulmonary function testing is not standard practice in the management of SCD in Nigeria probably as a result of limited information on the magnitude of the problem and its associations.

We aimed to determine the frequency and pattern of pulmonary dysfunction among adolescents and adults with SCD compared to healthy age- and gender-matched controls and also explored the association between pulmonary dysfunction and selected clinical and hematological variables.

Methods

This was a cross-sectional study conducted between August 2016 and September 2017 among patients with SCD attending the sickle cell clinic of a University Teaching Hospital in Lagos, Nigeria, and healthy age- and gender-matched controls without SCD among the staff and students of the university. Hb genotype is routinely confirmed and documented at the initial clinic visit for all patients.

Ethical consideration

We obtained ethical approval from the Health Research Ethics Committee and informed consent/assent from all participants before enrolment.

Participant recruitment

Probability sampling by simple random technique was utilized in selecting participants during clinic visits. Inclusion criteria were SS or SC genotype, age ≥14 years, and stable clinical condition. We excluded those with acute disease state, current or recent respiratory infection (within 2 weeks), current treatment for tuberculosis, decompensated heart failure, pregnancy, chest deformity, and current cigarette smoking or previous significant smoking (smoked at least 20 packs of cigarette in a lifetime or at least one stick of cigarette daily for 1 year). Controls were consenting healthy age- and gender-matched staff and students of the university who had previous genotype testing done and provided a self-report as either AA or AS. Genotype awareness is commonplace in Nigeria as testing is usually done during pre-school enrolment screenings. We excluded control participants who had the previous diagnosis of chronic respiratory conditions such as asthma, chronic obstructive pulmonary disease or any other medical condition capable of compromising lung function. In addition, all exclusion criteria for participants with SCD were also applied to the control participants.

Data collection

Trained interviewers used a standard pro forma to obtain information from participants with SCD. They completed the pro forma by face-to-face interview and obtained additional information from clinical chart review. The information included socio-demographic characteristics, respiratory symptoms, and respiratory diseases using the modified Medical Research Council (MRC) questionnaire,[17] frequency of sickle cell crisis, episodes of ACS, current medications, comorbidities, and complications of SCD. The MRC questionnaire is a 17-item questionnaire on respiratory symptoms (cough, phlegm, breathlessness, wheeze, and chest illnesses, at present and during the past 2 years), including detailed questions on smoking history and a checklist on past illnesses. It reliably relates symptoms and lung function and has been used to study respiratory epidemiology for several decades.[17] We recorded resting oxygen saturation (SPO_2) using an Econet® pulse oximeter and obtained venous blood sample under aseptic conditions. The blood samples were analyzed using the automated coulter machine to determine the Hb concentration, packed cell volume, platelet count, and white cell count (WBC), respectively. The level of fetal Hb (HbF) was also determined using high-performance liquid chromatography. Height in meters and weight in kilograms were measured using standard methods and the body mass index (BMI) was calculated.[18]

Similar interviews were conducted for age- and gender-matched control participants, but blood samples were not obtained due to funding limitations.

Lung function testing

We used the Vitalograph® Spirotrac V Pneumotrac spirometer to perform spirometry according to the American Thoracic Society/European Respiratory Society standards for the measurement of spirometry.[19] The forced expiratory maneuver with the largest sum of the forced expiratory volume (FEV1) in the first second and forced vital capacity (FVC) of three acceptable and repeatable recordings was chosen for analysis. Acceptable blows were free of artifacts, particularly in the first second, with a minimum expiratory time of 6 s or at least a 1 s plateau. We performed daily calibration checks on the equipment, and all tests results were individually and independently verified for quality. Tests that did not meet acceptability and repeatability criteria were rejected. The outcome measures on spirometry included the values of the FEVI, FVC, FEVI/FVC ratio, and the ventilatory pattern. The ventilatory pattern was characterized as:

- Obstructive – FEVI/FVC < the lower limit of normal (LLN) with FVC ≥ LLN
- Suggestive of restrictive – FVC < LLN with FEV1/FVC ≥ LLN
- Mixed (obstructive and suggestive of restrictive) – FEV1/FVC < LLN with FVC < LLN
- Normal – FEV1/FVC ≥ LLN with FVC ≥ LLN.

Normative values used for characterization of spirometry pattern were those of the Global Lung Function Initiative (GLI) reference equation for "others."[20]

Sample size estimation

The calculated sample size of 212 based on a frequency of abnormal spirometry pattern of 60% at 95% confidence interval with a confidence limit of 5%. A sample size of 127 participants in each group has 90% power to detect a 20% difference in the proportion of participants with abnormal pulmonary function between the two groups at a 95% confidence level.

Data analysis

We categorized the respiratory symptoms on the MRC questionnaire as "SHORTNESS OF BREATH" (breathlessness walking on level ground or a slight hill), "SLEEP RELATED SYMPTOMS" (sleep disturbance from wheeze or difficulty breathing), "TRIGGER RELATED SYMPTOMS" (wheeze or cough triggered by a dusty or smoky environment), "COUGH" (cough in the morning or at night or in cold weather on most days for as long as 3 months each year), "PHLEGM" (phlegm production in the morning or at night on most days for as long as 3 months each year). The presence of any of the above respiratory symptoms was categorized as "ANY RESPIRATORY SYMPTOM."

Findings are presented as median (interquartile range) and proportion as appropriate. Comparisons between the SCD and controls and spirometry patterns were performed using the Mann–Whitney U-test, Kruskal–Wallis test, and the Chi-square test as appropriate. For the regression analysis, we selected the variables to be included in the model based on current literature and the factors that influence pulmonary function (age, sex, and height) and also included additional predictors from the literature that influence pulmonary function in SCD (Hb, WBC). We also explored the relationship with additional parameters such as HbF, current use of hydroxyurea, platelet count, BMI, and SPO_2. Model fit was assessed using the analysis of variance. Only variables with a value of $P < 0.05$ were included in the multivariate model. Analysis was performed using Statistical Software for Social Sciences (SPSS) Version 22, (IBM corporation, Chicago, United States of America).

Results

We analyzed the data for 245 participants with SCD and 216 age- and gender-matched controls. Seventy spirometry tests that did not meet the acceptability criteria were rejected.

There were 122 (49.8%) and 107 (49.5%) male participants among the SCD and control groups respectively, ($\chi^2 = 0.003$, $P = 0.96$). The age range of participants was 14–64 years and 17–57 years for SCD and controls, respectively, and both groups were matched by age and height [Table 1]. The SPO_2 ranged from 81% to 99% and 95% to 99% for SCD and controls, respectively, and the median SPO_2 was significantly lower among SCD participants compared to controls [Table 1]. Three control participants had a history of tuberculosis, but none in the SCD group had a history of treated tuberculosis ($P = 0.06$).

Clinical and laboratory characteristics of participants with sickle cell disease

There were 225 (91.8%) and 20 (8.2%) SCD participants with SS and SC genotypes respectively. One hundred and seventy-eight (72.7%) had at least one sickle cell crisis in the preceding year, (91 males and 87 females). Priapism and leg ulcers were the most frequently documented complications in SCD [Table 2]. The past episode of ACS was documented for 34 (13.9%) participants of which 18 (7.3%), 10 (4.1%), 2 (0.8%), and 4 (1.6%) had one, two, three, and ≥5 episodes, respectively. Forty-eight participants (19.6%) were currently taking hydroxyurea, (31 males and 17 females). The laboratory parameters showed anemia and low levels of HbF [Table 2].

Table 1: Characteristics of participants with sickle cell disease and controls

Parameter	All (*n*=461)			Males (*n*=299)			Females (*n*=232)		
	SCD (*n*=245)	Control (*n*=216)	Statistics	SCD (*n*=122)	Control (*n*=107)	Statistics	SCD (*n*=123)	Controls (*n*=109)	Statistics
Age in years median (IQR)	25.0 (21.0-31.0)	24.0 (22.0-27.0)	Z=−0.45, P=0.65	25.0 (20.0-30.0)	25.0 (23.0-28.0)	Z=0.50, P=0.63	25.0 (21.0-32.0)	23.0 (22.0-26.0)	Z=−1.17, P=0.24
Age group (years) (%)									
14-24	118 (48.2)	122 (56.5)	χ^2=4.41, P=0.22	60 (49.2)	51 (47.7)	χ^2=1.08, P=0.78	58 (47.2)	71 (65.1)	χ^2=7.74, P=0.05
25-34	92 (37.6)	74 (34.3)		50 (41.0)	49 (45.8)		42 (34.1)	25 (22.9)	
35-44	26 (10.6)	14 (6.5)		7 (5.7)	4 (3.7)		19 (15.4)	10 (9.2)	
≥ 45	9 (3.7)	6 (2.8)		5 (4.1)	3 (2.8)		4 (3.3)	3 (2.8)	
Height in meters median (IQR)	1.67 (1.60-1.73)	1.67 (1.61-1.75)	Z=1.3, P=0.19	1.72 (1.65-1.77)	1.74 (1.68-1.79)	Z=−2.0, P=0.05	1.62 (1.58-1.67)	1.62 (1.59-1.69)	Z=−0.68, P=0.68
BMI in Kg/m^2 median (IQR)	20.1 (18.2-21.8)	22.6 (21.1-25.3)	Z=−10.10, P=<0.001	19.2 (17.7-21.3)	22.5 (21.2-24.9)	Z=−8.40, P=<0.001	20.5 (18.8-22.4)	22.7 (20.9-25.8)	Z=−5.95, P=<0.001
SPO2 in % median (IQR)	96.0 (94.0-98.0)	98.0 (98.0-98.0)	Z=−13.50, P=<0.001	95.0 (93.0-97.0)	98.0 (98.0-98.0)	Z=−10.40, P<0.001	96.0 (94.0-98.0)	98.0 (98.0-98.0)	Z=−8.61, P<0.001

IQR=Interquartile range, BMI=Body mass index, SPO2=Oxygen saturation, SCD=Sickle cell disease

Respiratory symptoms and pulmonary function among participants with sickle cell disease and controls

The frequency of all respiratory symptoms did not differ significantly between the SCD and control participants. There was a tendency toward a higher frequency of shortness of breath among the participants with SCD [Table 3].

The mean FEV1, FVC and FEV1/FVC respectively were significantly lower among participants with SCD compared to controls [Table 4]. Abnormal spirometry pattern was observed in 174 (71%) and 68 (31.5%) participants with SCD and controls, respectively [Table 4]. The pattern that was suggestive of restrictive was the most frequent abnormality in both SCD and controls. A physician diagnosis of asthma was reported in 3 (1.2%) of the SCD participants.

Association between pulmonary function parameters and selected clinical and laboratory parameters in sickle cell disease

We utilized the data for 188 participants with complete clinical and laboratory parameters (blood counts and HbF) for this analysis. Funding limitations did not permit blood tests on all participants and the tests were performed consecutively. This sub-group of 188 participants did not differ from the entire SCD group in gender distribution (51.6% of females and 48.4% of males), age distribution (48.9%, 35.1%, 11.7%, and 4.3% between the age group of 14–14 years, 25–34 years, 35–44 years, and ≥45 years, respectively), and respiratory pattern (33%, 39.9%, 13.8%, and 13.3% with normal, suggestive of restrictive, obstructive, and mixed spirometry patterns, respectively).

Table 5 compares frequencies and median values of clinical and laboratory parameters among normal and abnormal spirometry patterns. Among the 54 (28%) participants with respiratory symptoms, 42 (77.8%) had abnormal respiratory pattern, however, 84 (66.7%) participants with abnormal pattern had no respiratory symptom.

For linear regression analysis for associations with FVC, Hb concentration was independently and positively associated with FVC, while WBC was independently and negatively associated with FVC. Current use of hydroxyurea was associated with FVC only in univariate analysis [Table 6]. Linear regression model for associations with FEV1 demonstrated that Hb concentration was independently and positively associated with FEV1, while age was independently and negatively associated with FEV1 [Table 6]. There was no significant relationship between FEV1 or FVC with BMI, platelet count, SPO_2, and HbF.

Table 2: Clinical and laboratory parameters of participants with sickle cell disease

Parameters	All participants (*n*=245)	Males (*n*=122)	Females (*n*=123)
SCD complications (%)			
Priapism*	*	37 (30.3)	*
Leg ulcers	50 (20.4)	31 (21.4)	19 (15.4)
Acute chest syndrome	34 (13.9)	17 (13.9)	17 (13.8)
AVN of femoral head	19 (7.7)	7 (13.9)	12 (9.8)
Nephropathy	11 (4.4)	4 (3.3)	5 (4.1)
Stroke	3 (1.2)	2 (1.6)	1 (0.8)
Pulmonary hypertension	3 (1.2)	2 (1.6)	1 (0.8)
Cholelithiasis	3 (1.2)	0	3 (1.3)
Heart failure	3 (1.2)	0	3 (1.3)
Laboratory parameters#			
Hemoglobin g/dL (mean±SD)	7.8±1.6	8.0±1.7	7.65±1.46
PCV % (mean±SD)	23.1±5.1	23.72±5.5	22.56±4.66
HbF % (median (IQR)	4.8 (2.6-8.4)	4.4 (2.6-7.8)	5.5 (2.7-8.8)
WBC/mL (median (IQR)	9400.0 (7400-11575)	9300.0 (7400.0-11500.0)	9800 (7500-11600)
Neutrophil/mL (median (IQR)	5300.0 (3900-6900)	5100.0 (3900.0-7000.0)	5550 (4100-6850)
Lymphocyte/mL (median (IQR)	3400.0 (2600-4300)	3200.0 (2700.0-4250.0)	3500 (2525-4375)
Platelet count/mL (median (IQR)	271,500.0 (193,000-355,250)	249000.0 (19000.0-36000.0)	283000 (213000-338000)

*Males only, #Complete blood count and Hemoglobin F for 188 (91 males) and 196 (98 males) participants respectively. SCD=Sickle cell disease, PCV=Packed cell volume, HbF=Fetal hemoglobin, WBC=White cell count, IQR=Interquartile range, AVN=Avascular necrosis

Table 3: Comparison of respiratory symptoms among participants with sickle cell disease and controls

Parameter	All participants (*n*=461)			Males (*n*=229)			Females (*n*=232)		
	SCD (*n*=245)	Control (*n*=216)	Statistics	SCD (*n*=122)	Control (*n*=107)	Statistics	SCD (*n*=123)	Control (*n*=109)	Statistics
Shortness of breath (%)	52 (21.2)	30 (13.9)	χ^2=5.19, *P*=0.07	23 (18.9)	6 (5.6)	χ^2=9.04, *P*=0.003	29 (23.6)	24 (22.0)	χ^2=0.99, *P*=0.61
Sleep related symptoms (%)	13 (5.3)	11 (5.1)	χ^2=0.01, *P*=0.92	6 (4.8)	4 (3.7)	χ^2=3.0, *P*=0.56	7 (5.7)	7 (5.4)	χ^2=3.0, *P*=0.56
Trigger related symptoms (%)	33 (13.5)	30 (13.9)	χ^2=0.01, *P*=0.90	19 (15.5)	12 (11.2)	χ^2=0.96, *P*=0.62	14 (11.4)	18 (16.5)	χ^2=4.0, *P*=0.14
Cough (%)	2 (0.8)	5 (2.3)	χ^2=1.81, *P*=0.41	1 (0.8)	1 (0.9)	χ^2=0.03, *P*=0.93	1 (0.8)	4 (3.7)	χ^2=2.58, *P*=0.28
Phlegm (%)	10 (9)	6 (2.8)	χ^2=0.01, *P*=0.95	4 (3.3)	2 (1.9)	χ^2=1.89, *P*=0.39	6 (4.9)	4 (3.7)	χ^2=0.32. *P*=0.85
Any respiratory symptom (%)	70 (28.6)	54 (25.0)	χ^2=0.41, *P*=0.51	33 (27.0)	17 (15.9)	χ^2=5.16, *P*=0.08	37 (30.1)	37 (33.9)	χ^2=1.40, *P*=0.53

SCD=Sickle cell disease

Discussion

To the best of our knowledge, this study provides evidence of the frequency and pattern of pulmonary dysfunction among the largest number of participants yet with SCD in Nigeria. The main findings are that lung volumes are significantly lower among participants with SCD as compared to controls, but the frequency of respiratory symptoms did not differ between the two groups. Accordingly, the frequency of pulmonary dysfunction was significantly higher in SCD (70%) compared to controls (30%) with a predominance of the suggestive of the restrictive pattern. Hb concentration was independently and positively associated with both FEV1 and FVC, while WBC and age were negatively associated with only FVC and FEV1, respectively.

The absence of updated local reference data for spirometry values for Nigerians compelled comparison with a control group who are ethnically similar and likely to have similar nutritional and environmental exposures that may influence lung function.[21] This adds strength to our findings regarding the increased frequency of pulmonary dysfunction in SCD as a complication of the disease and less likely as an ethnic or environmental complication. It is worthy of note that the frequency of pulmonary dysfunction reported in the control group (31%) is substantial. Control participants did not have a previous chronic respiratory illness, tobacco smoking, or other factors likely to compromise lung function. The frequent finding of reduced FVC among Nigerian in the general population has been reported and may explain the increased incidence of suggestive of restrictive pattern in the control group.[22] In the population study in Nigeria, between 15% and 20% of adults had reduced FVC below the LLN using the GLI equation.[22] They further demonstrated a relationship between reduced FVC and the Gross National Income which alludes to the potential role of poverty-related

Table 4: Comparison of pulmonary function parameters among participants with sickle cell disease and controls

Parameter	All participants (*n*=461)			Males (*n*=299)			Females (*n*=232)		
	SCD (*n*=245)	Control (*n*=216)	Statistics	SCD (*n*=122)	Control (*n*=107)	Statistics	SCD (*n*=123)	Control (*n*=109)	Statistics
Measured values									
Median FEV1 in liters (IQR)	2.42 (2.12-2.89)	3.08 (2.60-3.59)	Z=−8.9, P=<0.001	2.87 (2.37-3.32)	3.49 (3.19-4.0)	Z=−8.2, P=<0.001	2.20 (1.91-2.49)	2.61 (2.33-2.92)	Z=−6.80, P=<0.001
Median FVC in liters (IQR)	3.06 (2.63-3.68)	3.55 (3.09-4.32)	Z=−7.1, P=<0.001	3.49 (3.09-3.99)	4.28 (3.79-4.70)	Z=−7.5, P<0.001	2.72 (2.42-3.06)	3.11 (2.78-3.44)	Z=−5.24, P=<0.001
Median FEV1/FVC (IQR)	0.81 (0.75-0.87)	0.85 (0.80-0.89)	Z=−4.7, P<0.001	0.81 (0.76-0.86)	0.84 (0.80-0.89)	Z=−3.1, P=0.002	0.80 (0.75-0.87)	0.85 (0.80-0.88)	Z=−3.57, P=<0.001
Pattern									
Normal (%)	71 (29.0)	148 (68.5)	χ^2=98.39, P=<0.001	36 (29.5)	74 (69.2)	χ^2=41.51, P=<0.001	35 (28.5)	74 (67.9)	χ^2=37.68, P=<0.001
Suggestive of restrictive (%)	118 (48.2)	50 (23.1)		65 (53.3)	29 (27.1)		53 (43.1)	21 (19.3)	
Obstructive (%)	29 (11.8)	16 (7.4)		6 (4.9)	4 (3.7)		23 (18.7)	12 (11.0)	
Mixed (%)	27 (11.0)	2 (0.9)		15 (12.3)	0 (0)		12 (9.8)	2 (1.8)	

FEV1=Forced expiratory volume in the 1st s, SCD=Sickle cell disease, FVC=Forced vital capacity

factors in predicting lung growth and lung function in our population.[22]

Lower lung volumes and a high frequency of pulmonary dysfunction with a predominance of the suggestive of a restrictive pattern among adults in our study corroborate and further substantiates previous reports from Nigeria and elsewhere.[11-13] The frequency in our study is lower than the reported frequency (90%) in the United States of America in which complete pulmonary function tests (PFTs) with diffusing capacity for carbon monoxide and total lung capacity (TLC) which is the gold standard for defining restrictive abnormalities were performed.[13] Only 48% of 78% of persons with restrictive abnormality defined by low TLC <80% predicted reported by Kling *et al*. had low FVC on spirometry suggesting that the frequency we have reported with spirometry data alone is likely to be an underestimate.[13] This highlights the modest utility of spirometry as a screening tool for the early detection of SCCLD. However, we recognize its value in resource limited settings such as ours where complete PFTs are not readily available.

The frequency of obstructive pulmonary defect in SCD in our study (23%) is higher than in previous Nigerian reports.[11] The higher frequency in this present study may be a reflection of our use of the GLI LLN which better identifies airway obstruction among young adults than a fixed cutoff.[23] However, only 1.2% of the participants in our study have previous physician diagnosis of asthma. This may be a reflection of the reported gaps in asthma diagnosis and management in Nigeria where many patients with typical symptoms of asthma are not diagnosed or treated.[24] Previous studies have documented higher frequencies of asthma diagnosis (17%),[25] airway obstruction on PFTs (54%),[26] and airway hyperreactivity (AHR) (77%) in SCD compared to the general population.[27] The prevalence of asthma and AHR in the general population in these studies were about 6% and 20%, respectively.[28,29] We also noted that more participants with a history of ACS had obstructive defect and previous studies have reported associations between airway obstruction, asthma, and ACS.[24,30] Patients with SCD who also have asthma are more likely to develop ACS during episodes of vaso-occlusive crisis.[24] Therefore, prior documentation of airway obstruction is important as it can identify patients who may benefit from additional treatment for vaso-occlusive crisis to forestall the development of ACS.

We found a lack of association between a suggestive of restrictive defect and history of ACS and level of HbF which is similar to previous reports.[4,13,31] Field *et al*., in a longitudinal study, reported an excess rate of decline in lung function over time which was not associated with the frequency of ACS.[31] This may be partly explained

Table 5: Comparison of clinical and laboratory parameters of participants with sickle cell disease among the spirometry patterns

Characteristic	Normal (*n*=62)	Suggestive of restrictive (*n*=75)	Obstructive (*n*=26)	Mixed (*n*=25)	Statistics (*P*)
Medians age in years	27	24	27.5	25	0.06
Male sex (%)	29 (46.8)	38. (50.7)	7 (26.9)	15 (60.0)	0.10
Positive history of ACS (%)	7 (11.3)	10 (13.3)	7 (26.9)	2 (8.0)	0.19
Currently taking hydroxyurea (%)	10 (16.1)	1 (12.0)	7 (26.9)	9 (36.0)	**0.04**
Shortness of breath (%)	8 (12.9)	21 (28.0)	6 (23.1)	4 (16.0)	0.32
Cough (%)	0	1 (1.3)	0	0	0.74
Phlegm (%)	2 (3.2)	6 (8.0)	1 (3.8)	1 (4.0)	0.85
Trigger-related symptoms (%)	6 (9.7)	11 (14.7)	5 (19.2)	1 (4.0)	0.31
Sleep related symptoms (%)	3 (4.8)	6 (8.0)	1 (3.8)	0	0.46
Any respiratory symptom (%)	12 (19.4)	29 (38.7)	8 (30.8)	5 (20.7)	0.06
Median SPO2%	96	96	95	95	0.83
Median hemoglobin g/dL	8.5	7.4	7.5	7.9	**0.005***
Median PCV%	25.4	22.0	21.9	23.7	**0.005**†
Median WBC/mL	9350	9700	10350	9200	0.36
Median neutrophil/mL	5350	5300	5500	4900	0.85
Median lymphocyte/mL	3000	3700	3650	2850	**0.02**‡
Median platelet/mL	267000	283000	2635000	254000	0.78
Median HbF%	4.7	3.6	7.5	6	**0.02**§
Median height in meters	1.67	1.63	1.65	1.71	0.05
Median BMI in kg/m^2	20.8	19.4	22.1	19.2	**0.000**‖

ACS=Acute chest syndrome, SPO2%=Oxygen saturation, PCV%=Packed cell volume, WBC=White cell count, HbF%=Fetal hemoglobin, BMI=Body mass index. *P* values in bold=Significant difference between patterns. *Pairwise comparison showed a significant difference between normal and suggestive of restrictive defect (*P*=0.003), †Pairwise comparison showed a significant difference between normal and restrictive pattern (*P*=0.004), ‡Pairwise comparison showed a significant difference between normal and restrictive pattern, §Pairwise comparison showed a significant difference between restrictive and obstructive defect, ‖Pairwise comparison showed significant difference between mixed defect and obstructive defect (*P*=0.02), Suggestive of restrictive defect and normal (*P*=0.02) and suggestive of restrictive defect and obstructive defect (*P*=0.003)

Table 6: Linear regression analysis for associations between selected parameters among participants with sickle cell disease and forced vital capacity and forced expiratory volume in the first second, respectively

Parameter	Unadjusted		Adjusted	
	OR (95% CI)	*P*	OR (95% CI)	*P*
FVC				
Sex (male)	0.53 (0.61-0.97)	<0.001	0.26 (0.20-0.58)	0.000
Hb concentration	0.22 (0.03-0.16)	0.001	0.16 (0.03-0.12)	0.002
WBC	−0.15 (0.0-0.0)	0.04	−0.14 (0.0-0.0)	0.01
Height	0.61 (0.04-0.06)	<0.001	0.47 (0.03-0.05)	0.000
Current use of hydroxyurea	0.23 (0.16-0.69)	0.002	0.06 (−0.10-0.31)	0.30
FEV1				
Sex (male)	0.53 (0.051-0.81)	<0.001	0.28 (0.19-0.51)	0.000
Age	−0.22 (0.03-0.01)	0.003	−0.16 (−0.02-0.0)	0.003
Hb concentration	0.24 (0.04-0.15)	0.001	0.20 (0.04-0.12)	0.000
Height	0.58 (0.03-0.05)	<0.001	0.42 (0.02-0.04)	0.000

Male sex and height are known to be positively associated with lung function OR (95% CI)=Odds ratio (95% confidence interval), Hb=Hemoglobin, ANOVA *P*<0.000 for model fit for FEV1 and FVC, respectively, FVC=Forced vital capacity, FEV1=Forced expiratory volume in the 1st s, WBC=White cell count

by the low frequency of episodes of ACS in most studies including ours that is possibly related to the use of hydroxyurea following ACS that potentially reduces recurrent episodes and subsequent pulmonary fibrosis.

Hb concentration was independently associated with higher FEV1 and FVC in this study and a similar association with Hb has been reported.[13] Other studies have also reported association between higher WBC and restrictive defect.[6,13,32] The relationship between WBC and restriction is plausible since higher WBC is associated with other poor outcome measures such as shortness of breath, strokes, ACS, cerebral infarction, and early death.[6,32,33] The mechanism by which raised WBC impairs pulmonary function is not clear, however, the ability of WBC to adhere to vascular endothelium leading to a cascade of inflammatory events that promote microvascular occlusions, erythrocyte, and WBC entrapment may contribute to pulmonary fibrosis and restrictive defect. Interestingly, we found that age was not associated with FVC and FEV1 as would be expected with normal age-related lung growth suggesting that

inherent disease-related factors in SCD may play a greater role in predicting pulmonary function.

The presence of respiratory symptoms in this study did not consistently herald the development of pulmonary dysfunction and hence may not be a sensitive indicator of SCCLD, making a case for routine screening. This is important because the "evidence based management of SCD report" by the National Heart, Lung, and Blood Institute recommends performance of PFTs only for those with signs and symptoms of respiratory disease.[34] The presence of respiratory symptoms may be an indicator of advanced pulmonary dysfunction and detection at this stage may limit the effectiveness of potential interventions.[3] However, a challenge to the recommendation for routine screening may be the unclear benefit of early detection as there are no current guidelines for management. The relationship between obstructive pattern, asthma symptoms, and response to inhaled steroids and bronchodilators remains inconsistent among adults. Current use of hydroxyurea which was positively associated with only FVC in univariate analysis in the present study has not been consistently reported to have beneficial effects in reducing the rate of lung function decline among adults, although beneficial effects have been reported among children.[35]

The strengths in our study are in the large sample size, comparison with a control group, use of quality assured spirometry data, and assessment of respiratory symptoms that highlighted the possible initial asymptomatic presentation of SCCLD. We recognize limitations in our inability to perform complete PFTs to better identify and characterize pulmonary function as well as the absence of chest imaging. Chest imaging would have related pulmonary dysfunction with parenchymal lung disease and identified chest wall and ribcage abnormalities that could lead to pain and apparent restrictive defect. Furthermore, there is limited generalizability of our results to the SCD population in Nigeria as our participants were from a single specialized clinic with potential access to better care. Although we did not test the Hb genotype of the control group, awareness of genotype is common in Nigeria, and it is unlikely that these participants falsely reported their genotypes under this circumstance. Despite these limitations, our findings bring to the fore the high burden of pulmonary dysfunction in SCD and serve as a call to action on stakeholders, policy makers, and researchers toward the development of strategies and policies for early detection and effective interventions to preserve pulmonary function.

Conclusion

There is a high burden of pulmonary dysfunction in SCD in Nigeria that warrants a call for routine screening and possible intervention that can delay lung function decline. There is a need for further research to evaluate likely risk factors and explore the effectiveness of potential interventions to harness the benefits from monitoring and early detection.

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Conflicts of interest

There are no conflicts of interest.

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