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Prevalence and Determinants Linked with Impaired Lung Function in Children with Sickle Cell Disease Compared with Non-Sickle Cell Disease: A Cross-Sectional Survey in Dodoma, Tanzania

Tatu Seif Mbotoni[1*], Shakilu Jumanne[2], Dina Mahamba[2]

[1]Department of Pediatrics & Child Health, Iringa Regional Referral Hospital, Iringa, Tanzania
[2]Department of Pediatrics & Child Health, University of Dodoma, Dodoma, Tanzania
Email: *tmbotoni1@gmail.com, shakiluj@gmail.com, dinamahamba@gmail.com

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Abstract

Background: Children with sickle cell disease (SCD) in Tanzania, which has the fourth highest prevalence of SCD globally, are at risk of recurrent lung injuries leading to impaired lung function. This study seeks to determine the prevalence and contributing factors of impaired lung function in children with SCD compared to those without the disease. **Methods:** A comparative cross-sectional study conducted from December 2021 to May 2022 examined 115 children aged 6 - 18 years, with 59 having sickle cell disease (SCD) and 56 without. Data was gathered through a semi-structured questionnaire, and lung function was assessed using spirometry, with impairment marked by values below the predicted lower limit of normal. Blood tests for hemoglobin level and electrophoresis were conducted. Statistical analysis was performed using SPSS version 26, utilizing binary logistic regression to identify factors linked to lung function impairment, with $p < 0.05$ deemed significant. **Result:** Out of 115 participants, 61 (53.04%) were females, with a mean age of 9.67 ± 3.07. In the SCD group, females comprised 35 (53.38%) with a mean age of 9.39 ± 3.04, while in the non-SCD group, males were predominant (30, 55.56%) with a mean age of 9.95 ± 3.09. Impaired lung function was found in 52.5% of children with SCD and 10.72% of those without. Significant factors associated with impaired lung function included low blood pressure, older age, age at starting SCD clinic, and fetal hemoglobin levels below 10%. **Conclusion**: Lung function impairment is common among Tanzanian children with sickle cell disease (SCD), primarily exhibiting a restrictive pattern. Protective factors in-

clude low blood pressure, while contributing factors are older age, the age at which sickle cell clinics are initiated, and low fetal hemoglobin levels.

Keywords

Children, Sickle Cell, Impaired Lung Functions

1. Background

Sickle cell disease (SCD) is the most common genetic disease globally, with the highest prevalence in sub-Saharan Africa [1]. It is an autosomal recessive disease due to a single gene mutation in which an amino acid, valine, substitutes for an acidic amino acid glutamate in the polypeptide beta globin gene chain at position 6 of chromosome 11. SCD is a syndrome which comprises 3 main genotypes with HbSS accounting for 70% in Africa due to inheritance of two S beta globin. Hemoglobin SC is the second most common (30%) disease while the co-inheritance of HbS and beta thalassemia leads to HbS/beta thalassemia [2]. SCD-related childhood mortality was high in sub-Saharan African countries with 50% - 90% of children with SCD dying before their fifth birthday [3].

Respiratory complication and lung function impairment are common globally in patients with SCD as compared to non-SCD children. Globally, there is a wide range of lung function impairment in children with SCD, ranging from 65% to 23.4% [4]. Sickle Cell Disease is a multisystem disorder due to abnormal sickle RBC clog the macro and microvasculature leading to hypoxia and infarction tissue injury, lung fibrosis, endothelial injury, release of oxygen reactive species, all of which may lead to lung injuries. If these events continue to occur repeatedly, the cumulative and repetitive lung injury may cause chronic lung injury.

Despite the reduction in mortality for children with SCD, the pulmonary-related morbidity remains high across all ages and there is limited understanding of disease evolution and complications [5]. Recurrent Acute Chest Syndrome (ACS) episode is the most known risk factor for Sickle Cell Chronic Lung Disease (SCLD) with lung function abnormalities being common in childhood [6]. Progressive lung function impairment is one among the complications related to SCD. For early detection and management regular lung function test should be conducted. Routine lung function test can be achieved by the use of spirometry which is the simple, easy and affordable test and can be conducted in most of hospital settings in developed countries, this may help clinicians to intervene in early stages and identify those who need specialized care [7].

In Sub-Saharan Africa including Tanzania where the prevalence of SCD ranges from 5 - 12 per 100,000 with incidence of about 11,000 sickle cell birth per year and about 20% have sickle cell trait [8], there is limited data on the magnitude of lung function impairment in children with sickle cell disease and associated risk factors, thus creating knowledge gap among the clinicians attending pediatric

SCD patient leading to delay in diagnosis, management and preventive measures which creates more burden of lung function impairment in adulthood.

There are about two hundred children with SCD attending SCD clinics in the Dodoma Region, and many of them have been admitted several times with acute complications of pulmonary disease like pneumonia and acute chest syndrome (out of 10 SCD patients admitted, about 3 of them have a diagnosis of ACS/pneumonia) as well as recurrent infections outside the lungs (unpublished data from inpatient registry at DRRH). Currently, many hospitals do not perform lung function tests at the clinic as routine care, nor is it recommended by the new Tanzanian sickle cell disease guideline. The aim of this study was to determine the prevalence and factors associated with lung function impairment.

The findings of this study will highlight the magnitude of the problem and its associated factors to clinicians for proper management and possible prevention plans and serve as the baseline data for further research.

2. Methods and Materials

2.1. Study Design

This was a cross-sectional comparative study to assess lung function impairments in children with SCD and non-SCD children; the group was conducted from 20 December 2021 to 25 May 2022.

2.2. Study Area

This study was conducted at two major SCD clinics of Dodoma Regional Referral Hospital (DRRH) and St Gemma Hospital for the SCD group, and two schools, Amani Primary School and Kikuyu Secondary School, were used to recruit the non-SCD group. DRRH is a regional referral hospital for the Dodoma region, which also serves for other neighboring regions of Singida, Morogoro, Manyara, and Iringa, leading to a total catchment population of 6 million people. DRRH is also a teaching hospital for the University of Dodoma. The Pediatric Department offers inpatient services and outpatient specialist clinics, such as the Care and Treatment of children with SCD and a general pediatric clinic. St. Gemma Hospital is a designated district hospital owned by the Catholic Church located in the city of Dodoma. Both DRRH and St. Gemma Hospital run a once-weekly SCD clinic (on Wednesdays at DRRH and Thursdays at St. Gemma Hospital) with an average attendance of 25 children for both clinics. Among 25 children, only 3 children aged 6 to 18 years attend the SCD clinic weekly for both clinics. Children with SCD at the two clinics get routine SCD care, including general health assessment, Hydroxyurea, penicillin prophylaxis, folic acid, and hemoglobin level checkups.

2.3. Study Population

All children aged 6 to 18 years with or without sickle cell disease. Children aged 6 to 18 years with confirmed SCD (HbSS, HbSC, and HbSb0) by Hb electrophoresis

in a steady state for a period of 4 weeks or more. The criteria for the non-SCD control group were children aged 6 to 18 years, not known to have SCD or signs and symptoms suggestive of the disease and not known and confirmed (either by previous test or being on treatment) to have any chronic cardiopulmonary disease. Study participants were excluded if they had bronchodilator use 4 hours prior to the spirometry test and were performing an unacceptable spirometry test (acceptability in spirometry is the term used to describe how each blow is checked from start to finish to make sure it is of good quality; the checks are done by assessing each blow on the flow/volume and time/volume graphs, which are produced automatically by the machine during the test).

2.4. Sample Size Determination and Sampling Procedures

Was calculated using the proportionate formula by Kohn & Senyak

$$Total\ group\ size = N = (A+B)^2 / C$$

whereas

$N = Total\ group\ size$

$A = Z_\alpha \sqrt{P(1-P)(1/q_1 + 1/q_0)}$

$B = Z_\beta \sqrt{P_1(1-P_1)(1/q_1) + P_0(1-P_0)(1/q_0)}$

$C = (P_1 - P_0)^2$

$Pooled\ proportion = P = (q_1 * P_1) + (q_0 * P_0)$

Z_α = Threshold probability for rejecting the null hypothesis. Type I error rate = 1.96;

Z_β = Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate = 0.8416;

q_1 = Proportion of subjects known with Sickle Cell Disease (group 1) = 0.487;

q_0 = Proportion of subjects in the non-Sickle Cell Disease group (group 0) = 0.514;

P_0 = Proportions of lung function impairment in unexposed = 5.6%;

P_1 = Proportions of lung function impairment in exposed = 26.3%;

P_0 and P_1 were obtained from the previous study in Kuwait [9].

Therefore, the estimated sample size was found to be 115 with 59 subjects in the study group and 56 subjects in the control group.

Children with SCD at steady state and who appeared for routine SCD clinic visits during the study period were serially recruited in the study until the desired sample size was attained. Non-SCD children from two schools were obtained through random sampling by lottery method from a normal variant in a population that was not known to have sickle cell diseases or any respiratory conditions, in which each identified student was assigned numbers, which were mixed in a box, and then the researcher drew numbers from the box randomly. Until the sample size was reached. The schools were chosen by convenience since they are public schools and easily accessible to the researcher. The primary and secondary schools were chosen so as to meet the age range of the study. Refer to **Diagram 1**.

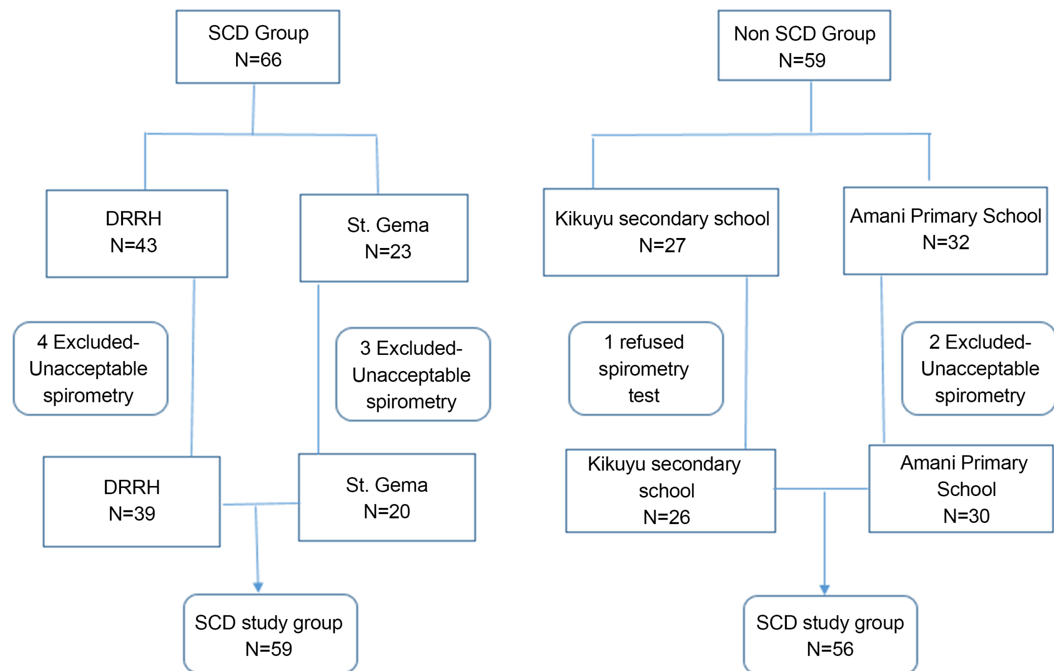

Diagram 1. Flowchart of enrolled children.

2.5. Data Collection Procedure

After obtaining consent and assent, data collection was done by using a semi-structured pretested questionnaire, which was administered through an interview to the study subjects and parents or caretakers, performed by the principal investigator and two trained research assistants. The questionnaire contained questions on demographic details of both children with SCD and non-SCD and parents/caretakers; clinical details (clinical history, anthropometric measure, vital signs, systemic examination findings, diagnosis details, complications of SCD, and medication history); laboratory results (Hb level and Hb electrophoresis results); and lung function test results (FEV1, FVC, FEV1/FVC, FEV1 predicted, and FVC predicted). Demographic data for caretakers were obtained from the caretakers for the SCD group and for the non-SCD group; the information was obtained through calling the caretakers (questionnaires were sent to caretakers in whom caretakers' phone numbers were written). For students, age was obtained through the school register and confirmed by parents via phone. Hemoglobin electrophoresis and hemoglobin level were done in the SCD group, while for non-SCD, hemoglobin level was checked only. And it was SCD versus school-based because we want to know if lung function is impaired in SCD children in comparison with their age mates who are non-SCD.

2.6. Study Procedure

A thorough physical examination, vital signs, anthropometric measurements, and laboratory tests, including spirometry tests, were done to all study participants. The weight in kilograms and height in meters were measured for all study partic-

ipants. A balance with stadiometer participants. A stadiometer scale (SECA Model 700) made in a stadiometer in Germany was used. The calibration to zero was made every time before measuring the weight. BMI is calculated for every participant by computing weight (kg) per height (meter squared) (BMI is squared) and interpreted using WHO growth reference for age charts in order to get the nutritional statuses of the study participants with categories of underweight (<−2 SD), overweight (−2 SD to <+1 SD), normal (−1 SD to +1 SD), overweight (+1 SD to +2 SD), and obese (>+2 SD). The subjects were >+2 and asked to remove their shoes and any object in their possession during the weighing procedure.

Pulse rate and oxygen saturation were measured using a pulse oximeter (MaxRox, German) by placing an index finger from any hand. An axillary temperature was measured in degrees Celsius using a digital thermometer (DERMOTHERM, Germany) and was cleaned using 70% alcohol before being used on another subject. The blood pressure was measured using a manual pediatric sphygmomanometer (Welchallyn, USA). The left and right arm BP was taken manually, and the average BP was recorded with the appropriate cuff used with subjects in a seated position and in a quiet and relaxed condition. The first and fifth Krokoff sounds were recorded for systolic and diastolic readings, respectively. Respiratory rate (RR) was counted using a stopwatch (Medline, China) in one minute when the child was relaxed. Thorough was relaxed. Thorough observation of chest upward and downward movement interruption was avoided during the count.

On general examination, pallor, finger clubbing, and difficulty in breathing were assessed and recorded if present. A respiratory and cardiovascular examination using a Littman Stethoscope class II was done, where crackles, wheezes, and cardiac murmurs were recorded if picked up.

Under aseptic technique using a 70% alcohol swab, 3 milliliters of blood were drawn from a peripheral vein with a 5 cc syringe and put in a Diamine Tina Acetic Acid (EDTA) container for analysis of hemoglobin level by Hemo-Cue 201+ made in Diamineinom, Sweden, and HB electrophoresis by Gazelle macinthe Gazellehine designed in the USA and the Gazelle made in India. Internal Quality Control in the USA: An internal quality control check was done every day before starting testing by using samples with known results.

A lung function test was done using an automated and easy One™ spirometer, which was manufactured by Medizintechnich Switzerland, model: 2001/72950/2009, and incorporated with global lung initiative 2 reference values and complied with the American Thoracic Society and European Respiratory Society standards. Quality control checks were done on a daily basis before using spirometry, but calibration was automatically done. The subjects were prepared for a test by loosening tight clothing, making them relaxed, and for those with dentures, the dentures were removed. The breathing maneuver was demonstrated by the investigator in order to emphasize filling lungs completely, sealing tips around the disposable spirometer to overcome leakage, taking care to avoid breaking its opening using teeth or tongue, and avoiding biting down excessively.

The spirometer machine was connected to the laptop containing a software program for the test with pediatric incentives (cakes and balloons) to motivate the children to perform the test correctly. When the participant had well understood the instructions, he or she was guided in performing maneuvers. The instructions were repeated as per need with vigorous coaching. The minimum of 3 maneuvers was repeated but not more than 8 times. A total of two acceptable tests were obtained. Each test was automatically graded using the machine. The spirometer automatically selected the trial with the largest sum of FVC and FEV1 to give the observed FVC, FEV1/FEV1, and FEV1/FVC ratios of each patient. Threshold of FVC the threshold of normality was considered at the fifth per the threshold is the fifth percentile of the predicted value. Infection prevention continued.

The fifth prevention and control were followed as per WHO guidelines. Hereby symptomatic screening of COVID-19 guidelines was performed using vital signs and a disposable spirometry mouthpiece with a filter (bacterial and viral 99.9% filter) to avoid contamination.

The investigator used all necessary protective gear, including face masks, gear, masks, sanitizers, masks and 70% alcohol for spirometry machine decontamination. One by one, study participants entered the room for sanitization to avoid overcrowding. Spirometry results were interpreted based on the Global Lung Initiative 2012 reference values, where FEV1, FVC, and FEV1/FVC less than the predicted lower limit of normal established at below the fifth percentile were regarded as lung function impairment. The predicted values were derived from the equation incorporated in the spirometry machine, which was giving results automatically.

$$\textbf{Predicted value} = e^{a} \times H^{b} \times A^{c} \times e^{d \times group} \times e^{spline}.$$

where a is the intercept, H is the height (cm), b is the exponent for height, A is age (years) and c is the exponent for age and spline is the contribution from age spline, group is African and takes the value of 0 [10].

2.7. Study Validity and Reliability

Data collection was preceded by training research assistants for two days and pretesting research instruments, which was done using a small sample size (10 participants) at Benjamin Mkapa Hospital for SCD group, and for Non SCD group it was done at Mlezi primary and Hazina secondary schools, where 5 children were piloted from each school. The pilot study participants were similar to those in the study area. Using beam balance with stadiometer scale, weight and height were measured and BMI calculated based on WHO BMI z-score charts and spirometry test was done as per global lung iniative 2012 reference values, complying with the American Thoracic Society and European Respiratory Society standards. Also, laboratory procedures such as Hb and Hb electrophoresis were done according to Tanzania national guideline proven standard operating procedures adapted for each hospital. The quality control for each analyzing machine was performed before analyzing the samples every day.

2.8. Data Analysis

The data from the questionnaire were entered into the Microsoft Excel version 2016 for cleaning and coding and then exported to SPSS version 26 for analysis. Descriptive statistics such as frequency and proportions were used to describe categorical variables, while mean or median was used to describe continuous data. The distribution of laboratory and spirometry results was approximately normally distributed as tested using a normal curve. Two sample independent t-tests were performed to compare means of laboratory and spirometry results for SCD and non-SCD patients. Binary logistic regression was used to determine factors associated with lung function impairment in children with SCD and non-SCD separately. Results from logistic regression were reported as an odds ratio (OR) and adjusted odds ratio (AOR). The significance of all statistical tests was determined by a p-value of <0.05.

2.9. Ethical Consideration

The University of Dodoma's Institutional Research Review Committee (IRREC) provided ethical approval (Reference No. MA.84/261/102). Permission to perform the study was also obtained from the appropriate council and hospital authorities, and formal clearance was provided prior to data collection. Children who were eligible to participate provided assent and consent, which was followed by informed consent from their parents or guardians. The permission procedure included an explanation of the study's goal and value, as well as the opportunity for participants to withdraw at any time without compromising the hospital's services. The confidentiality and privacy of participants' information were rigorously upheld throughout the study.

3. Results

3.1. Baseline Characteristics of Enrolled Children in the SCD and Non-SCD Groups

Out of the 59 children with SCD, 35 (59.32%) were females, while 53.57% (30/56) of children in the non-SCD group were males. The mean age for children with SCD was 9.39 ± 3.04, while the mean age for the non-SCD group was 9.95 ± 3.09. In children with SCD, 50/59 (84.74%) belong to the age range between 6 and 12 years, while non-SCD children, 45/56 (80.35%), had an age range between 6 and 12 years. Out of 29/56 (49.15%) children with SCD, 20/59 (33.89%) were pale and had finger clubbing. Refer to Table 1.

Table 1. Baseline characteristics of enrolled children in the SCD and Non SCD group.

Variable	SCD n (%)	Non SCD n (%)
Sex of the child		
Male	24 (40.67)	30 (53.57)
Female	35 (59.32)	26 (46.42)

Continued

Age of the child in years (Mean ± SD)	9.39 ±3.04	9.95±3.09
6 - 12	50 (84.74)	45 (80.35)
13 - 18	9 (15.25)	11 (19.64)
Respondent relationship with the child		
Parent	50 (84.74)	44 (78.57)
Caretaker	9 (15.25)	12 (21.42)
Level of education		
Informal education	9 (15.25)	9 (16.07)
Formal education	50 (84.74)	47 (83.92)
Passive indoor smoking		
Yes	6 (10.17)	9 (10.07)
No	53 (89.83)	47 (89.93)
Pallor	29 (49.15)	2 (3.57)
Finger clubbing	20 (33.89)	0 (00.00)
Wheezes on auscultation	0 (00.00)	1 (1.78)
Crackles on auscultation	1 (1.69)	0 (0.00)
Cardiac murmurs on auscultation	5 (8.47)	0 (0.00)
Hemoglobin level (g/dl)		
Severe < 7	13 (22.03)	0 (0.00)
Moderate 7 - 9.9	43 (72.88)	5 (8.92)
Mild 10 - 10.9	1 (1.69)	5 (8.92)
Normal ≥ 11	2 (3.38)	46 (82.14)

3.2. Baseline Clinical and Laboratory Findings for SCD

The mean age at first diagnosis of SCD was 2.53 ± 2.32 whereby 31/59 (52.54%) were diagnosed at the age above 1 year.

Mean age at starting SCD clinic was 5.03 ± 3.62 whereby majority started by the age ≥ 2 years 48/59 (81. 36%). Common complication occurred for past one year were painful crisis 37 (62.71%) and anemia 33 (55.93%). 40 (67.8%) of the study participants were admitted following SCD complications in past one year.

Hydroxyurea use reported by 33/59 (55.93%) and 57/59 (96.61%) report to use folic. The mean age of starting medication was 6.20 ± 4.09 and majority started clinic at the age > 1 year. Refer to Table 2.

Table 2. Baseline clinical and Laboratory findings for SCD.

Variable	n (%)
Age of the caregiver [Mean ± SD 40.42 ± 9.11]	
≤30	9 (15.25)
31 - 40	27 (45.76)
41 - 50	14 (23.72)
51+	9 (15.25)

Continued

Age of children at first SCD diagnosis [Mean ± SD 2.53 ± 2.32]	
≤1	28 (47.46)
>1	31 (52.54)
Age of starting SC clinic	
<2	11 (18.64)
+2	48 (81.36)
SCD related complication in past year	
Anaemia	33 (55.93)
Painful crisis	37 (62.71)
Acute chest syndrome	14 (23.73)
Frequency of complications in a year	
1	19 (32.20)
>1	40 (67.80)
History of hospital admission in a year	40 (67.8)
Hydroxyurea use	
Yes	33 (55.93)
No	26 (44.07)
Folic acid use	
Yes	57 (96.61)
No	2 (3.39)
No admission past 1 year [3.78 ± 2.64]	
<1	41 (69.49)
>1	18 (30.51)
Age of starting medication [6.20 ± 4.09] years	
≤1	16 (27.12)
>1	43 (72.88)
Fetal hemoglobin [7.18 ± 7.24]	
<10	36 (61.02)
10+	23 (38.98)

3.3. Prevalence of Impaired Lung Function

Out of the 59 children with SCD, 52.54% (31) had lung impairments, of which 42.37% (25/59) had restrictive while 10.17% (6/59) had obstructive lung disease. And out of the 56 children with non-SCD, 6 (10.71%) had lung impairments, of which 5 (8.93%) were restrictive, and 1 (1.79%) had obstructive lung disease. Refer to Figure 1.

3.4. Laboratory Result and Spirometry Result

Among children with SCD compared to the non-SCD group, there was a significant mean difference for most of the parameters measured, such as weight, height, blood pressure, and lung function parameters, which were lower in children with SCD. Refer to Table 3.

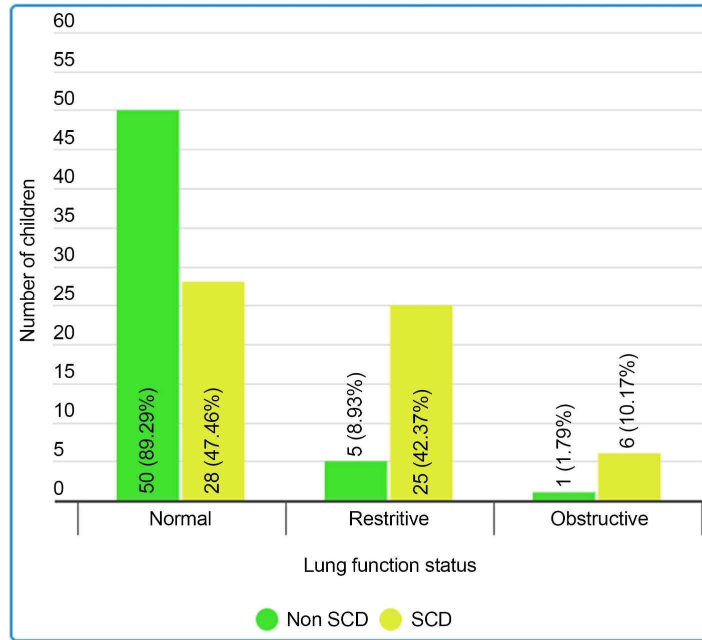

Figure 1. Lung function abnormalities among pediatric patients with SCD and Non SCD.

Table 3. Clinical and spirometry result for SCD and non SCD groups.

	SCD		Non SCD		Test statistics	
Label	**Mean ± Std**	**Range**	**Mean ± Std**	**Range**	**T test**	**p-value**
Respiratory rate	21.85 ± 3.83	14.00 - 30.00	20.84 ± 3.82	16.00 - 29.00	1.41	**0.1607**
Age	9.39 ± 3.04	6 - 18	9.95 ± 3.09	6 - 17	−0.97	0.3323
Weight	24.89 ± 7.49	14.00 - 58.00	33.46 ± 10.0	21.00 - 72.00	−5.21	0.0300
Height	124.55 ± 13.7	100.0 - 163.00	136.40 ± 15.16	110.00 - 169.0	−4.40	<0.0001
BMI	15.84 ± 2.06	11.30 - 21.80	17.65 ± 2.41	12.80 - 28.10	−4.34	<0.0001
Temperature	36.60 ± 0.56	35.80 - 39.90	36.37 ± 0.49	34.80 - 37.20	2.29	0.0236
PR	96.66 ± 10.64	66.00 - 120.00	84.77 ± 9.20	63.00 - 100.00	6.40	<0.0001
Systolic BP	105.49 ± 8.08	90.00 - 120.00	108.31 ± 6.21	90.00 - 120.00	−2.09	0.0387
Diastolic BP	67.44 ± 6.98	58.00 - 95.00	70.82 ± 6.33	60.00 - 80.00	−2.72	0.0076
spo02	94.00 ± 3.37	87.00 - 99.00	96.57 ± 1.68	89.00 - 99.00	−4.83	<0.0001
Hemoglobin level	7.86 ± 1.39	5.00 - 11.30	12.33 ± 1.68	8.00 - 15.80	−15.57	<0.0001
FEV1	1.12 ± 0.32	0.48 - 1.98	1.58 ± 0.47	0.56 - 2.62	−6.10	<0.0001
FVC	1.25 ± 0.41	0.50 - 2.10	1.63 ± 0.52	0.32 - 3.24	−4.45	<0.0001
FEV1/FVC	91.87 ± 12.89	46.00 - 109.20	96.66 ± 9.80	63.90 - 135.20	−2.24	0.0273
FVC PREDICTED	1.19 ± 0.36	0.66 - 2.37	1.51 ± 0.43	0.86 - 2.53	−4.32	<0.0001
FEV1 PREDICTED	1.20 ± 0.37	0.63 - 2.47	1.52 ± 0.44	0.88 - 2.56	−4.27	<0.0001

3.5. Factors Associated with Impaired Lung Function among Children with Sickle Cell Disease

Following multivariate logistic regression (factors such as age of caretaker, age of child, sex of child, relationships of caretaker, finger clubbing, blood pressure, age

of starting CSD clinic, SPO_2, BMI, hemoglobin, number of admissions, age of starting medication, and fetal hemoglobin level; all these variables entered into the final model), factors that were associated with impaired lung function were: - Low blood pressure (AOR = 0.220, 95% CI [0.054, 0.899], p = 0.0350); age of the child (being old) (AOR = 2.908, 95% CI [1.220, 16.554], p = 0.0367); age of starting SCD clinic (AOR = 1.920, 95% CI [1.226, 4.603], p = 0.0498); and fetal hemoglobin < 10% (AOR = 12.048, 95% CI [1.98, 21.429], p = 0.0061). Refer to Table 4.

Table 4. Factors associated with impaired lung function among children with sickle cell disease.

Variable	**Unadjusted logistic**		**Adjusted logistic**	
	OR [95%CI]	P-value	AOR [95%CI]	P-value
Sex of the child				
Male	Ref			
Female	1.576 [0.554, 4.482]	0.3939		
Age of caregiver				
≤30	Ref		Ref	
31 - 40	1.161 [0.255, 5.286]	0.8472	1.979 [0.310, 12.641]	0.4708
41 - 50	1.250 [0.233, 6.715]	0.7947	1.535 [0.184, 12.816]	0.6924
51+	4.375 [0.564, 33.948]	0.1580	7.982 [0.508, 51.255]	0.1254
Respondent relationship with child				
Parent	Ref			
Caretaker	2.000 [0.450, 8.897]	0.3628		
Finger clubbing				
Yes	1.161 [0.394, 3.425]	0.7867		
No	Ref			
BP				
Normal (systolic > 100- ≤ 120)	Ref		Ref	
Low (systolic < 100)	0.320 [0.100, 0.320]	0.0550	0.220 [0.054, 0.899]	0.0350
BMI				
Normal (−2 - +1 SD)	Ref		Ref	
Under weight (<−2SD)	7.913 [0.90, 69.242]	0.0616	3.132 [0.288, 34.027]	0.2561
Over weight (+1 - +2SD)	1.130 [0.067, 19.118]	0.9323	10.797 [0.333, 35.458]	0.2046
HB				
<7 g/dl	Ref			
7 - 9.9 g/dl	0.625 [0.178, 2.199]	0.4640		
Number of admission past one year				
≤1	Ref			
>1	0.528 [0.172, 1.617]	0.2633		
Age of the children (years)				
6 - 12	Ref		Ref	
13 - 18	3.792 [0.716, 20.072]	0.1170	2.908 [1.220, 16.554]	0.0367

Continued

Age at starting CS clinic(years)				
<2	Ref			
2+	1.905 [0.509, 3.975]	0.0692	1.920 [1.226, 4.603]	0.0498
SPO$_2$ (%)				
≤94	Ref			
>94	0.547 [0.194, 1.543]	0.2544		
Age of starting medication(year)				
≤1	Ref			
>1	0.530 [0.153, 1.844]	0.3184		
Fetal hemoglobin				
<10	2.445 [0.836, 7.14]	0.1024	12.048 [1.98, 21.429]	0.0061
10+	Ref		Ref	

4. Discussion

Sickle cell anemia is a multi-organ disease characterized by acute and chronic manifestations in affected organs. The current improvement in survival of children with SCD mean that more children will live to adulthood and experience chronic complications such as progressive lung function decline. This possibility calls for strategies to be put in place for prevention and early detection of this complication. The current study aimed to establish the burden of pulmonary lung function impairments among children with SCD compared to a non SCD group at two major SCD clinics in the city of Dodoma.

The prevalence of lung function impairment in the index study was 52.54% out of it 42.37% and 10.17 having restrictive and obstructive patterns respectively for SCD group while for non SCD the prevalence of lung function impairment was 10.72% out of it 1.79% having obstructive patterns and 8.93% having restrictive pattern. These findings were consistent with what has been reported in previous studies showing a high prevalence of lung function impairments in children with SCD as compared with non SCD children [9]. A study done in Washington by Intzes et al reported almost similar prevalence of lung function impairment of 58% in children with SCD while a study done in USA by Koumbourlis *et al.* reported a prevalence of 43% the similarity of finding with index study may be due to enrollment of same age group 6 - 18 years [5].

A study done in Kuwait reported prevalence of lung function impairment to be 26.3% among children with SCD which is lower comparing to the findings of current study [9]. Other study reported prevalence of 23% which is also low, the possible reasons behind lower prevalence being the use of other lung function test like body plethysmography while in the index study spirometry alone was used and this has been implicated to increase prevalence of restrictive lung disease [11]. In addition, they excluded children who were on Hydroxyurea and chronic blood transfusion, these children may have severe disease and more likely to have lung

function impairment. In contrary, a higher prevalence was reported by a study done in UK and Nigeria which was 65%, this difference can be due to including two countries with different economic status. Literatures report that children who live in developed countries have higher obstructive lung disease while those in developing countries restrictive lung disease are dominant so combining these two study sites may cause higher prevalence compared to the index study [12].

In children with no SCD, previous studies reported a prevalence of 3.7% which was lower as compared to the index study [13]. The observed difference may be explained by interpretation of lung function impairment pattern which was done using percentage predicted while the index study interpreted lung function impairment by using the obtained value below lower limit of normal. Another study done in Nigeria found a prevalence of 5.6% which is lower than the index study [4]. Reason for lower prevalence may be due to enrolling participants aged 6 to 12 years while the index study enrolled participants aged 6 to 18 years, it is well known that age is the independent risk factor for lung function impairment. In contrary to previous study which found the lung function status was compared between Nigeria and United Kingdom, reported a slightly higher prevalence of lung function impairment of 12.5% among children with no SCD. The reason behind this difference may be due to use of different study sites and large sample size [12].

Different studies have reported inconsistent lung function impairment patterns in children with SCD. A study done in Nigeria reported restrictive pattern of 22.1% [13], another study done in Kinshasa reported restrictive pattern of 30.3% [12]. The findings of all these mentioned studies had similar dominant restrictive lung function impairment as the index study, This similarity in pattern may have been contributed by use of Spirometry alone, almost the same age group 6 to 18 years and participant being at the steady state [13], same study area which is SSA where there is higher prevalence of restrictive pattern due to chronic lung injury as compared to high income countries [7].

Dominant obstructive pattern in children with SCD was reported to be (35%) [14]. The difference in pattern in comparison to the index study may be explained by study site difference where all these mentioned studies were done in developed countries where it has been reported that obstructive pattern to be more prevalent in children with SCD from high income countries. This dissimilarity probably reveals more severe chronic lung disease in children with SCD leaving in developing countries [4].

In children with no SCD, we found a predominate restrictive pattern of lung function impairment over obstructive pattern. This finding was similar to other previous studies done which revealed 1.9% for restrictive and 0.9% for obstructive [13], 8% restrictive and 4% obstructive [4]. This similarity in pattern may have been contributed by use of Spirometry alone, same age group and study site which are SSA where there is higher prevalence of restrictive lung disease compared to high income countries. In contrast, previous studies revealed a slightly obstructive

pattern predominance as compared to restrictive pattern [4]. Reasons to these differences may be due to enrollment of lower age of 6 to 12 years among the control group, as it well known that lower age has higher obstructive lung disease compared to advanced age.

In this study, low HbF, increased age of the child, older age at starting SCD clinic and low blood pressure were significantly associated with lung function impairment. Low HbF below 10% was associated with increased risk of lung function impairment in the index study which was in line with findings from study done in Nigeria [15]. Findings from other studies reported to be no statistical significance association between HbF and lung function impairment [16]. Studies done in Boston and Tanzania reported positive association between low HbF and low level of Oxygen saturation [17]. HbF is an important parameter in reverting most of complications related to SCD and hence good clinical outcome [18].

It is a minor hemoglobin of adult but has major clinical importance in SCD since it can change disease pathophysiology and clinical course as low HbF is associated with more severe disease [19]. Higher levels of HbF were associated with marked reduced rate of complications implicated to sickle vaso-occlusion and blood viscosity such as painful crisis, ACS and disease severity reduction [20]. Attaining high level HbF is the mainstay of Hydroxyurea therapy， so the finding of this study may also be contributed to low coverage of Hydroxyurea (55.93%) among SCD participant. Literature reported low level of HbF due to availability of different HbF haplotype with different mean from 5% in Bantu to 30% in Cameroon, Arab-India (AI) haplotype where disease can be relatively benign if HbF is 30% and not the case if it is 5% [19].

We found that children with SCD had significantly lower mean blood pressure as compared to children with no SCD, which also found to be a protective factor for lung function impairment. This finding is in line with previous studies done, but they didn't relate these findings with lung function impairment [21]. SCD may result in hypertrophy and dilatation of myocardium leading to systolic and diastolic dysfunction, lower systolic and diastolic blood pressure in patient with SCD shows reduction of vascular resistance and the increase of peripheral blood flow but the real mechanism is not yet to be well clarified, the hypothesized mechanism reported in literature is presence of autonomic dysfunction in SCD [22].

Arterial stiffness has been associated with increased vascular resistance which increases pulmonary hypertension and hence increasing risk for lung function impairment. Therefore, having low blood pressure in children with SCD signifies less arterial stiffness and vascular resistance which may have protective effects on lung function [23]. This study did not find the association of low blood pressure and lung function impairment, though a study done in China among children with no SCD reported low blood pressure to be significant risk factor for lung function impairment [24]. This calls out more research to determine the effect of hypotension in lung functions impairment in SCD children.

Age above 2 years at starting SCD clinic was among the factors associated with

increased risk of lung function impairments in our study, this is generally expected as early initiation of comprehensive SCD care is likely to reduce the frequency and severity of acute SCD related complications including acute chest syndrome and severe pneumonia hence prevent progressive lung parenchyma damage [25], this finding may be due to disease progression, recurrent complication due to not using medications like hydroxyurea, folic acid, Penicillin V, and persistent low hemoglobin level leading to more chronic complication including lung function impairment. This is the area for further research to explore a relationship of lung function impairment and age at starting SCD clinic.

Age of the children 13 to 18 years with SCD was found to be a significant factor associated with lung function test, this finding is in line with studies done in Democratic Republic of Congo which reported every additional year of age to be associated with increased risk of lung function impairment [12]. A study done in Egypt reported decreased lung function test with age where those aged above 12 years was found significantly associated with lung function impairment [16]. This similarity may be due to the same study design, same age range and use of spirometry alone as the index study. Aging cause tissue changes of the lung in individuals even without having SCD that leads to an increase in alveolar size without destruction of alveolar walls, this leads to lowering of alveolar surface tension and reduces the recoil elasticity of the lung hence lowering lung function parameters [26]. Given the pathogenesis of SCD and its effect on the lung, children with SCD may deteriorate faster as they grow older than the general population [27]. There were no factors found in the index study to be associated with lung function impairment among children with non SCD.

5. Conclusion and Recommendation

Lung function impairment is more prevalent in SCD children than in their non-SCD peers; delayed age at commencing SCD clinic and longer age might expose children with SCD to developing lung function impairment. Low blood pressure and low fetal hemoglobin levels were protective factors. The pattern of restricted lung function impairment is prevalent. Advocating for early enrollment of SCD patients in a sickle cell disease clinic is advised. Early screening of lung function impairment in children with SCD by advocating for a change in guidelines to include lung function tests in comprehensive SCD care and monitoring of fetal hemoglobin levels and values less than 10% should increase the suspicious index of lung function impairment, as should monitoring vital signs, including blood pressure, at each clinic visit.

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Authors' Contributions

TM proposal development, conceptualization, data collection, formal analysis, investigation, project administration, and developing manuscripts. SJ and DM supervised the study, providing technical support and reviewing each step.

Limitations of the Study

This study used a comparative cross-sectional design, which made it impossible to determine a causal effect link between SCD and reduced lung function, as well as characteristics related to lung function impairment. A lack of total lung capacity and functional residual volume might have provided further information about the kind of lung function impairment. Bias may have occurred as a result of including children who were in a stable condition on their own.

Strength of the Study

The study used a comparative component, which helped to find prevalence and risk factors associated with lung function in children with SCD with reference to non-SCD in the general population.

Conflicts of Interest

The authors stated that there was no conflict of interest.

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