

Spirometric Patterns and Pulmonary Function Abnormalities in Adult Patients with Sickle Cell Disease

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ABSTRACT

Background: Sickle cell disease is a common genetic disorder that impairs hemoglobin, leading to organ damage, with the lungs being a major target. Pulmonary complications, particularly acute chest syndrome and chronic lung disease, significantly reduce lung function and are major causes of morbidity and mortality in affected patients. This study focuses on the characterization of lung function using spirometry (restrictive, obstructive, mixed patterns) in adult SCD patients.

Method: This is one-year cross-sectional case-control study at NAUTH, Nnewi, assessed lung function in participants using a MicroLab 3500 spirometer to measure FVC, FEV1, and FEV1/FVC ratio. Procedures followed ATS/ERS guidelines, with predicted values calculated using GLI 2012 equations. Data were entered and analyzed using Statistical Package for Social Sciences (SPSS version 21.0).

Result: The age range (AR) of the patients was 18-35 years with a mean of 24.20 ± 2.53 years. The spirometry outcome showed that 32(64%) study subjects had abnormal ventilatory function while 18(36%) had normal ventilatory function. 32(64%) of the subjects had abnormal lung function while 18(36%) had normal lung function. One (9.09%) of study subjects with mild sickle cell disease severity score (SCDSC) had abnormal oxygen saturation (SpO₂) while 13 (33.33%) of study subjects with mild SCDSC had normal SpO₂ ($p < 0.003$). Two (18.18%) of the study subjects with moderate SCDSC had abnormal SpO₂ while 15 (38.46%) with moderate SCDSC had normal SpO₂ ($P = 0.07$).

Conclusion: Adult sickle cell disease patients frequently exhibit restrictive ventilatory defects, reduced spirometric parameters, and abnormal oxygen saturation, especially in severe cases. These abnormalities are likely due to recurrent acute chest syndrome, fibrosis, and progressive lung damage, underscoring the need for early detection, optimal management, and preventive interventions to preserve pulmonary function.

Keyword: Sickle Cell Disease, Adult, Spirometry, Pulmonary

INTRODUCTION

Sickle cell disease (SCD) is a chronic genetic disorder that affects hemoglobin production, causing red blood cells to become rigid and sickle-shaped. This leads to reduced blood flow, tissue damage, and organ damage due to inadequate oxygen supply. It's one of the most common genetic diseases globally.(1,2)

The lung is one of the organs in the body affected by sickle cell disease.(3) and pulmonary complications are the leading cause of morbidity and mortality in these patients.(4) Pulmonary involvement occurs in two major forms:

Acute Chest Syndrome and Sick Cell Chronic Lung Disease.(4) ACS is one of the major causes of hospital admissions in patients with sickle cell disease and is responsible for up to 25% of deaths. Acute chest syndrome has been reported to occur in 15% to 43% of patients with SCD. Reoccurrence of episodes occur in up to 80% of those who had ACS.(5,6)

Various studies have shown that there is reduced pulmonary function in adult patients with sickle cell disease compared to that of persons without sickle cell disease.(3) However, the impact of acute chest syndrome on lung function from the suggested pathological mechanisms include interstitial lung abnormalities, airway hyperactivity, nocturnal oxyhaemoglobin desaturation, pulmonary hypertension, pulmonary thromboembolism and pulmonary function test abnormality.(7,8)

The median life expectancy for individuals with Hb-SS is 42 years for males and 48 years for females.(9) Notably, pulmonary complications – including acute chest syndrome, pulmonary hypertension, and pulmonary fibrosis – contribute significantly to mortality, accounting for 20-30% of deaths within this population, yet often remain underdiagnosed by healthcare providers.(10)

This study focuses on the characterization of lung function using spirometry (restrictive, obstructive, mixed patterns) in adult SCD patients. It also analyses the associations with disease severity, hemoglobin concentration, or oxygen saturation.

MATERIALS AND METHOD

This cross-sectional case-control study was conducted over a one-year period (January 1 to December 30, 2018) at the Haematology Clinic of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Nigeria. It aimed to evaluate spirometric patterns and pulmonary function abnormalities among adult patients with sickle cell disease (SCD), specifically those with haemoglobin SS genotype (HbSS), compared to healthy controls. Ethical approval was obtained from NAUTH's ethical committee, and written informed consent was secured from all participants.

Study Population and Sampling

The study included adult HbSS patients aged 18–35 years in a stable clinical state, defined as the absence of pain crises or acute illness, and who had been regularly attending the outpatient clinic. The control group consisted of healthy HbAA genotype adults (medical students) matched for age and sex. A calculated sample size of 41 participants per group was derived using a statistical formula based on the estimated 3.1% prevalence of SCD. However, to increase the study's statistical power, 50 subjects were recruited for both the case and control groups. SCD patients were recruited consecutively, while controls were randomly selected from a pool of eligible medical students using a lottery method.

Inclusion and Exclusion Criteria

Participants included were those aged 18–35, confirmed to be HbSS or HbAA by electrophoresis, who consented to participate. Exclusion criteria encompassed individuals with spinal deformities, cardio-respiratory diseases, or a history of smoking, which could interfere with lung function.

Data collection procedures

Demographic, anthropometric, and clinical data were collected using an adapted St. George's Respiratory Questionnaire, including respiratory history, allergies, exposures, and medications. Measurements included weight, height, BMI (WHO classification), blood pressure, and respiratory rate, following standardized procedures.

Pulmonary function testing

Spirometry was performed using a Micro Lab 3500 spirometer to assess Forced Vital Capacity (FVC), Forced

Expiratory Volume in one second (FEV1), and the FEV1/FVC ratio. Participants performed at least three acceptable maneuvers, and the best value was selected. Pre-test procedures included loosening tight clothing and applying nose clips. Predicted values were derived using the Global Lung Initiative (GLI) 2012 equations. Based on the American Thoracic Society/European Respiratory Society guidelines and Pellegrino et al.'s algorithm, spirometric patterns were classified as:

1. Normal: FEV1/FVC and FVC > LLN
2. Obstructive: FEV1/FVC < LLN, FVC > LLN
3. Restrictive: FEV1/FVC > LLN, FVC < LLN
4. Mixed: Both FEV1/FVC and FVC < LLN

Bronchodilator reversibility was assessed in patients with obstructive patterns using 400 mcg of inhaled salbutamol. A $\geq 15\%$ increase in FEV1 post-bronchodilator was considered reversible obstruction.

Laboratory investigations

SCD diagnosis was confirmed using haemoglobin electrophoresis with cellulose acetate strips. Haemoglobin concentration was measured from venous blood samples using an automated Sysmex KS21N machine within two hours of collection.

Scd severity scoring

A modified scoring system developed by Hedo et al. was employed to assess SCD severity based on clinical complications and laboratory parameters over the previous year. Parameters included the frequency of crises, transfusion history, presence of complications (e.g., pneumonia, osteomyelitis, acute chest syndrome, organ failure), and degree of anaemia. Severity was graded as:

1. Mild: Score ≤ 3
2. Moderate: Score >3 and ≤ 7
3. Severe: Score >7

Determination of oxygen saturation

This was done using Pulse Oximeter (model MD300A), a noninvasive method of determining oxygen saturation of haemoglobin in pulsating arterial blood vessels. This works by comparing the amount of red light absorbed to the amount of infrared light absorbed by both deoxygenated haemoglobin and oxyhaemoglobin. This was carried out when patients had rested and was done for about 2 minutes on two occasions with the average was calculated and documented. Oxygen saturation should be categorized into: 104 Normal SpO₂ > 95%; Abnormal SpO₂ $\leq 95\%$

Data analysis

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS version 21.0). Results were presented as mean + standard deviation (SD) for continuous variables while categorical variables were expressed as proportions or percentages. Graphs and tables were used to illustrate results where appropriate.

Continuous variables were compared using the student's t-test, while proportions or categorical parameters were compared with the chi-square test or two-tailed Fisher's exact test as appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

One hundred (100) participants were studied comprising 50 adult sickle cell disease (SCD) patients in steady state (subjects) and 50 normal adults (control).

Table 1: Age/ Sex Distribution

Age (in years)	Subject(n=50)				Control(n=50)			
	M (%)	F (%)	TOTAL	P Value	M (%)	F (%)	TOTAL	P Value
≤20	1(3.57)	1(4.54)	2(100)	0.321	2(6.67%)	2(10.0)	4(100)	0.423
21-25	12(42.86)	13(59.09)	25(100)		18(60.0)	14(70.0)	32(100)	
26-30	13(46.43)	7(31.81)	20(100)		9(36.0)	4(20.0)	13(100)	
31-35	2(10.71)	1(4.54)	3(100)		1(3.33)	-	1(100)	

Age/ sex distribution

The age range (AR) of the patients was 18-35 years with a mean age of 24.20(2.53) years. That of the control was 18-35 years with a mean of 22.56(2.2) years. The age range (AR) of male and female study subjects were 20-35 and 18-33 respectively while the age range of male and female control subject were 18-35 and 19-32 respectively. There were 28 (56.0%) males and 22 (44.0%) females in the patient group; while the control group had 30 (60.0% of control group) males and 20 (40.0%) females. The mean ages of male and female sickle cell anaemia subjects were 23.6(2.1) and 24.6(2.4) years respectively ($p=0.903$). The mean ages of the male and female control subjects were 21.8 (2.1) and 23.32(2.2) years respectively ($p=0.912$). The ages in both groups were therefore similar being a case-controlled study. These are as shown in table 1. The difference in ages was not statistically significant ($p=0.423$). Hence, a male to female ratio of 1:1.3 and 1:1.5 for sickle cell disease and control populations respectively. The sex difference between these populations was insignificant ($p=0.231$).

Table 2: Spirometry Outcome Among Participants

Spirometry results categorization	Respondent category		
	Subject N=50	Control N=50	P value
Normal	18(36)	49(98)	0.012
Abnormal	32(64)	1(2)	
Total	50(100)	50 (100)	

Spirometry outcome among participants

The spirometry outcome showed that 32(64%) study subjects had abnormal ventilatory function while 18(36%) had normal ventilatory function, whereas all control subjects had normal ventilatory function except one that had mild obstructive ventilatory function which showed reversibility with bronchodilation ($p=0.012$). This is as seen in Table 2.

Table 3: Overall Lung Function Patterns in Study Participants

Normal	Frequency (Percent)	Frequency (Percent)	X ²	P value
	Subjects(n=50)	Controls (n=50)		
	18 (36.0)	49 (98.0)	5.127	0.051
Mild obstruction	1* (2.0)	1* (2.0)		
Mild restriction	10(20.0)	-		
Moderate restriction	13(26.0)	-		
Severe restriction	8(16.0)	-		

***Post-bronchodilator FEV1 ≥ 15% of Pre-bronchodilator FEV1**

Overall ventilatory function pattern

Various pattern of ventilatory function have been described among SCD patients. In this study, 32(64%) of the subjects had abnormal lung function while 18(36%) had normal lung function. Of these, 21/32(65.6%) had moderate to severe restrictive pattern while 10/32(31.3%) had mild restrictive pattern and only 1/32(3.1%) had obstructive pattern, whereas all the control groups had normal lung function pattern except one that had mild obstructive pattern.($P<0.051$)

Table 4: Relationship Between Lung Function Pattern and Oxygen Saturation

Subjects				
	Abnormal SP02(N=11)	Normal SP02(N=39)	X ²	P value
Normal	-	18(46.15)	4.917	0.011
Mild obstruction	-	1(2.56)		
Mild restriction	-	10(25.64)		
Moderate restriction	3(27.27)	10(25.64)		
Severe restriction	8(72.73)	-		

Relationship Between Oxygen Saturation and Ventilatory Function Pattern According to Gender

In this study 11/32 of subjects with moderate-severe restrictive lung disorder had abnormal SpO₂ while 20/32 of subjects with mild and moderate restrictive lung function pattern had normal SpO₂. All patients with severe restriction had abnormal SpO₂, whereas most subject with moderate restrictive disease 10/13 had normal SpO₂ and 3/13 had abnormal SpO₂

Table 5: Relationship Between the Severity Score and Oxygen Saturation of the Test Participants

Sickle -cell disease severity score	SPO2			
	Abnormal SP02(N=11)	Normal SP02(N=39)	X ²	P value
Mild I	1(9.09)	13(33.33)	5.731	0.013
Moderate II	2(18.18)	15(38.46)		
Severe III	8(72.73)	11(28.21)		

Relationship Between the Severity Score and Oxygen Saturation of the Test Participants

In table 5, One (9.09%) of study subjects with mild sickle cell disease severity score (SCDSC) had abnormal oxygen saturation (SpO₂) while 13 (33.33%) of study subjects with mild SCDSC had normal SpO₂ ($p<0.003$). Two (18.18%) of the study subjects with moderate SCDSC had abnormal SpO₂ while 15 (38.46%) with moderate SCDSC had normal SpO₂.($P=0.07$). Eight (72.73%) of the study subjects with severe SCDSC had abnormal SpO₂ while 11(28.21%) of the study subjects with severe SCDSC had normal SpO₂ ($P<0.013$).

DISCUSSION

The study participants age range of 18-35 years aligns with previous research, potentially due to the high mortality rate associated with sickle cell disease (SCD) or limited healthcare access and utilization in older populations. Some individuals may have opted for alternative treatments or foregone medical care altogether. The similarity in anthropometric parameters between the study and control groups suggests that the tertiary care center provided high-quality healthcare services to the subjects. Notably, the average body weight and BMI of Hb-SS subjects in this study were comparable to those reported by Ozoh et al(11)., likely due to the stable condition of patients receiving standard medical care at the teaching hospital where the study took place.

The spirometric parameters were found to be significantly lower in the SCD group comparable to the control group, and even lower than the predicted values. These finding may be associated with recurrent acute chest syndrome with the attendant consequences as obtained in other studies. (12,13)

The finding of restrictive ventilatory pattern in this study is similar to other studies. The reason for this cannot be explained but other studies suggest acute chest syndrome. The proportion in this study was lower than what was noted by Dei-Adomakoh et al and Oko-ose et al.(14,15) This was possibly due to recent use of hydroxyurea as a routine

Klings et al. (16) reported a 90% prevalence of restrictive ventilatory function defects in their study, potentially attributed to their use of both spirometry and total lung capacity measurements. According to American Thoracic Society (ATS) guidelines, total lung capacity measurement is the gold standard for diagnosing restrictive ventilatory defects.(17) Unfortunately, this study was limited by the unavailability of total lung capacity measurement facilities at the study site

It was noted that 4% of the study participants had obstructive ventilatory defect which reversed following bronchodilation. This could be explained by the fact that some sickle cell patients exhibit airway hyperresponsiveness. The 4% is in contrast to previous studies and this could be attributed to decrease episode of acute chest syndrome in this era due to increase use of hydroxyurea. Dei-Adomakoh et al(14) in Ghana found out that the proportion of adult sickle cell patient with obstructive defect was 16% and Willian et al(18) found out that 19.5% of the adult sickle cell population had obstructive ventilatory defect. The cause of obstruction in SCD are complex and quiet unclear but thought to include inflammation, effects of hypoxia, and oxidative stress on the bronchial tree.(19) It was also observed that increased respiratory system resistance was associated with low forced expiratory flows, but normal FEV1 in young adults with SCD.(8) A similar result was obtained by Komboulis et al(20) in a study of 63 patients, 35% had obstructive ventilatory function pattern while 8% had restrictive disease. The difference might be due to direct measurement of respiratory resistance using forced oscillation method unlike in this study which was dependent on FEV1% measurement.

In this study, It was noted that the highest proportion of the adult sickle cell disease patients with abnormal oxygen saturation had severe restrictive ventilatory lung function. The observation that abnormal oxygen saturation was associated with severe restrictive lung function in this study could be explained by the presence of fibrosis with attendant impairment of gaseous exchange. This is in contrast to the study done by Dei-Adomakoh et al(14) who reported that there was no significant difference between the abnormal mean oxygen saturation of sickle cell disease patients with ventilatory function outcome. They however, concluded that steady-state haemoglobin showed positive correlation with FEV1% and possibly free haemoglobin significantly predicted abnormal FEV1%. The work done by Fawibe et al(21) on adult sickle cell patients with CT evidence of interstitial lung disease and concomitant restrictive ventilatory defect showed abnormal oxygen saturation ranged from 91 to 94%. Others studies also documented restrictive ventilatory defect with mild hypoxemia. (16,22,23) Dosunmu et al(24) found that in patients with abnormal lung function, the mean oxygen saturation was reduced compared to those with normal lung functions. He concluded that there was no significant difference in the oxygen saturation of participants with lung lesion and those without lung lesion. He mentioned that low affinity for oxygen associated with haemoglobin SS may contribute to this observation. Studies have reported abnormal mean oxygen saturation lower than the control subjects, and are due to change in haemoglobin concentration and low affinity for oxygen which are similar to the findings in this study.(23,25) Fonseca et al(13) found no association between spirometric alterations and values of percutaneous oxygen saturation, because it was considered that pulse oximetry had little specificity to determine the actual oxygen saturation. However, they suggested pulse oximetry could still be useful as a screening tool to identify patients at risk of chronic pulmonary function alterations.

Highest proportion of study subjects with abnormal oxygen saturation had severe form of sickle cell severity score. The reason was due to the fact that increasing sickle cell severity is associated with progressive decline in lung function from end-organ damage.

Participants with severe sickle cell disease had severe restrictive pulmonary defects, likely due to recurrent acute chest syndrome leading to fibrosis and scarring in the lungs, ultimately causing a decline in pulmonary function. This is similar to the work done by Kling's et al,(16) who documented an association between the presence of

restrictive lung disease and a more severe HbSS phenotype. This might be explained by the fact that the more severe HbSS phenotype was associated with recurrent acute chest syndrome episodes. This was backed by the fact that recurrent episodes of acute chest syndrome were associated with progressive decline in ventilatory function. Dei-Adomakoh et al(14) also documented that abnormal lung function, particularly restrictive ventilatory defect in sickle cell disease patients was shown to be more prevalent in those with severe cases of sickle cell anaemia.

LIMITATIONS OF THE STUDY

Lung function was assessed with spirometer only; this is less sensitive than when DLCO and body plethysmography are incorporated. Airway obstruction could not be measured directly using forced oscillation method which is more sensitive than spirometer only. More important limitations to note include the following. Firstly, it was conducted at a single center, which may limit the generalizability of the findings to broader populations with varying genetic, environmental, and healthcare characteristics. Secondly, the cross-sectional design prevents determination of temporal or causal relationships between disease severity and pulmonary impairment. Thirdly, the recruitment of medical students as the control group may introduce selection bias, as their socioeconomic status, educational background, and health behaviors could differ from the general population. Despite these limitations, this study provides valuable baseline data on spirometric patterns among adults with sickle cell disease and establishes a framework for future multicenter and longitudinal investigations.

RECOMMENDATIONS

Future research should aim to expand upon these findings through multicenter studies involving larger and more heterogeneous populations to enhance external validity. Longitudinal follow-up of individuals with sickle cell disease would provide important insights into the natural progression of pulmonary impairment and clarify causal associations with clinical factors such as disease severity, acute chest syndrome, and treatment interventions. Incorporating additional pulmonary evaluations—such as diffusing capacity for carbon monoxide (DLCO), six-minute walk testing, echocardiography, and high-resolution chest imaging—would strengthen the physiological and structural understanding of SCD-related lung disease. Moreover, including control participants from the general community rather than academic cohorts may improve representativeness and reduce potential selection bias. All sickle cell disease patients should have their ventilatory function assessed. Frequent screening of the oxygen saturation of adult sickle cell patients is recommended as it could help identify those at risk of developing sickle cell chronic lung disease.

CONCLUSION

The predominant ventilatory function pattern in adult sickle cell disease patients in this study is the restrictive pattern seen in 62.0% of the subjects. Restrictive lung function defect was associated with severe sickle cell disease as well as low oxygen saturation. Adult sickle cell disease patients frequently exhibit restrictive ventilatory defects, reduced spirometric parameters, and abnormal oxygen saturation, especially in severe cases. These abnormalities are likely due to recurrent acute chest syndrome, fibrosis, and progressive lung damage, underscoring the need for early detection, optimal management, and preventive interventions to preserve pulmonary function.

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