PREVALENCE AND FACTORS ASSOCIATED WITH IMPAIRED SIX MINUTE WALK TEST IN CHILDREN WITH SICKLE CELL DISEASE AT THE KENYATTA NATIONAL HOSPITAL

A DISSERTATION IN PARTIAL FULFILLMENT FOR THE DEGREE OF MASTERS OF MEDICINE IN PAEDIATRICS AND CHILD HEALTH, UNIVERSITY OF NAIROBI

Dr Aisha Jahadmy (MBChB)

H58/10825/2018

2021

DECLARATION

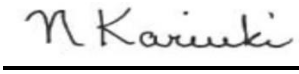
This dissertation is my original work and has not been presented for the award of a degree in any other university.

Signed:  Date: **9th November 2021**

Dr. Aisha Jahadmy (MBChB)

Registrar, Department of Paediatrics and Child Health, University of Nairobi

This dissertation has been presented with our full approval as supervisors:

Signed:  Date**: 9th November 2021**

Dr. Nyambura Kariuki,

Senior lecturer and Paediatric Haematologist,

Paediatrics and Child Health, University of Nairobi

Signed:  Date: **9th November 2021**

Dr. Diana Marangu,

Lecturer, Paediatrician and Pulmonologist (MBChB, MMed, MPH, MPhil, PhD)

Department of Paediatrics and Child Health, University of Nairobi

COLLABORATING INSTITUTIONS

1. University of Nairobi

2. Kenyatta National hospital

FUNDING

This research project was fully self-funded.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank the Almighty God for His grace and mercy that have enabled me to successfully complete my dissertation.

I wish to express my sincere gratitude to my supervisors Dr. Nyambura Kariuki and Dr. Diana Marangu for their immense support towards completion of this thesis.

I would also like to thank Professor Elizabeth Obimbo for her guidance and unwavering support.

Finally, I am extremely for thankful to my family and friends for the patience, love and support they have accorded me during the time I spent doing my research.

LIST OF ABBREVIATIONS

6MWD	Six minute walk distance
6MWT	Six minute walk test
ATS	American Thoracic Society
BMI	Body Mass Index
BP	Blood pressure
CHD	Congenital Heart Disease
CO	Cardiac output
CPET	Cardiopulmonary exercise test
DMD	Duchenne muscular dystrophy
ERS	European respiratory society
ESRD	End stage renal disease
FC	Functional capacity
FEV1	Forced expiratory volume in 1 second
HIV	Human immunodeficiency virus
HR	Heart rate
HRdiff	Heart rate difference
HRQOL	Health related quality of life
LLL	Lower limb length
NYHA	New York Heart association
PEFR	Peak Expiratory Flow Rate
QOL	Quality of life
SBP	Systolic Blood Pressure
SpO2	Transcutaneous Oxygen Saturation

DEFINITION OF TERMS

Cardiopulmonary exercise test (CPET): is a highly sophisticated laboratory-based test that measures a person's functional capacity through minute-by-minute analysis of inspired oxygen and expired carbon dioxide while exercising on a treadmill or ergometer, along with electrocardiographic (ECG), spirometric and serum lactate measurements. It is the gold-standard modality of measuring and evaluating functional capacity.

Dependent (outcome) variable: is the variable of interest on which the influence of other variables (predictor or independent variables) are being tested. Six-minute walk distance (6MWD) is the dependent variable in the index study.

Functional capacity (or functional exercise capacity): is the ability of a person to perform day-to-day activities of living such as walking or doing chores.

Heart rate difference (HRdiff): is the difference between the post-exercise heart rate (PostHR) and the pre-exercise heart rate (PreHR).

Heart failure (HF): is an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues.

Independent (predictor) variables: are variables that are thought to have influence on the outcome variable.

Maximal (or peak) oxygen consumption (VO2max or VO2peak): is the maximum oxygen consumed by an exercising individual.

Peak expiratory flow measurement: a measure of the maximal flow rate that can be achieved during forceful exhalation following full inspiration. It reflects the large airway flow and depends on both the muscle strength and voluntary effort of the patient. It is performed by most patients older than 5 years and is measured by a peak flow meter.

Rating of perceived exertion (RPE) scale: is a visual and numerical chart that is used to objectively quantify a person's perceived level of tiredness or fatigue before, during and after an exercise test.

Respiratory failure: This occurs when the rate of gas exchange between the atmosphere and the blood is unable to meet the body's metabolic demand.

Reliability (or reproducibility): is the consistency with which a tool measures the construct it is supposed to measure. In this study, it is the degree to which an individual achieves similar scores of the 6MWD when repeated over time

Six-minute walk distance (6MWD): The distance a person covers in six meters during a 6MWT.

Six-minute walk test (6MWT): A test that measures a person's functional capacity using the distance walked in six minutes at a self-selected pace.

Validity: It is the degree or extent to which the 6MWT truly measures functional capacity.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Background: The six-minute walk test is a simple, reproducible, reliable and valid tool for evaluation of baseline functional capacity in chronic diseases like sickle cell disease (SCD).

Objectives: Primarily determine the prevalence of impaired functional exercise capacity using the six-minute walk test (6MWT), in children 6 to 12 years of age with SCD on follow-up at the haematology clinic at Kenyatta National Hospital(KNH) and secondarily to determine demographic, anthropometric and physiologic factors associated with impaired exercise capacity in children with SCD.

Methodology: A cross-sectional study design that recruited 99 children with SCD from the paediatric haematology clinic in KNH by consecutive recruitment. Data was collected by means of a questionnaire, pre and post 6MWT walk vitals form and the 6MWT lap counter worksheet. The 6MWT was conducted as per the American Thoracic Society (ATS) guidelines. Impaired 6MWT was defined as a distance less than 80% of predicted distance based on Tunisian predictive reference equations.

Data analysis: Data was analysed using R (V3.4.3, R core team, 2017). The impaired 6MWT was presented as a prevalence with 95% confidence interval. A multivariable logistic regression model was used to determine demographic, anthropometric and physiologic factors associated with the impaired 6MWT. A p-value of <0.05 was considered to be significant

Results: The prevalence of impaired 6MWT was found to be 69.7% (95% CI 60.1 - 77.9%).Age was independently associated with impaired 6MWT when adjusted for Gender, Haemoglobin level, use of hydroxyurea and age specific heart rate, respiratory rate and body mass index Z-score – (adjusted odds ratio 1.4(1.1-1.9), p value 0.034).

Conclusion: In this study, the prevalence of impaired 6MWT was very high at almost 70%.

The only factor associated with the walk test was Age. Simple tests like 6MWT can be used to provide data on the degree of functional impairment which could be used to suggest cardiorespiratory compromise in patients with chronic diseases like SCD

1.0 BACKGROUND

Sickle cell disease (SCD) is a hereditary haemoglobinopathy that is defined by the deoxygenation of red blood cells and their consequent sickening. The red blood cells have less ability to deform and are more fragile leading to anemia and vascular occlusions. (1)

SCD has been declared a public health priority by the World Health organization. Annually, 300,000 children are born with SCD, and more than two thirds of affected births occur in Sub Saharan Africa with about a half of those affected dying in childhood.(2)

Sickle cell disease is associated with decreased functional capability (or exercise intolerance). This associated functional impairment further worsens the affected individual's health-related quality of life (HRQOL), morbidity, and mortality, in addition to the effects of the underlying ailment.

Outpatient monitoring of these patients should include evaluating functional capacity(FC) but there are insufficient studies worldwide conducted on children and young people with SCD (3).This may be done by conducting an exercise test to assess the child's physical ability and compare it to what is normal for age and sex. Two methods for outlining the extent of exercise limitation - the 6-minute walk test (6MWT) and the cardiopulmonary exercise testing (CPET) -, have been performed in clinical practice. (4)

The 6MWT is a measure of distance, which is considered submaximal and perhaps more closely measures the capacity to perform activities conducted in daily life. Its clinical attraction also lies in the fact that it does not need specialized equipment, and can be performed by the majority of patients. It has been used widely to evaluate functional capacity in children with chronic diseases such as SCD(5). The CPET requires the highest of efforts and provides a direct measure of oxygen consumption (V_{O_2}) along with a series of derived, measured respiratory variables with a robust body of evidence supporting its predictive ability. (4)

Optimization of the quality of life and long-term outcome of children with chronic disorders needs detection and objective quantification of the degree of this functional impairment and monitoring the response to therapy targeted at both the underlying disease and the associated functional impairment, as well as determining appropriate interventions(6). Poor exercise tolerance has been reported to have significant correlations with quality of life, hospitalizations, use of medications, survival time and clinical prognosis(7).The 6MWT, being a simple and cost-effective validated

tool may serve as an alternative to the Cardiopulmonary exercise test which is generally not readily available in Kenya.

1.1 SICKLE CELL DISEASE

The commonest subtype of SCD worldwide is homozygous SCD, categorized by the presence of two copies of the β-globin S (β^S) mutation that codes for sickle cell hemoglobin (Hb S). Homozygous SCD is also known as sickle cell anemia, Hb SS, SS, SS disease, or sickle cell disease-SS. There exists a close relationship between SCD and endemic *Plasmodium falciparum* . (8).

The genetic defect is a point mutation in codon 6 of the β globin gene that results in the formation of Haemoglobin S (Hb S). The mutation results in glutamic acid instead of valine.

In hypoxic situations (exertion, fever, Infections, dehydration, altitude),HbS polymerizes and alters properties of the red blood cell membrane. The latter are deformed into a sickle, lose their flexibility, modify their density and adhere abnormally to the vascular endothelium.(8)

In children, sickle-shaped red blood cells get lodged in the spleen, leading to mortality before the age of seven years from a sudden profound anaemia linked to a rapid enlargement of the spleen. Between 6 and 18 months of age affected children present with dactylitis, acute chest syndrome), bone necrosis, priapism or failure of the kidneys.

SCD can cause underlying damage to multiple organs including the heart and lungs. (9)

Cardiac complications determine the morbidity and mortality of children with sickle cell disease. Some of these conditions, mainly dilated or restrictive cardiomyopathies and pulmonary arterial hypertension, are often unrecognized in children.

Pulmonary complications are also quite common. In addition to acute chest syndrome and asthma, concomitant pulmonary hypertension significantly increases morbidity and/or mortality. (10)

1.2 FUNCTIONAL EXERCISE CAPACITY IN CHILDREN WITH SICKLE CELL DISEASE

Functional exercise capacity is a function of the combined state and efforts of the cardiopulmonary, hematological, musculoskeletal and metabolic systems involved in exercise activity. Thus, disorders of any of these organ-systems may be associated with impaired functional capacity(11). Chronic disorders of childhood such as SCD, have been associated with impaired functional capacity (12).

Impaired functional exercise capacity (or functional impairment) is the reduced ability to perform or sustain daily activities due to fatigue or dyspnea(11).Since most childhood activities like playing, running or skipping revolve around walking, an impairment of the ability to satisfactorily engage in these activities will negatively impact their quality of life and hence, morbidity and mortality (6)(13). Evaluation of this ability, or of its impairment, is thus important in the management and prognostication of chronic disorders as it provides a baseline for monitoring response to interventions aimed at both the underlying disease and the associated functional impairment, thus improving overall outcomes (6)(11).

A number of studies have analysed likely factors which could be responsible for the decreased exercise performance in SCD patients and they include: – Inadequate oxygen carrying capacity caused by low Hb levels, chronic anaemia leading to both functional and/or structural cardiac adaptations, having numerous episodes of acute chest syndrome which can end up causing pulmonary parenchymal dysfunction, pulmonary vascular disease and peripheral vascular impairments due to numerous and recurring occlusions of the microvasculature.

The lungs are mainly affected leading to chronic lung disease in adulthood. Abnormalities in pulmonary function tests are early independent signs of the development of chronic lung disease in SCD. About 10–30% of adults suffer from cardiac damage, mostly left ventricular hypertrophy or congestive heart failure(14).The development of heart dysfunction in SCD has several causes and has been attributed to chronic anemia, myocardial ischemic injury, overload of iron, and myocardial fibrosis(15).

SCD is also associated with undernutrition and lack of adequate growth in adolescents(16). A study done by Barden *et al* which looked at 36 children of African American descent with SCD showed a 10–20% increase in resting energy expenditure (REE) than in those without SCD, due

to higher protein turnover and increased cardiac output. Therefore, to maintain their daily total energy expenditure to the same level as that of healthy children, they had to decrease their physical activity energy expenditure. Chronic anaemia may be the main reason for a decrease in their PAL(17).

The functional outcome model includes disease pathology resulting in a physical or physiological impairment which then results in impaired functional capacity and impaired performance of daily activities. In sickle cell disease, presence of abnormal haemoglobin results in repeated sickling and unsickling, haemolysis and anaemia. This leads to reduced oxygen-carrying capacity, hypoxemia, reduced VO2max and hence reduced functional capacity. The reduced functional capacity may in turn manifest as reduced functional performance (18).

1.3 THE SIX-MINUTE WALK TEST

The use of 6MWT in paediatric subjects was first reported in 1996 by Gulmans *et al* in Dutch children(19) and Nixon *et al* in North American children (20) and both studies reported strong correlations between 6MWTand CPET in children with cystic fibrosis and suggested the 6MWT as a valid tool for quantifying functional capacity in sick children.

For standardization of the test, the American Thoracic Society (ATS), in 2002, published consensus guidelines for the administration of the 6MWT in clinical settings (21).

1.4 CLINICAL UTILITY AND INDICATIONS OF THE SIX-MINUTE WALK TEST

The 6MWT is used to quantify the degree of functional exercise impairment at baseline, to monitor its response to interventions, to evaluate the prognostic implication of the functional impairment and to guide prescription of appropriate level of rehabilitative or therapeutic exercises.

Assessment of functional capacity

The 6MWT is used to quantify significant functional impairment in children and adolescents with congenital heart diseases, asthma, sickle cell disease, cerebral palsy, hemophilia, spina bifida,

obesity, juvenile idiopathic arthritis, pulmonary artery hypertension, end-stage renal diseases and Type 1 Diabetes mellitus(22)(23)(24)(25).

Evaluation of the effectiveness of therapy

The 6MWT has been used to monitor response to pharmacologic, surgical and rehabilitative interventions aimed at addressing the underlying disease pathology and/or associated functional impairment in DMD, PAH, congenital heart disease and others. This is done by taking repeated measures of the 6MWD at intervals- before, during and after the intervention of interest- and comparing the scores to baseline 6MWD, to predicted 6MWD or to scores attained by controls.

Prognostic significance of the 6MWT

The Six-minute walk distance has been used to identify patients with poorer prognoses who may be prioritized for more aggressive or less-available interventions such as lung transplantation in patients with end-stage lung diseases or heart transplant in advanced chronic heart diseases.

Exercise prescription

The six-minute walk test has been used in determining the appropriate and safe level of therapeutic exercise to prescribe to patients with chronic diseases like congenital heart disease (after corrective intervention), asthma, sickle cell disease, cerebral palsy, and leukaemia. The 6MWT is useful not only in establishing the degree of physical impairment in these conditions but, based on the degree of this impairment, can be used to prescribe safe and appropriate intensity, grade and frequency of exercise.

1.5 ADMINISTRATION OF THE SIX-MINUTE WALK TEST

The American Thoracic Society, European Respiratory Society and Polish Respiratory Society recommended the administration of the 6MWT along an indoor or outdoor 30-metre long layout on a flat, hard-surfaced corridor, hallway, walkway or sidewalk. These guidelines are meant for adults; no guidelines specifically for children are currently available.

The primary outcome measure during the test is the distance walked in six minutes (6MWD).

Secondary measures taken during the 6MWT include pre- and post-test blood pressure, heart rate, oxygen saturation and subjective measure of fatigue or dyspnea [Rating of Perceived Exertion

(RPE) scale] or borg scale. These secondary variables are used to determine the patient's physiological reaction to the exercise activity, judge the intensity of the exercise and thereby gauge the extent of tolerance of sub-maximal activities of daily living. A normal result is defined as a 6MWD more than or equal to 80% of that predicted for age(21).

1.6 SAFETY AND CONTRA-INDICATIONS OF THE SIX-MINUTE WALK TEST

The 6MWT has been proven to be safe and well tolerated. It has been performed without reports of serious adverse events in thousands of sick and healthy children and adults, including elderly subjects. It is a self-paced test and the patient is permitted to decelerate, rest or stop in the event of any discomfort. In children, there are no established contra-indications, however testing may be stopped in the event of intolerable chest pain or dyspnea, leg cramps, instability, diaphoresis or pale/ashen appearance (21).

1.7 SICKLE CELL DISEASE AND THE SIX MINUTE WALK TEST

The 6MWT is a below maximal exercise test which has been in use in all age groups who have been affected by an extensive range of chronic diseases so as to analyse their exercise capacity. In both children and adolescents, the factors affecting the 6MWD are explicit.

Several studies utilizing the 6MWT have been done on children with SCD and they have examined different factors related to the walk test. These range from demographic, anthropometric and physiological. It has been successfully been conducted in children with SCD**.**

2.0 LITERATURE REVIEW

Several studies addressing the 6MWT in children with SCD were identified in the literature. Most of the studies were from Brazil as SCD is reported to be the commonest monogenic hereditary disorder in that population.

In a study published by Sandro and colleagues, the functional exercise capacity was lower than the predicted for healthy children and that patients with homozygous SCD had a below average presentation with regards to total distance walked, heart rate and oxygen saturation after 6MWT, compared to patients with the heterozygous type(3).They did not, however, quantify the prevalence of impairment.

Nivaldo Melo *et al*, evaluated the physical activity level (PAL) and performance in the six-minute walk test in children and young adults with SCA in Brazil and noted that the main determinant for the 6MWT in children and adolescents with SCA was age. An inverse correlation was made between body mass index and the 6MWT. Patients with SCA had lower PALs compared to healthy controls(26).Other variables like haemoglobin level were not found to be associated with 6MWD in this study.

Dedeken *et al*, noted that impaired 6MWT in children with SCD was related with a silent infarct based on a single center study in Belgium.46 children were evaluated and 14 patients had an abnormal 6MWT and 6 out of the 14 were noted to have a silent infarct as compared to 6 out of the 32 patients with a normal 6MWT.The prevalence of impaired 6MWT was 30% in the study population.

Vieira *et al*, conducted spirometry and the 6MWT on 70 children and young adults in Brazil and the majority of patients had restrictive lung disease(12.5%) with 7 patients(10.9%) having an obstructive picture.26.1% of patients had an impaired six minute walk distance and 52.2% of the patients were reported to have a desaturation of more than 3% using pulse oximetry(27).

Waltz *et al*, also in Brazil, aimed to determine the haematological and haemorheological parameters, pulmonary function together with the performance of the walk test in 42 stable children with sickle cell anemia and the results showed that a low level of RBC deformability, a high level of anaemia and a low fetal haemoglobin level were separate predictors of an impaired

6MWT performance in SCD children. Hydroxyurea therapy was then suggested to have positive impact on the exercise capacity of SCD patients(25).

Ohara *et al*, evaluated several parameters in addition to the functional capacity using the walk test in 21 adults with SCD. The conclusion from the study was that SCD modifies both lung function and functional capacity and impairs the 6MWD(28).

In the United States, one study found in literature was by Caboot and looked at several anthropometric, lung function, haemoglobin, airway hyper reactivity and the six-minute walk distance in 44 asymptomatic children with SCD ages 6 to 19 years. The Mean 6MWD was found to be 514 m and significantly correlated with age and height. Conclusion made was that children with SCD have impaired less than normal exercise capacity as compared to normal children(29).

The other study by Minniti *et al*, evaluated 400 children with SCD and the effects of haematological and echocardiographic variables on their six-minute walk distance and monitored the changes over 18-24 months. The 6MWD was significantly shorter in these subjects and once followed up, the 6MWD had a decline in 25% of the patients(30)

A study published in the American Hematology Journal by Liem *et al.*, evaluated FC in 77 children and young adults with SCD, who also had underlying cardiopulmonary disease. Baseline degrees of anemia was shown to be much lessened in the study particiants with a history of recurrent acute chest syndrome and it impacted their FC (31)

Table 1: Studies done on the 6MWT in SCD

STUDY TITLE	STUDY DESIGN,POPULATION,SETTING	RESULTS
Sandro *et al*,(3)	46 patients aged 6-12 Cross-sectional study Brazil,2013	Patients with HbSS walked a shorter distance than patients with HbSC (459.39 ± 57.19 vs. 502.39 ± 73.60 m)
Caboot *et al*(29)	44 children Cross -sectional study Philadelphia, 2010 6 to 19 years old	Mean 6MWD was 514m 6MWD was sign correlated with age and height.
Waltz *et al*(25)	42 children 8-17 years old, Cross sectional Brazil,2013	Percentage of predicted distance walked was 74.5 ± 10.0%.
Minniti *et al*(30)	400 children ,Cross sectional study USA,2010	Median 6MW in severe SCD genotype was 444m, 461 m in milder SCD genotypes.
Dedeken *et al*(32)	46 patients, cross sectional study ,Brazil ,2013	Prevalence of impaired 6MWT was 30%
Vieira et al(27)	70children,8-15years, Cross sectional study, Brazil ,2016	Prevalence of impaired 6MWT was 26.1%
Liem et al(31)	77 children, 10-24 years Cross sectional study,Chicago,2009	Moderate to severe limitations in FC as measured by exercise testing, exist in children and young adults with SCD.
Nivaldo Melo et al(26)	57 patients and 58 controls 8-14years,2017, Cross sectional.	Patients with sickle cell anemia had a lower physical activity level compared to healthy controls.

2.1 REFERENCE VALUES AND EQUATIONS IN CHILDREN AND ADOLESCENTS

Reference values and predictive equations have been published from healthy Caucasian (Europe), Asian (Thailand, Hong Kong, Taiwan, India), Swiss, Turkish, American and North Africans (Tunisia) children and adolescents. The subject's ages ranged from 3-19 years with use of varying methodologies.

A systematic review by Takken *et al* (33) recommended a reference value (RV) for every World region and ethnicity because a standard reference value could not be made due to a large variation in sample characteristics and the methodology chosen by different authors. If no reference value is available for a particular country as is the case in this study, a Reference value can be selected from the available one which has similar characteristics to the study. Since we have no reference value in Kenya, my findings will be compared to Tunisian reference ranges as they are closest to my proposed study.

Table 2: Published reference equations in Paediatrics (healthy children)

COUNTRY	AUTHOR, AGES	EQUATION
Austria	Geiger(34) 3-18	M: 6MWD = 196.72 + (39.81 x A) – (1.36 x A2) + (132.28 x H) R^2 = 0.49 F: 6MWD = 188.61 + (51.50 x A) – (1.86 x A2) + (86.10 x H) R^2 = 0.50 Average 6MWD 624±74m
Hong Kong	Li(35) 7-16	M: 6MWD = 554.16 + (HRdiff x 1.76) + (123 x H); R^2=0.43 F: 6MWD = 526.79 + (HRdiff x 1.66) + [62 x H]; R^2=0.37
Tunisia	Saad (36) 6-16	Both 6MWD = (463 x H) – (3.53 x W) + (10.42 x A) + 56.32 R^2 = 0.60 Average 6MWD 700±73m
Brazil	Prienitz(37) 6-12	Both: 6MWD =145.343+ (11.78×A) +(2.92 × H) + (0.611 × HRdiff) -(2.684 × W) R^2 = 0.37 Average 6MWD 579 ±68m
Switzerland	Ulrich(38) 5-17	Both: 6MWD= 161.55 + (192.69 x H) + (1.27 x PostHR) Average 6MWD 618±79m
Nigeria	Odion(39) 6-11	6MWD=337.0 + 15.4(Age) + 19.5(Sex) + 1.6(HRdiff) + 1.2(SBPdiff); R^2 =0.282 Average 6MWD 503.2 ±64.3m

6MWD: six-minute walk distance in meters; Both : total sample i.e. both sexes ; M : boys; F:girls; A:age in years; H:height in meters; W:weight in kg; HR: heart rate in beats/min; HRdiff :heart rate difference;R2:coefficient of determination; PostHR: post-exercise heart rate.

2.2 RELATIONSHIP BETWEEN DEMOGRAPHIC FACTORS AND 6MWT

The 6MWD achieved by an individual is influenced by demographic, anthropometric, physiologic, and factors related to mode of administration. Additionally, possible racial, genetic and sociocultural factors, account for significant variations reported in the 6MWD of adult and paediatric populations from different geographic regions(40).

Other factors influencing the 6MWD relevant to patients with SCD includes chronic pain and skeletal mechanics like osteopenia and osteonecrosis(41).

Sex

Saad (36), Klepper and Muir (42), Priesnitz (37), and Lammers (43) reported no significant sex difference in the 6MWD of North African, North American, South American and English children and adolescents, respectively. This observation has been attributed to similar musculoskeletal characteristics in both sex until after puberty when boys begin to have relatively more lean muscle mass in contrast to increasing adiposity in girls. This relatively higher lean muscle mass, and hence higher muscle strength, in post pubertal boys translates to longer stride length, faster walking pace and longer 6MWD.

Age

In children with SCD, age was found to be a significantly correlated to the 6MWD(29).

It was also the best single independent determinant of the 6MWD of Austrian, English, Swiss, Belgian and Brazilian children. The 6MWD increases linearly with increasing age till it peaks at about 8-13th year of life and then rises less steeply until about the 18th year. This may be related to the increasing length of the lower limbs that occurs in children up to mid- and late adolescence, after which the rate of lower limb growth is reduced relative to the trunk(44).

2.3 RELATIONSHIP BETWEEN ANTHROPOMETRIC FACTORS AND 6MWT

The performance of children and adolescents on the 6MWT is reported to be influenced by anthropometric parameters such as height, LL Length, weight and BMI.

Height is the most consistently reported independent anthropometric variable that predicts the 6MWD in paediatric age-groups. Height was the best independent predictor of 6MWD among Austrian, Indian and Chinese children and adolescents. Lammers(43) and Goemans (45) observed that the 6MWD of British and Belgian children respectively increased linearly until about 130-

135cm after which it gradually plateaued. Taller individuals have longer stride lengths and, hence, cover longer distances over a given time.

Children of same age and height from different races may have different leg lengths, and hence different 6MWD, due to differences in body proportions. For example, black children have longer legs compared to whites of similar height (46).

Most paediatric studies reported increasing walk distance with increasing weight. This may be due to increasing weight that occurs with increasing age and height (43).

Saad (36), Geiger (34), and Foeldvari (47) ,reported positive influence of BMI on 6MWD in North African, Austrian and German children, respectively. This was contrary to findings by Klepper and Muir who reported a weighted negative correlation between BMI and 6MWD of 7-11-year old boys living in the United States. Overweight/ obese children were more sedentary with associated reduced physical fitness and reduced 6MWD (48).

A study by Hugo Niveldo *et al*, in both children and adolescents with SCD found that BMI was inversely associated with the 6MWD(p value 0.047)(26).

2.4 RELATIONSHIP BETWEEN PHYSIOLOGIC FACTORS AND 6MWT

The Peak expiratory flow rate (PEFR) was measured in children with homozygous sickle cell and this study disclosed that there was a huge reduction in PEFR in children who had suffered more than one episode of acute chest syndrome when they were compared with those who had not had any episodes(49).

Both forced vital capacity (FVC), forced expiratory volume in first second (FEV1) and PEFR in sicklers were noted to be much lower ($p < 0.001$ respectively) than values obtained from patients with no sickle cell. The impact of SCD on lung functions increases with ageing and this has implications for the timing of initiation of therapy aimed at decreasing chronic pulmonary complications in the SCD population.

The distances walked by North African, Chinese and Caucasian children correlated positively with measures of pulmonary function such as forced vital capacity (FVC), forced expiratory volume in

one second (FEV1), forced mid-expiratory flow (FEF) and peak expiratory flow rate (PEFR) (35)(50)(36).This has been attributed to the positive correlation between 6MWD and height- a strong predictor of lung function.

Daniela *et al* , evaluated lung function parameters in SCD patients and correlated with the 6MWD and she found a positive correlation between patients with a restrictive ventilatory pattern or mixed ventilatory pattern and distance walked in the 6MWT(28).

Anaemia

A study done in Brazil by Xavier Waltz correlated degree of anaemia , low red blood cell deformability and low fetal hemoglobin expression with a reduced/impaired 6MWT performance in children with SCD (25).

Marcello *et al*, looked at adults with COPD and anaemic subjects in his study presented a diminished exercise capacity, expressed as a low 6MWD and maximal oxygen consumption, a higher degree of dyspnoea and a worse health related quality of life compared with non-anaemic patients(51).

Campbell *et al* , showed that exercise induced desaturation in children with SCD was more related to the degree of anaemia and can thus lead to a decreased six-minute walk test performance(52).

However, Jason Caboot, in his study of children with SCD, found no correlation between haemoglobin level and 6MWD(29).

Use of hydroxyurea

Xavier *et al*, did a study on children with SCD and made an observation that children with low readings of Hemoglobin F had a deteriorated six-minute-walk test performance and patients on HU had better performance hence hydroxyurea therapy is quite useful to improve on the exercise capacity of SCA patients(25).

A study by Taysir *et al*,looked at the impact of hydroxyurea (HU) medication in adults with SCD and how it impacted the 6MWD and found that the patients on HU medication compared to those who are not on the medication had significantly longer distances (491 ± 64.4 m vs 428.6 ± 54.3 m, $p < 0.005$)(53)

Cardiac function effect on 6MWD

Heart rate difference (HRdiff) is the difference between the post-exercise heart rate and pre-exercise (baseline) heart rate. It reflects the degree of effort and motivation exerted during an exercise activity(54). It positively correlated with 6MWD in Thai, Chinese, Brazilian and Nigerian children(40)(37)(55).Individuals with cardiac disease had an impaired chronotropic response to exercise and were unable to increase their HR in response to the metabolic demand of exercise.

There was an inverse correlation between the severity of pulmonary hypertension in sickle cell and the 6MWD and an improved walk distance once therapy for pulmonary hypertension was started (25).

2.5 STUDY JUSTIFICATION AND UTILITY

Sickle cell disease, being a chronic disorder, is commonly linked to damage of functional capacity (ability to perform activities of daily living), hence, there is a dire need to routinely evaluate and study this impairment both at the baseline and in response to interventions as part of standard of care. The local prevalence of impairment of functional capacity is unknown.

Impaired functional exercise capacity has been shown to be a marker of cardiorespiratory compromise .The six-minute walk test (6MWT) has been defined as one of the most simple and common modalities to monitor, prognosticate and measure functional capacity and has observed growing use as a both reliable and validated tool for the objective quantification of the functional capacity among all age groups in the population.

The findings of the study will provide data on the baseline of cardio-pulmonary function compromise in children with SCD in our setup and will be used to advocate for early screening and interventions to address the degree of impairment.

2.6 RESEARCH QUESTION

What is the prevalence and factors associated with impaired functional exercise capacity in children aged between 6 and 12 years with Sickle cell disease attending the haematology clinic at Kenyatta National Hospital using the six-minute walk test?

2.7 RESEARCH OBJECTIVES

2.7.1 Primary objective

To determine the prevalence of impaired functional exercise capacity in children between the ages of 6 and 12 years of age with sickle cell disease attending the haematology clinic in Kenyatta National Hospital using the six-minute walk test

2.7.2 Secondary objectives

To determine demographic, anthropometric and physiologic factors associated with impaired exercise capacity as measured by the six-minute walk test in children with SCD.

3.0 METHODOLOGY

3.1 STUDY DESIGN

The study utilized a cross sectional study design

3.2 STUDY SITE

The Paediatric haematology clinic at Kenyatta National Hospital. This hospital is based in Upper hill and is the leading public referral and teaching hospital in Kenya. It has more than 6000 staff members, including consultants, medical officers, residents and nurses, and a 2000 bed capacity and they provide various health care services ranging from basic to specialized care services.

The paediatric haematology clinic is located at unit number 23 in the outpatient department of KNH. It runs on Mondays from 9.00 am to 1 pm and an average of 20 patients ranging from 0 to 13 years of age with sickle cell are seen weekly by the consultant haematologists/haemato oncologists and paediatric registrars.

3.3 SOURCE POPULATION

The study's subjects were chosen from paediatric SCD patients who receive care from the paediatric haematology clinic at KNH. The study population consisted of both male and female patients who were evaluated to ascertain eligibility as per the inclusion / exclusion criteria.

3.4 STUDY PERIOD

Three-month period, between October 2020 and January 2021.

Inclusion criteria

1. Children between the ages of six to twelve years. This age was used as 6 year olds are able to understand and follow instructions for the test and our paediatric clinic takes children up to the age of 13 before transition to adult care.
2. They had a confirmed sickle cell disease diagnosis by Hb electrophoresis (HbSS).
3. The children were on follow up at the hematology clinic.
4. They had consent from the caregiver and consent/assent from the child if aged ten years or older.

Exclusion criteria

1. Any recent (preceding 4 weeks) or current severe illness that impacted their exercise capacity.
2. Children who had significant motor disabilities and were unable to do the 6-minute walk.
3. Children with significant cognitive disabilities who were unable to follow instructions.

Case definitions

Functional Capacity as measured by 6MWT:

A normal result is defined as a 6MWD more than or equal to 80% of predicted for a specified population using reference equations.

Impaired 6MWT is defined as 6MWD less than 80% of predicted for specified population using reference equations.

Clinical factors of interest:

a. Anaemia in SCD has been defined as a haemoglobin of less than 8 g/dl.
b. Impaired cardiac function has been defined as either having abnormal heart rate for age (tachycardia) or rhythm, displaced apex beat, abnormal heart sounds or signs of impending cardiac failure. (References in appendix 4).
c. Impaired respiratory function was defined as a respiratory rate higher than the expected for age. (References in appendix 4)
d. Hypoxia was defined as an SPO_2 of less than 95%.

3.5 SAMPLE SIZE DETERMINATION

The sample size was determined using the Fisher's Formula:

$$\boldsymbol{n = \frac{Z^2 p(1-p)}{d^2}}$$

n = Estimated sample size Z = 1.96 (standard normal deviate for 95% CI (1.96)

p = 50% d = level of precision (10%)

n = 96 patients

This study included children with sickle cell between ages of 6 to 12 and the approximate number of patients in this age group seen weekly at the haematology clinic are 10.Given an estimated prevalence (p) of 50% of the outcome, as we currently did not have data on the prevalence of impaired six minute walk test, and a level of precision of 10% (d) , the study sample size(n) using the Fischer's formula came to 96 patients but I used 99 patients from the clinic.

3.6 SAMPLING METHOD

Consecutive recruitment until the desired sample size was reached.

3.7 STUDY PROCEDURES

Paediatrics patients with SCD meeting the inclusion criteria were identified from the pediatric haematology clinic in the KNH (clinic 23) conducted every Monday between 9am to 1pm. Patients/ parents or caregivers were informed of the study after which a consent form and an assent (above 10 years) / consent form was filled. Upon filing the assent/ consent form, a study registration number was issued and noted by the study assistant. This was to avoid double registration of patients during subsequent visits.

A paper-based assessment questionnaire was then administered to the participants and had details on the demographics and questions on the general well-being of the patients. If meeting one or more of the exclusion criteria, these patients did proceed for the 6MWT.

Physical examination procedure

Anthropometrics of the children were measured using standardized techniques. Height was measured using a portable stadiometer, children were in an upright position, with bare feet placed slightly apart, arms extended and head positioned parallel to the floor. After height, a flexible tape was used to measure leg length, which was the distance from the anterior superior iliac spine to just below the medial malleolus in an upright position and was reported as centimeters.

Body weight was assessed using a digital scale with a precision of±100g, and the children had only light clothing, bare feet, and stood straight at the center of the weighing scale. Body mass index (BMI) was calculated from these results. The recorded anthropometric measurements were then

plotted in the respective WHO anthropometric charts to determine the nutritional status in terms of BMI for age.

A physical cardiorespiratory examination was conducted by checking for conjunctival and palmar pallor, cyanosis, finger-clubbing, pulses(radial, femoral and any radio radial or radio femoral delays), pedal edema, chest inspection and palpation, abdominal palpation for hepatomegaly, and finally auscultation of cardiac and breath sounds and the findings were recorded. Transcutaneous oxygen saturation was measured on the left thumb with a portable finger pulse oximeter. Respiratory rate and heart rate was counted for a full minute and the patient was shown a pictorial rating of perceived exertion (RPE) scale and asked to point to the color that best describes how tired he or she felt. The corresponding numerical value was then recorded as the RPE value in the pre 6MWT form (Appendix 4).

Procedure for the six-minute walk test

The 6MWT was performed as per the guidelines by the American Thoracic Society (ATS) by two persons at a time, the tester (the investigator or any of the research assistants trained for 6MWT administration) and the test assistant. The patients were instructed to walk as fast as possible but not to jog or run and were allowed to stop whenever they want. The researcher or assistant demonstrated if the instructions were not clear to the child. Standardized encouragements were done after every one-minute lapse (Appendix 3).

This 6MWT took place in a flat and straight corridor with a hard surface. The course was 30 meters long and there were marks placed at each end of the course. The number of laps completed were ticked in the lap counter worksheet and the final uncompleted lap was recorded as distance in meters walked and then added to the total distance calculated for the laps.

Immediately after the walk, the oxygen saturation was measured, heart rate and the patient then rated their overall fatigue using the RPE scale. These findings were recorded in the post 6MWT form. The patient then proceeded to do a haemoglobin level.

Laboratory test

This was conducted in the bleeding center at clinic 23 in KNH. The child was asked to sit in the procedure room. An explanation of the procedure by the laboratory technician was provided. The venipuncture site (antecubital) was cleaned by a cotton swab dipped in methylated spirit and then

pricked.1 milliliter of blood was collected in a properly labelled purple topped EDTA (ethylenediaminetetraacetic acid) vacutainer bottle and taken for analysis. The pricked site was dressed with a dry cotton swab with strapping to achieve hemostasis. The results were sent to the researcher for recording in their respective forms.

Sample transporting

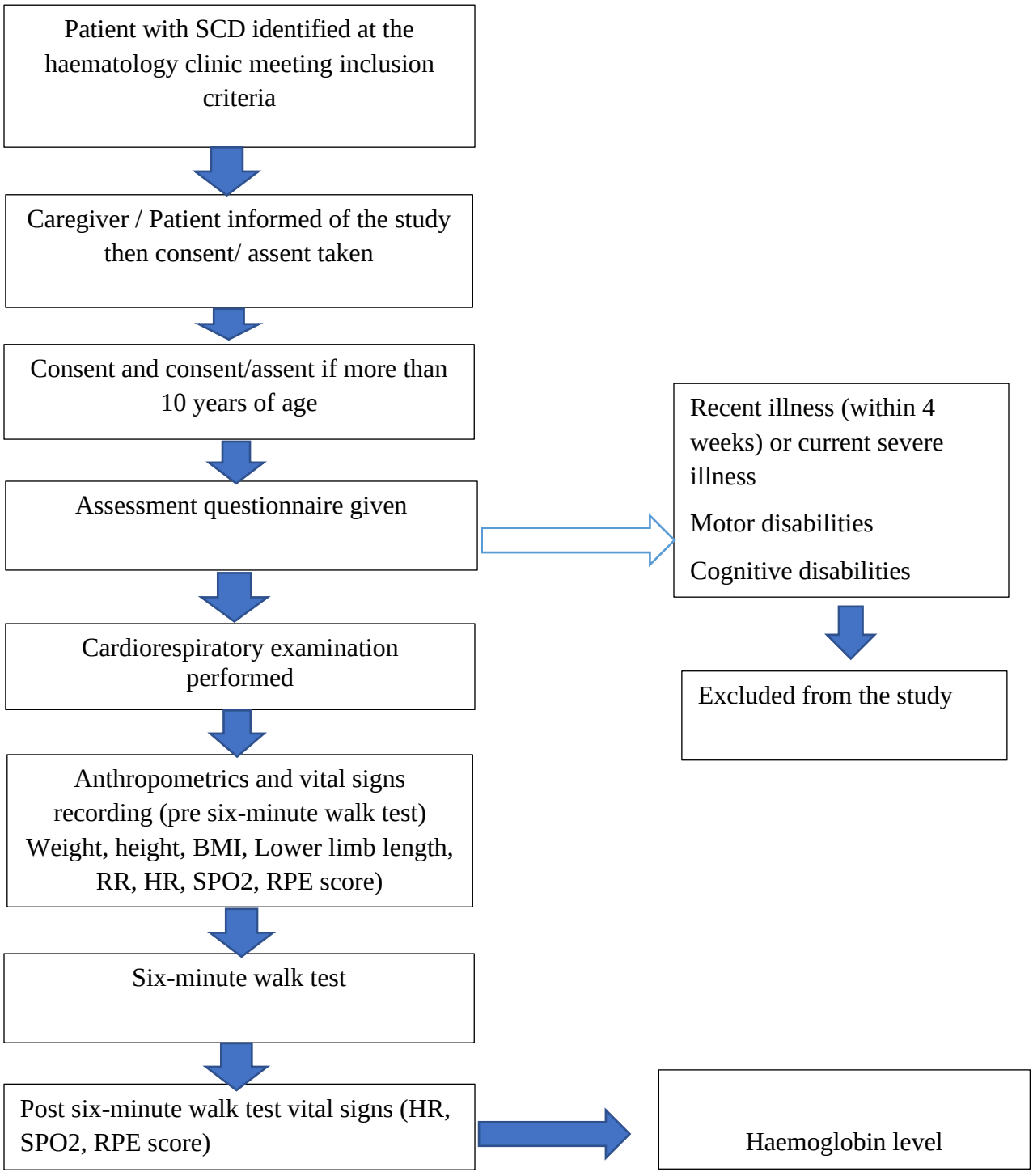
The specimen bottle was placed on a rack in a cool box and taken to the KNH haematology laboratory within 1-2 hours of sample collection together with the laboratory request form.

Sample processing and analysis.

Blood samples were received by a laboratory technician at the laboratory. The specimen was logged in a book and assigned a specimen lab no, then processed within 2 hours. The machine used for a haemoglobin level is the Sysmex XN1000 analyzer. The turnaround time was two hours.

3.8 QUALITY CONTROL OF THE LABORATORY

Quality control measures and standard operating procedures were adhered to at all times during the research. Specimens were collected using proper collection methods and stored in appropriate and sterile containers. The samples collected were clearly labeled immediately before collection. Specimens were then stored at room temperatures. Internal and external quality was undertaken at the KNH haematology laboratory. Internal quality control was once daily. External quality checks run 3 times annually.



BMI-Body mass index for age, RR-respiratory rate, HR-heart rate, SPO2-oxygen saturation

RPE-rating for perceived exertion

Figure 1: Patient flow chart

PARTICIPANTS SAFETY

Although the 6MWT is generally safe, even in sick and compromised patients, precautions were taken to ensure adequate safety

1. Participation was entirely voluntary without coercion by the researcher or assistants.
2. The 6MWT was conducted within the hospital, preferably close to the paediatric emergency unit where access was easier in cases of emergency.
3. Safe test sites were carefully selected by avoiding corridors with bumps or anything that could trip or hurt the participants.
4. Basic resuscitation devices were made available on-site (manual bag and mask) and assistants trained on the resuscitation procedure.
5. Participants were not allowed to carry out the test in slippers, high-heel shoes or barefoot to avoid getting injuries.
6. Participants were free to slow down, rest or stop during the test in the event of any intolerable discomfort.
7. Tape measure, stethoscope and pulse oximeter was periodically wiped with methylated spirit to limit cross-infection

3.9 ETHICAL CONSIDERATIONS

Ethical approval was sought from the KNH/UoN research and ethics committee. Data collection and analysis was not commenced before ethical approval.

A written informed consent was obtained from parents or guardians of the study participants before enrollment. The details, procedures and protocols of the study was explained to the parents or guardians in their preferred language and a translator used during the explanation where applicable. They were assured of continued same standard of care should they decline to participate in the study.

Consenting participants were also informed that they could opt out of the study at any point without being disadvantaged in any way.

Patients found to have a low body mass Index (Z score less than -2) were referred to the nutrition clinic for weight monitoring and nutritional support.

Patients found to have abnormal cardiac findings were sent to for an echocardiogram at the cardiac clinic and were to be reviewed by the paediatric cardiologist.

Patients with abnormal respiratory examination were sent for specific tests depending on the findings of the examination and further referred to the pulmonologist.

Patients with reduced 6MWD as per compared reference values were then referred to the pulmonologist for further investigations and management.

3.10 STUDY DISSEMINATION PLAN

The study findings shall be presented to the UoN department of Paediatrics and Child Health as part of the requirements of the MMed Program in both hard and soft copies. Hard copies of the results shall be sent to the University of Nairobi repository for storage. The findings shall also be shared with the office of the head of department of Paediatrics in KNH with a view of dissemination of the new knowledge that has been generated to improve patient care. The findings shall also be submitted for publication in peer reviewed scientific journals

3.11 DATA COLLECTION

Data was collected by the principal investigator and study assistants. Research assistants were hired with an aim to aid the principal investigator with data collection. The research assistants were registered clinical officers working within the hospital. The principal investigator trained and supervised the research assistants on how to administer the questionnaire and to conduct the six-minute walk test as per ATS guidelines. Precaution was taken to ensure that the research assistants were competent. The principal investigator also ensured that the individuals had resuscitation skills in case it was needed.

3.12 DATA MANAGEMENT

The questionnaire was checked for completeness and accuracy. The collected study data was entered into a customized password protected MS Access data base.

The Anthroplus ® software was also used to derive each's subject's BMI, BMI-for-age z-score (BAZ), height-for-age z-scores (HAZ) and weight-for-age z-score (WAZ).Classification of subjects' nutritional status was based on WHO criteria: BAZ ≥ -2 to +1 was defined as normal weight, BAZ > +1 to ≤ +2 as overweight, BAZ > +2 to +3 as obese, BAZ > +3 as severely obese, and BAZ < -2 as wasted. WAZ <-2 was defined as underweight and HAZ < -2 as stunted.

3.13 DATA ANALYSIS.

After completion of data entry, the data was exported from the access database to R statistical software for cleaning, verification and analysis (V3.4.3, R core team, 2017).

The continuous variables were presented as medians and interquartile ranges as they were skewed, while categorical data were presented as frequencies and proportions.

The impaired six-minute walk distance was presented as a prevalence with 95% confidence interval.

A multivariable logistic regression model was used to determine the demographic, anthropometric and physiologic factors associated with the impaired six-minute walk distance. A p value of ≤ 0.05 was considered as significant**.**

4.0 RESULTS

Introduction

The results of the study are presented in this chapter. The broad objective of the study was to determine the prevalence and factors associated with impaired functional exercise capacity in children 6 to 12 years of age with sickle cell disease on follow-up at the haematology clinic in Kenyatta National Hospital using the six-minute walk test.

4.1 DESCRIPTIVE CHARACTERISTICS

The study recruited 99 children where 54 (54.5%) were female and 45(45.5%) were male. The median age was 9 years (IQR 8-10 years), where the youngest child recruited in the study was 6 years and the oldest being 12 years. The median weight for age Z score was -0.57 (IQR -1.11 – 0.13), while that of Height to age Z score was -0.26 (IQR -1.12 – 0.53), and Body mass index Z score was -0.77 (IQR -1.43 – 0.05) which interprets to normal weight and height for age. The median Haemoglobin level was 8.3g/dl which is a normal value in patients with SCD.(Table 3)

Hydroxyurea use was reported in 93.9% of the children and on clinical examination, 57.6% of them had normal cardiac exam with 11.2% having a normal respiratory system examination (Figure 2).

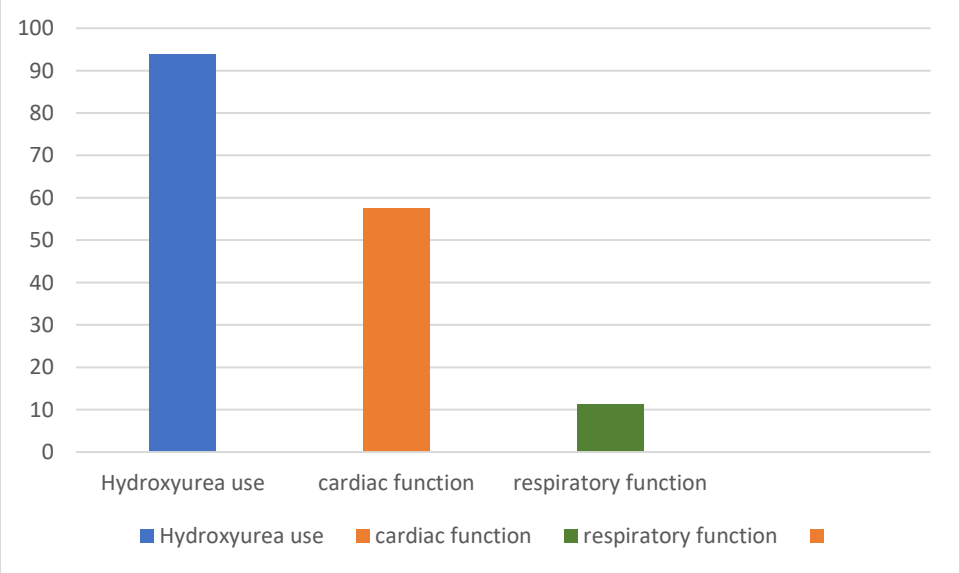


Figure 2: Use of hydroxyurea and examination findings

Table 3: Patients characteristics

Sex	**Frequency (N=99)**	**Percentage (%)**
Male	45	45.5
Female	54	54.5
	Median	**IQR**
Age(years)	9.0	8.0 – 10.0
Height(cms)	130.5	125.0 – 141.0
Weight(Kgs)	26.0	22.0 – 31.5
BMI(kg/m2)	15.15	13.95 – 16.51
LL Length(cms)	75.0	72.0 – 80.0
Haemoglobin level(g/dl)	8.3	7.8 – 9.7
RR(breaths/min)	24.0	20.0 – 25.0
WAZ	-0.57	-1.11 – 0.13
HAZ	-0.26	-1.12 – 0.53
BAZ	-0.77	-1.43 – 0.05
SPO2 (Baseline)(%)	92.0	89.0 – 96.0
SPO2 (After 6MWD)(%)	87.0	84.0 – 90.0
HR (Baseline)(beats/min)	94.0	84.0 – 102.0
HR (After 6MWD)	116.0	108.0 – 124.0

BAZ-Body mass index for age Z score, *WAZ*-Weight for age Z score, *HAZ*-Height for age Z score

Patient's clinical and anthropometric characteristics only:

Results of anthropometric measures taken showed that 88.9% and 89.9% of the participants patients had a normal weight as per the BAZ and WAZ score and 88.9% were of normal height. Only 1 patient was found to be obese using the WAZ score and 3 out of the 99 using the BAZ.11.9% of the participants were stunted.92.9% of the patients had hypoxia at rest (SPO2 less than 92%) with 21.2% having tachypnoea and 42.4% having tachycardia.

Table 4: Patients anthropometrics and clinical characteristics

WAZ	**Frequency (N=99)**	**Percentage (%)**
Underweight	9	9.1
Normal	89	89.9
Over	1	1.0
HAZ		
stunted	11	11.1
Normal	88	88.9
BAZ		
wasted	8	8.1
Normal	88	88.9
Over	3	3.0
RR-Age specific Tachypnoea		
Yes	21	21.2
No	78	78.8
Age specific Tachycardia		
Yes	42	42.4
No	57	57.6
Pulse oximetry		
Normal	11	11.1
Hypoxic	88	88.8

Table 5: 6MWD

The median distance walked for all the patients was 510 (IQR 446 – 541) metres. Male patients walked longer distances- 11.5 m more during the 6MWT than the female patients. This is in keeping with all the previous studies done where the boys walked longer distances.

	Median	IQR
Male	515.0	437- 569
Female	503.5	450-534

4.2 PREVALENCE OF IMPAIRED SIX-MINUTE WALK TEST

The prevalence of impaired 6MWT was 69.7% translating to only 30 out of 99 participants having a normal walk test. The prevalence was determined by first entering selected parameters of each of the children into the Tunisia reference equation, and thereafter the results were then categorized into impaired (≤0.080) or not impaired (>0.80) for each child. The prevalence was therefore the proportion of those impaired over the sample size. The results are as shown in Figure 4 and Table 6 below.

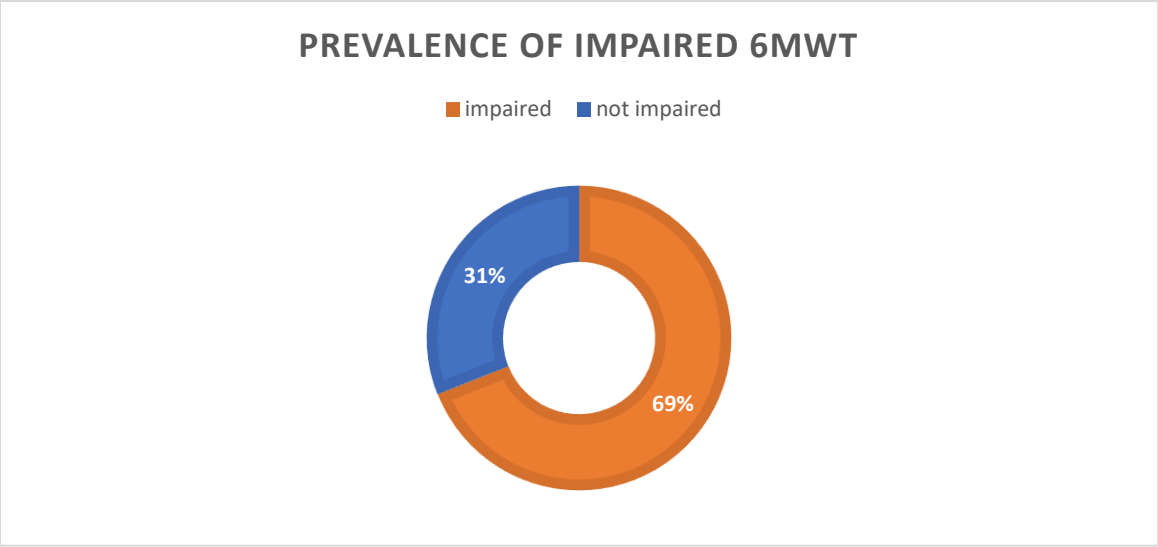


Figure 3 : Impaired 6MWT Prevalence

Table 6 : Prevalence of impaired 6MWT

Impaired	Frequency (N=99)	Percentage (%)
Tunisia		
Yes	69	69.7
No	30	30.3

Table 7: Impaired 6MWT according to percentages

IMPAIRED	FREQUENCY (N=99)	PERCENTAGE (%)
Less than 60%	**18**	**18**
60-80%	**51**	**51**
81-100%	**30**	**28**

4.3 FACTORS ASSOCIATED WITH THE IMPAIRED 6MWT

The factors which were associated with the impaired walk test were stratified into sociodemographic, anthropometric and physiological factors.

Sociodemographic factors associated with impaired 6MWT

Age was the only factor found to be statistically associated with being impaired where each unit increase of age increases the risk of being impaired by 30%) OR 1.3(95% CI 1.0-1.7, p=0.032). Others factors were not statistically significant but revealed that males were 10% less likely to have an impaired 6MWT than females, OR 0.9 (95% CI 0.4-2.2, p = 0.873)

Table 8: Demographic factors associated with impaired 6MWT

	Impaired	**Not impaired**	**COR (95% CI)**	**p-value**
Age *(median, IQR)*	10.0 (8.0 – 11.0)	9 (7.0 – 10.0)	1.3 (1.0 – 1.7)	0.032
Gender *(n, %)*				
Male	31 (44.9)	14 (46.7)	0.9 (0.4 – 2.2)	0.873
Female	38 (55.1)	16 (53.3)	Reference	

Anthropometric factors associated with impaired 6MWT

Patients who are wasted are 3 times more likely to have an impaired 6MWT, OR 3.1(95% C1 0.4-26.4, p =0.3). The results also indicated that being stunted was protective in reference to the normal height which contradicts several studies. Patients with a WAZ score of less than -2 SD (underweight) were 20% less likely to have an impaired 6MWT.

Table 9: Anthropometric factors associated with impaired 6MWT

	Impaired	**Not impaired**	**COR (95% CI)**	**p-value**
BAZ (n, %)				
wasted	7 (10.1)	1 (3.3)	3.1 (0.4 – 26.4)	0.301
Normal	61 (88.4)	27 (90.0)	Reference	
Overweight	1 (1.4)	2 (6.7)	0.2 (0.02 – 2.5)	0.226
HAZ (n, %)				
Stunted	7 (10.1)	4 (13.3)	0.7 (0.2 – 2.7)	0.613
Normal	59 (85.5)	24 (80.0)	Reference	
WAZ (n, %)				
Underweight	6 (8.7)	3 (10.0)	0.8 (0.2 – 3.6)	0.797

Normal	63 (91.3)	26 (86.7)	Reference	
Overweight	0 (0.0)	1 (3.3)	-	

BAZ-Body mass index for age Z score, HAZ-Height for age Z score, WAZ- Weight for age Z score

Physiological factors associated with impaired 6MWT

Participants with tachypnoea, anemia and a post 6MWT hypoxemia were less likely to have impairment of the 6MWT (OR 0.6 with 95% CI 0.2-1.8, OR 0.6 with 95% CI 0.2-1.5 and OR 0.4 with a 95% CI 0.04-3.1) respectively. Patients with Age specific tachycardia was 2.1 times more likely to have an impaired 6MWT (OR 2.1,95% CI 0.9-5.3 p=0.103)

Table 10: Physiological factors associated with impaired 6MWT

	Impaired	**Not impaired**	**COR (95% CI)**	**p-value**
RR(Agespecific Tachypnoea)				
Yes	13 (18.8)	8 (26.7)	0.6 (0.2 – 1.8)	0.384
No	56 (81.2)	22 (73.3)	Reference	
HR (Age specific Tachycardia)				
Yes	33 (47.8)	9 (30.0)	2.1 (0.9 – 5.3)	0.103
No	36 (52.2)	21 (70.0)	Reference	
Hb Level *(n, %)*				
<8	18 (26.1)	11 (36.7)	0.6 (0.2 – 1.5)	0.290
>8	51 (73.9)	19 (63.3)	Reference	
Hydroxyurea				
Yes	64 (92.8)	29 (96.7)	0.4(0.05 – 3.9)	0.464
No	5 (7.2)	1 (3.3)	Reference	

Post6MWT oxygen sats *(n, %)*				
Normal	6 (8.7)	1 (3.3)	Reference	
Hypoxic	63 (91.3)	29 (96.7)	0.4(0.04 – 3.1)	0.357

Multivariable analysis

On multivariable analysis, age was the only factor statistically associated with the the impaired 6MWT when adjusted with other factors, where each unit increase of age increases the risk of having an impaired 6MWT by 40% (AOR 1.4 95% CI 1.1-1.9 p=0.034). The males were 1.6 times more than the females to be impaired (AOR 1.6 95% CI 0.6-4.6 p=0.386).Children who were stunted were 10% more at risk of having an impaired test (AOR 1.1 95%CI 0.2-7.4 p=0.885) Being underweight was also found to be protective. Patients who had a lower haemoglobin, tachypnoeic, tachycardic and hypoxic had were less likely to have an impaired 6MWT but these were not statistically significant (P value>0.05).

Table 11: Multivariable analysis of factors associate with impaired 6MWT

	Impaired	**Not impaired**	**COR(95%CI)**	**p-value**	**AOR (95% CI)**	**p-value**
Age *(median, IQR)*	10.0(8.0-11.0)	9 (7.0 – 10.0)	1.3 (1.0 – 1.7)	0.032	1.4 (1.1 – 1.9)	0.034
Gender *(n, %)*						
Male	31 (44.9)	14 (46.7)	0.9 (0.4 – 2.2)	0.873	1.6 (0.6 - 4.6)	0.386
Female	38 (55.1)	16 (53.3)	Reference		Reference	
BAZ *(n, %)*						
wasted	7 (10.1)	1 (3.3)	3.1 (0.4 – 26.4)	0.301	3.0 (0.3 – 36.0)	0.385
Normal	61 (88.4)	27 (90.0)	Reference		Reference	
Overweight	1 (1.4)	2 (6.7)	0.2 (0.02 – 2.5)	0.226	0.1 (0.003-4.6)	0.245
HAZ *(n, %)*						
Stunted	7 (10.1)	4 (13.3)	0.7 (0.2 – 2.7)	0.613	1.1 (0.2 – 7.4)	0.885
Normal	59 (85.5)	24 (80.0)	Reference		Reference	
WAZ *(n, %)*						
Underweight	6 (8.7)	3 (10.0)	0.8 (0.2 – 3.6)	0.797	0.4 (0.1 – 3.3)	0.423
Normal	63 (91.3)	26 (86.7)	Reference		Reference	
Overweight	0 (0.0)	1 (3.3)	-		-	

RR(Age specific Tachypnoea)						
Yes	13 (18.8)	8 (26.7)	0.6 (0.2 – 1.8)	0.384	0.7 (0.2 – 2.4)	0.597
No	56 (81.2)	22 (73.3)	Reference		Reference	
HR (Age specific Tachycardia)						
Yes	33 (47.8)	9 (30.0)	2.1 (0.9 – 5.3)	0.103	3.1 (1.0 – 9.3)	0.051
No	36 (52.2)	21 (70.0)	Reference		Reference	
Hb Level *(n, %)*						
<8	18 (26.1)	11 (36.7)	0.6 (0.2 – 1.5)	0.290	0.6 (0.2 – 1.6)	0.296
>8	51 (73.9)	19 (63.3)	Reference		Reference	
Hydroxyurea						
Yes	64 (92.8)	29 (96.7)	0.4 (0.05 – 3.9)	0.464	0.2 (0.02 – 3.2)	0.278
No	5 (7.2)	1 (3.3)	Reference		Reference	
Post 6MWT oxygen saturations *(n, %)*						
Normal	6 (8.7)	1 (3.3)	Reference		Reference	
Hypoxic	63 (91.3)	29 (96.7)	0.4 (0.04 – 3.1)	0.357	0.7 (0.1 – 7.0)	0.763

BAZ-Body mass index for age Z score, HAZ-Height for age Z score, WAZ- Weight for age Z score

5.0 DISCUSSION

Our study determined the prevalence of impaired functional exercise capacity using the six-minute walk test (6MWT), in children aged between 6 and 12 years with SCD on follow-up at the haematology clinic at Kenyatta National Hospital. Distances from the patients were compared to the Tunisian predictive reference equation. Impaired 6MWT was defined as a distance walked of less than 80% of the predicted as per the reference formula.

This study demonstrated that the prevalence of impaired six minute walk test was almost 70% in patients with sickle cell disease. This was conducted on 99 children who were on follow up at the haematology clinic. One in every 1.4 children had some degree of cardiorespiratory impairment which impacted their exercise capacity. Most of the studies on patients with sickle cell have been conducted in Brazil as SCD is one of the public health problems. Studies done in Brazil by Dedeken *et al*.,(32) and Vieira *et al*., (27) showed a 30% and 26.1% prevalence of impaired six-minute walk distance in 46 children with sickle cell disease. This is much lower than what was found in our setup.

Similar studies by Sandro *et al*.,(3) Nivaldo Melo *et al*., (26) which looked at the functional exercise capacity in both SCD children and adolescents using the six-minute walk test also concluded that functional exercise capacity was lower than the predicted for healthy children and that patients with homozygous sickle cell disease had a below average performance regarding total distance walked. The prevalence of impairment was not quantitated.

Caboot in the US also concluded that children with SCD have impaired submaximal exercise capacity as compared to normal children.(29)

Literature suggests that patients with SCD have reduced cardiorespiratory capacity and which is explained by the abnormal configuration of red blood cells, leading to a sickle-like shape when deprived of oxygen, preventing the acquisition and diffusion of O_2, causing hypoxemia, dyspnoea, muscle acidosis and a diminished exercise tolerance as consequence. (31)

Additionally, studies done in SCD patients show a decreased functional exercise capacity as a result of low volumes of the lungs in these children.(31)

Recurrent painful crises, common in patients with SCD, may also have added on to the decline in physical capacity. Pain hampered functional ability and predisposes those affected with this condition to a more sedentary lifestyle with minimal physical activity, which may lead to peripheral muscle weakness and to decreased functional capacity, as was discovered in this study. This, coupled with parental overprotection (out of fear of activity-induced worsening of symptoms) or restrictions imposed by healthcare professionals, teachers or the patients themselves leads to worsening of functional capacity, quality of life and outcomes.(57)

The higher prevalence could also be due factors such as anthropometry, body composition and body proportion are racially and genetically determined, hence reference equation from Tunisian children (and indeed from other regions of the world) are not likely to be reliable in Kenyan subjects.

The difference in the 6MWT may also have contributed to the very high prevalence of those who were impaired. It has been shown that the shorter the walking course, the shorter the distance attained and vice versa. Our study used 30m walk distance as per the ATS recommendation but Tunisian study used 40m-long courses. A longer course is associated with fewer turns and hence longer distances. Also, while subjects in the current study performed the test only once, the Tunisian subjects performed the test twice and the best of the two walk tests was reported for each subject. Practice walk tests are known to result in longer walk distance because of a learning effect that results from better coordination and conditioning during the subsequent walk tests.

Our 6MWT results were uniform to those reported in literature which show that these children have, in general, lower measures of fitness compared to normal children.

This study identified that the variable independently associated with the 6MWD was age. This agrees with several studies including Jason Caboot *et al*.,(29) found that the mean 6MWD significantly correlated with age and height. Another similar study by Nivaldo *et al*.,(26) also found that age and BMI were the variables independently associated with the 6MWT.This can be explained that children with SCD tend to have more complications and increased hospitalisations which could contribute to them having a more impaired functional exercise capacity in the 6MWT.

Other factors that had been associated with 6MWD in similar studies: level of haemoglobin, BMI, hydroxyurea use, heart rate and low oxygen saturation at and after the exercise were not significantly associated in this study.

Tachycardia was observed in 92.9% of the children. This may be due to the hyperdynamic circulatory state as a response to chronic anaemia, however a study done in Sudan by Ali *et al*., found that tachycardia was the commonest presenting symptom in children with cardiovascular abnormalities which were confirmed by an ECHO hence our patients need a thorough evaluation before contributing the elevated heart rate solely on the anemia.(58)

Hypoxia was also detected in 88% of the children using pulse oximetry. This was much higher than a study done in Nigeria which found 13% of patients with SCD having hypoxia. This wide variation can be explained by the fact that we used cut off values of below 95% as hypoxia while the Nigeria study used a cut off of 90%.(59)

Hypoxemia could also be due to intrapulmonary shunting, membrane diffusion defects, and an eventual shift of the dissociation curve to the right. This leads to restrictive lung condition. (60)

Male patients were 60% more likely to have an impaired 6MWT.This can be explained by the fact that they walked longer distances than the females and hence to were more likely to get more tired and have an impaired test.

Genetic predisposition, anxiety, self-motivation, sociocultural influences, individual habitual speed of walking, sensory and perceptual ability, cognition, environmental influences and motor skills are other factors with possible varying influence on the 6MWD. These difficult-to-measure factors account for about 40-64% of the variability in reported 6MWD in children from various ethno-geographic regions.(39)

Gaps identified in literature is that although the International guidelines on SCD recommend the use of a 6MWT in patients with SCD ,there are very few studies done worldwide and this is rarely being conducted in our setup .Another gap identified is the lack of a local reference value for our study population. To the investigator's knowledge, this is the only study conducted in Kenya and it provides the degree of functional impairment in our children with SCD. This may not be an accurate representation as there are significant variations in the 6MWD from country to country despite fairly similar anthropometric variables.

5.1 STRENGTHS OF THE STUDY

Despite these limitations, the main strengths of the 6MWT stem from its simplicity in concept and performance, low cost, ease of standardization, and acceptance by test subjects, including those who have chronic conditions.

This simple test can be used as a guide for both prognostication and monitoring these patients. This study done will serve to show the severity of compromise in these patients and advocate for the importance of early recognition of cardiopulmonary involvement.

5.2 STUDY LIMITATIONS

The study was done in only one clinic site in Kenya, therefore the results cannot be generalized to other children with sickle cell disease in different counties.

Other tests would have been included in the pulmonary examination including conducting Peak Flows or spirometry to all the patients but due to the covid era and inadequate resources available, only a clinical cardiorespiratory assessment was performed.

The study sample size was small and was not powered to determine associated factors. Further studies with a larger sample size could be undertaken to test for these associations.

5.3 CONCLUSION

In this study, the prevalence of impaired 6MWT in children with SCD is extremely high at approximately 70%.

Age was the only factor significantly associated with an impaired 6MWT.The older the patients were, the more likely to have an impaired 6MWT.

5.4 RECOMMENDATIONS

Since the study findings were compared to the Tunisian derived references as we do not have published predictive equations in our population, In agreement with earlier recommendations by the American Thoracic Society (ATS), there is need to have separate reference values and equations unique to each study population using standardized protocols.

There is need to derive local predictive equation based on the factors that uniquely influence the 6MWD of the study subjects.

Referral of the patients with abnormal cardiac and respiratory examinations to the pulmonologist and cardiologists should be done for further investigations to ascertain the degree of systemic involvement .The 6MWT is simple, feasible and can be efficiently performed by SCD patients.

6.0 REFERENCES

1. Mahaa DR, Swaleh S. Frequency and factors associated with hospitalisation of children with Sickle cell anaemia in Kenyatta National Hospital and Gertrudes children's hospital. University of Nairobi; 2018.
2. Wonkam A, Makani J. Sickle cell disease in Africa: an urgent need for longitudinal cohort studies. Lancet Glob Heal. 2019;7(10):e1310–1.
3. Hostyn S V., De Carvalho WB, Johnston C, Braga JAP. Evaluation of functional capacity for exercise in children and adolescents with sickle-cell disease through the six-minute walk test. J Pediatr (Rio J). 2013;89(6):588–94.
4. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-Minute Walk Test and Cardiopulmonary Exercise Testing in Patients With Chronic Heart Failure. Circ Hear Fail. 2009;2(6):549–55.
5. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. Am J Respir Crit Care Med. 2002;166(1):111–7.
6. Riner WF, Sellhorst SH. Physical activity and exercise in children with chronic health conditions. J Sport Heal Sci. 2013;2(1):12–20.
7. Giannitsi S, Bougiakli M, Bechlioulis A, Kotsia A, Michalis LK, Naka KK. 6-minute walking test: a useful tool in the management of heart failure patients. Ther Adv Cardiovasc Dis. 2019;Vol. 13: 1–10.
8. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle Cell Disease in Africa. Am J Prev Med. 2011;41(6):S398–405.
9. Sachdev V, Rosing DR, Thein SL. Cardiovascular complications of sickle cell disease. Trends Cardiovasc Med. 2021;31(3):187–93.
10. Khoury RA, Musallam KM, Mroueh S, Abboud MR. Pulmonary complications of sickle cell disease. Hemoglobin. 2011;35(5–6):625–35.
11. Bui KL, Nyberg A, Maltais F, Saey D. Functional tests in chronic obstructive pulmonary

disease, Part 1: Clinical relevance and links to the international classification of functioning, disability, and health. Ann Am Thorac Soc. 2017;14(5):778–84.

12. Owens S, Gutin B. Exercise intolerance. Pediatr Rev. 2000;21(1):6–9.

13. Teoh OH, Trachsel D, Mei-Zahav M, Selvadurai H. Exercise Testing in Children with Lung Diseases. Paediatr Respir Rev. 2009;10(3):99–104.

14. Schrier SL. Sickle Cell Disease: Basic Principles and Clinical Practice. Stephen H. Embury , Robert P. Hebbel , Nara Mohandas , Martin H. Steinberg. Q Rev Biol. 1995;70(4):541–2.

15. Rai P, Niss O, Malik P. A reappraisal of the mechanisms underlying the cardiac complications of sickle cell anemia. Vol. 64, Pediatric Blood and Cancer. 2017. p. 541–2.

16. Platt OS, Rosenstock W, Espeland MA. Influence of Sickle Hemoglobinopathies on Growth and Development. N Engl J Med. 1984;311(1):7–12.

17. Barden EM, Zemel BS, Kawchak DA, Goran MI, Ohene-Frempong K, Stallings VA. Total and resting energy expenditure in children with sickle cell disease. J Pediatr. 2000;136(1):73–6.

18. Stull DE, Leidy NK, Jones PW, Ståhl E. Measuring functional performance in patients with COPD: A discussion of patient-reported outcome measures. Curr Med Res Opin. 2007;23(11):2655–66.

19. Gulmans VAM, Van Veldhoven NHMJ, De Meer K, Helders PJM. The six-minute walking test in children with cystic fibrosis: Reliability and validity. Pediatr Pulmonol. 1996;22(2):85–9.

20. Nixon PA, Joswiak ML, Fricker FJ. A six-minute walk test for assessing exercise tolerance in severely ill children. J Pediatr. 1996;129(3):362–6.

21. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–7.

22. Andrade LB de, Silva DARG, Salgado TLB, Figueroa JN, Lucena-Silva N, Britto MCA. Comparison of six-minute walk test in children with moderate/severe asthma with

reference values for healthy children. J Pediatr (Versão em Port. 2014;90(3):230–57.

23. Jegdic V, Roncevic Z, Skrabic V. Physical fitness in children with type 1 diabetes measured with six-minute walk test. Int J Endocrinol. 2013;2013.

24. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, Haworth SG. Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with pulmonary hypertension. Arch Dis Child. 2011;96(2):141–7.

25. Waltz X, Romana M, Hardy-Dessources MD, Lamarre Y, Divialle-Doumdo L, Petras M, et al. Hematological and hemorheological Determinants of the Six-Minute Walk Test Performance in Children with Sickle Cell Anemia. PLoS One. 2013;8(10):e77830.

26. Melo HN, Stoots SJM, Pool MA, Carvalho VO, Almeida LOC, Aragão MLDC, et al. Physical activity level and performance in the six-minute walk test of children and adolescents with sickle cell anemia. Rev Bras Hematol Hemoter. 2017;39(2):133–9.

27. Vieira AK, Alvim CG, Carneiro MCM, Ibiapina C da C. Pulmonary function in children and adolescents with sickle cell disease: Have we paid proper attention to this problem? Vol. 42, Jornal Brasileiro de Pneumologia. 2016. 409–15.

28. Ohara DG, Ruas G, Walsh IAP, Castro SS, Jamami M. Lung function and six-minute walk test performance in individuals with sickle cell disease. Brazilian J Phys Ther. 2014;18(1):79–87.

29. Caboot JB, Jawad AF, Bowdre CY, Arens R, Marcus CL, Mason TA, et al. The Six-Minute Walk Test In Children With Sickle Cell Disease. In 2010. A3306.

30. Minniti C, Alam S, Kato GJ, Nouraie M, Sable C, Ensing G, et al. Evaluation of Exercise Capacity In Children with SCD by Six Minute Walk Test. Blood. 2010;116(21):2664–2664.

31. Liem RI, Nevin MA, Prestridge A, Young LT, Thompson AA. Functional capacity in children and young adults with sickle cell disease undergoing evaluation for cardiopulmonary disease. Am J Hematol. 2009;84(10):645–9.

32. Dedeken L, Chapusette R, Lê PQ, Heijmans C, Devalck C, Huybrechts S, et al. Reduction of the six-minute walk distance in children with sickle cell disease is correlated with silent

infarct: Results from a cross-sectional evaluation in a single center in Belgium. PLoS One. 2014;9(10).

33. Mylius CF, Paap D, Takken T. Reference value for the 6-minute walk test in children and adolescents: a systematic review. Expert Rev Respir Med. 2016;10(12):1335–52.

34. Geiger R, Strasak A, Treml B, Gasser K, Kleinsasser A, Fischer V, et al. Six-Minute Walk Test in Children and Adolescents. J Pediatr. 2007;150(4).

35. Li AM, Yin J, Au JT, So HK, Tsang T, Wong E, et al. Standard reference for the six-minute-walk test in healthy children aged 7 to 16 years. Am J Respir Crit Care Med. 2007;176.

36. Saad H Ben, Prefaut C, Missaoui R, Mohamed IH, Tabka Z, Hayot M. Reference equation for 6-min walk distance in healthy North African children 6-16 years old. Pediatr Pulmonol. 2009;44(4):316–24.

37. Priesnitz CV, Rodrigues GH, Da Silva Stumpf C, Viapiana G, Cabral CP, Stein RT, et al. Reference values for the 6-min walk test in healthy children aged 6-12 years. Pediatr Pulmonol. 2009;44(12):1174–9.

38. Ulrich S, Hildenbrand FF, Treder U, Fischler M, Keusch S, Speich R, et al. Reference values for the 6-minute walk test in healthy children and adolescents in Switzerland. BMC Pulm Med. 2013;13(1).

39. Ubuane PO, Animasahun BA, Ajiboye OA, Kayode-Awe MO, Ajayi OA, Njokanma FO. The historical evolution of the six-minute walk test as a measure of functional exercise capacity: a narrative review. J Xiangya Med. 2018;3:40–40.

40. Cacau L de AP, de Santana-Filho VJ, Maynard LG, Neto MG, Fernandes M, Carvalho VO. Reference values for the six-minute walk test in healthy children and adolescents: A systematic review. Brazilian J Cardiovasc Surg. 2016;31(5):381–8.

41. Goel R, Hassell KL, Machado RF, Barst RJ, Yovetich N, Kato GJ, et al. Non-Cardiopulmonary Factors Affecting the Six-Minute Walk Distance in Patients with Sickle Cell Disease: Results From the Walk-PHaSST Study. Blood. 2011;118(21):1074–1074.

42. Klepper SE, Muir N. Reference values on the 6-minute walk test for children living in the

United States. Pediatr Phys Ther. 2011;23(1):32–40.

43. Lammers AE, A.A. Hislop, Flynn Y, Haworth SG. The 6-minute walk test: Normal values for children of 4-11 years of age. Arch Dis Child. 2008;93(6):464–8.

44. Bogin B, Varela-Silva MI. Leg length, proportion, health and beauty: A review. Anthropologischer Anzeiger. 2009. 439–59.

45. Goemans N, Klingels K, Boons S, Verstraete L, Peeters C, van den Hauwe M, et al. O50 – 1933 Normative data of the 6-minute walk test in healthy boys aged 5–12 years and correlations with anthropometric variables and myometry. Eur J Paediatr Neurol. 2013;

46. Lee S, Bountziouka V, Lum S, Stocks J, Bonner R, Naik M, et al. Ethnic variability in body size, proportions and composition in children aged 5 to 11 years: Is ethnic-specific calibration of bioelectrical impedance required? PLoS One. 2014;9(12).

47. Foeldvari I, Himmelmann G. AB0685 Results for 6 minute walk values in healthy german children show similar results as from britain. Ann Rheum Dis. 2013;72(suppl 3):A997.3-A997.

48. Pathare N, Haskvitz EM, Selleck M. 6-Minute Walk Test Performance in Young Children who are Normal Weight and Overweight. Cardiopulm Phys Ther J. 2012;23(4):12–8.

49. Adeniyi AF, Saminu KS. Local incentive spirometry improves peak expiratory flow rate in teenage sickle cell anaemia patients: A randomized pilot trial. Afr Health Sci. 2011;11(3):303–8.

50. Saraff V, Schneider J, Colleselli V, Ruepp M, Rauchenzauner M, Neururer S, et al. Sex-, age-, and height-specific reference curves for the 6-min walk test in healthy children and adolescents. Eur J Pediatr. 2015;174(6):837–40.

51. Ferrari M, Manea L, Anton K, Bruzzone P, Meneghello M, Zamboni F, et al. Anemia and hemoglobin serum levels are associated with exercise capacity and quality of life in chronic obstructive pulmonary disease. BMC Pulm Med. 2015;58(15):1.

52. Campbell A, Minniti CP, Nouraie M, Arteta M, Rana S, Onyekwere O, et al. Prospective evaluation of haemoglobin oxygen saturation at rest and after exercise in paediatric sickle cell disease patients. Br J Haematol. 2009

53. Garadah T, Jaradat FMA, Thani K Bin. The effects of hydroxyurea therapy on the six-minute walk distance in patients with adult sickle cell anemia: An echocardiographic study. J Blood Med. 2019;10:443–52.

54. Britto RR, Probst VS, Dornelas De Andrade AF, Samora GAR, Hernandes NA, Marinho PEM, et al. Reference equations for the six-minute walk distance based on a Brazilian multicenter study. Brazilian J Phys Ther. 2013;17(6):556–63.

55. Tonklang N, Roymanee S, Sopontammarak S. Developing standard reference data for thai children from a six-minute walk test. J Med Assoc Thail. 2011;94(4):470–5.

56. Callahan LA, Woods KF, Mensah GA, Ramsey LT, Barbeau P, Gutin B. Cardiopulmonary responses to exercise in women with sickle cell anemia. Am J Respir Crit Care Med. 2002;165(9):1309–16.

57. Connes P, MacHado R, Hue O, Reid H. Exercise limitation, exercise testing and exercise recommendations in sickle cell anemia. Clin Hemorheol Microcirc. 2011;49(1–4):151–63.

58. Ali GOM, Abdal Gader YS, Abuzedi ES, Attalla BAI. Cardiac manifestations of sickle cell anaemia in Sudanese children. Sudan J Paediatr. 2012;12(1):70–708.

59. Chinawa JM, Ubesie AC, Chukwu BF, Ikefuna AN, Emodi IJ. Prevalence of hypoxemia among children with sickle cell anemia during steady state and crises: A cross-sectional study. Niger J Clin Pract. 2013;16(1):91–5.

60. Fawibe A. Sickle cell chronic pulmonary disease among Africans: the need for increased recognition and treatment. Mera African J Respir Med. 2008 Apr 1;13(3):13–6.

7.0 APPENDICES

APPENDIX 1a: CONSENT FORM FOR PARTICIPATION IN THE STUDY

Study title: Prevalence and factors associated with impaired six- minute walk distance in children with sickle cell disease

Name of researcher: Dr Aisha Jahadmy

Supervisors: Dr Nyambura Kariuki and Dr Diana Marangu

I am a postgraduate student at the University of Nairobi pursuing a Master of Medicine degree in Paediatrics and Child Health.

I am conducting a study on the prevalence and factors associated with impaired six- minute walk distance in children using the six-minute walk test in children 6 to 12 years with sickle cell disease on follow up at the haematology clinic in Kenyatta National Hospital.

The purpose of this consent form is to give you the information you will need to help you decide whether or not your child should participate in the study.

The aim of the study is to know how far your child with sickle cell disease, can walk in six minutes (this is a measure of their physical fitness). This test is simple and is not stressful. Your child will be told to walk along a selected corridor, hallway or walkway within the hospital for six minutes without running or jogging. He/she will be allowed to stop or rest during the test if he/she wants. The distance walked at the end of the sixth minute will be recorded as a measure of your child's physical fitness. This distance taken will allow the health workers to monitor how well your child is responding to treatment.

Before the test, your child will be asked some questions on his age and general well-being. A physical chest and heart exam will be conducted. Your child's weight, height and leg length will be measured. A simple painless device will be attached to your child's finger to check oxygen level and heart beat (pulse oximeter) and your child will be asked about how tired he/she feels by pointing to a scale and then rating it on a score of 1-10 (rating of perceived exertion scale).

After the test, your child will be sent to do a blood test, at the bleeding center in clinic 23, KNH and the cost for the test will be met by the researcher. The test is called a haemoglobin level and it

checks how much blood your child has. Participation of your child in this study is free and may be an opportunity for health screening.

The results of the test will be made available to you if you so wish. You are free to ask any question on things you do not understand at any point in time. Your child's participation in this study is a contribution to the care of sickle cell disease children.

Kindly understand the following: -

Participation is voluntary.

Confidentiality shall be maintained at all times. We shall use a code number to identify your child in a password-protected computer database and will keep all of our paper records in a locked file cabinet.

Refusal of any participation in the study will not attract any penalties. Your child shall continue to receive treatment as required.

Risks: There are minimal risks in participating in this study, however your child may experience tiredness and leg pains when walking during the test. The hemoglobin level test may cause pain and swelling at the puncture site. During the walk test, if the child feels he/she needs to take a break or cannot continue walking due to pain or discomfort, he/she will be provided a seat immediately and will only continue once he/she sees fit. If the patient is noted to require oxygen or having a sickle cell crisis or severe chest pain, it will require immediate referral to the emergency department for management and oxygen support. Resuscitation equipment including a bag valve mask will be at hand during the walk test.

Benefits: Any abnormality picked up during the cardiac and respiratory examination will be addressed by sending the child for an echocardiogram and review by a cardiologist at the cardiac clinic. Patients with low BMI for age will be referred to the nutrition clinic for nutritional support and follow-up.

Any child found to have reduced six-minute walk distance shall be closely followed up by the pulmonologist. There is no monetary compensation for participating in this study, however the haemoglobin shall be paid for by the researcher.

If you have further questions or concerns about your child participating in this study, please call or send a text message to the study staff on 0722456381(Dr Aisha Jahadmy). For more information

about your child's rights as a research participant, you may contact the Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke.

Your decision to have your child participate in this research is voluntary. You are free to decline or withdraw participation of your child in the study at any time without injustice or loss of benefits (Just inform the study staff and the participation of your child in the study shall be stopped). You do not have to give reasons for withdrawing your child if you do not wish to do so. Withdrawal of your child from the study will not affect the services your child is otherwise entitled to in this health facility or other health facilities.

CONSENT FORM (STATEMENT OF CONSENT)

The person being considered for this study is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age). You are being asked to give your permission to include your child in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had my questions answered by him or her in a language that I understand. The risks and benefits have been explained to me. I understand that my participation and that of my child in this study is voluntary and that I may choose to withdraw it any time. I understand that all efforts shall be made to keep information regarding me and my child's personal identity confidential. By signing this consent form, I have not given up my child's legal rights as a participant in this research study.

I voluntarily agree to my child's participation in this research study: Yes No

I agree to provide contact information for follow-up: Yes No

Parent/Guardian signature _____ Date _____

Parent/Guardian printed name: _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.

Printed Name: _____Date: _____

Signature: _____

APPENDIX 1b: IDHINI YA KUSHIRIKISHWA KATIKA UTAFITI

Idadi ya watoto wenye upungufu wa utembeaji kwa dakika sita wenye ugonjwa wa sickle cell

Jina la mtafiti: Dr Aisha Jahadmy

Wasimamizi: Dr. Nyambura Kariuki na Dr. Diana Marangu

Mimi ni mwanafunzi wa uzamili katika Chuo Kikuu cha Nairobi ninayesomea shahada ya afya na magonjwa ya watoto.

Ninafanya utafiti juu ya idadi ya watoto wenye upungufu wa utembeaji kwa dakika sita kwa watoto wa umri wa miaka sita mpaka kumi na miwili wenye ugonjwa wa sickle cell wenye kufuatiliwa kwa cliniki ya damu hospitali kuu ya Kenyatta. Lengo la hii fomu ni kukupatia taarifa ili kukuwezesha kuamua iwapo utamruhusu mtoto wako kushirikishwa kwenye utafiti huu.

Utafiti huu ni wa kujua umbali ambao watoto wenye ugonjwa wa sickle cell wanaweza kutembea kwa dakika sita.Hii itatuonyesha usawa wa mwili wao.Mtihani huu ni wa urahisi.

Kabla ya kuanza kutembea,mtoto wako ataulizwa maswala kuhusu afya yake.vipimo vya urefu, kilo zake na urefu wa miguu vitachukuliwa na oksijeni yake itapimwa Mtoto wako ataambiwa atembee kwenye sehemu iliyochaguliwa kwa dakika sita bila ya kukimbia.Yeye anaweza kusimama na kupumzika atakapo. Umbali aliotembea kwa hizo dakika sita utaandikwa.Umbali huu utasaidia wauguzi kufuatilia matibabu ya mtoto wako na afya yake. Akishindwa kutembea kabla hajamaliza muda wake,atapatiwa kiti na apumzike mpaka awe tayari kuendelea.Akiwa anaumwa sana na viungo ama kifua atapelekwa emergency ashungulikiwe.Tutakuwa na kifaa cha oxygieni iwapo atakihitaji kiasi cha kumpeleka emergency.

.Baada ya hapo atatakiwa apime kiwango chake cha damu kwa kliniki 23. Akimaliza munaruhusiwa kuenda nyumbani.Matokeo ya mazoezi yatakuwa wazi kwako kama unapenda.Una ruhusa ya kuuliza maswala yeyote ambayo hujafahamu.

Tafadhali elewa yafuatayo: -

Ushiriki ni kwa hiari. Nitaitunza siri yako. Vipimo vya mtoto wako vitahifadhiwa kwenye kompyuta iliyo na neno siri na kufungiwa kwa kabati .Kukataa kushiriki katika utafiti hautavutia adhabu yoyote. Mtoto wako ataendelea kupokea matibau anayo stahili.

Mtoto wako anaweza kuskia uchovu wa mwili akitembea kwa muda huo.Kiwango cha damu pia kinaweza kuleta maumivu pahali alipodungwa.

Mtoto akipatikana na shidaya lishe,akiwa na uzito wa chini ataonekana na mtaalamu wa lishe bora(nutrionist)ili amhudumikie na amfuatilie kilo zake.

Mtoto yeyote atakayepatikana na shida ya zoezi hili atapelekwa kuonekana na mtafiti wa mapafu.

Mtoto wako akipatikana na shida ya roho,atapelekwa kliniki ya roho afanyiwe picha ya roho na aonekane na daktari anayehusika

Hakuna fidia ya fedha kwa ajili ya kushiriki katika utafiti huu lakini pesa za kufanyia kiwango cha damu(haemoglobin level) zitalipwa na mimi.

Uko na uhuru wa kukataa kuhusishwa katika utafiti huu wakati wowote.Ukiwa na maswala kuhusu utafiti huu ama unataka maelezo zaidi,piga simu ama tuma ujumbe mfupi kwa nambari 0722456381(Dr Aisha Jahadmy).

Utakapobadilisha nia ya uhusisho unaweza andika barua pepe au kupiga simu kwa kamati ya maadili ya hospitali kuu ya Kenyatta kwa nambari 2726300 Ext. 44102 ama barua pepe: uonknh_erc@uonbi.ac.ke.

Kauli ya mzazi

Nimeisoma fomu hii ya idhini na kuelewa inavyoagiza. Nimejadiliana na mshauri wa utafiti barabara na maswali yangu yamejibiwa kwa lugha ninayoielewa. Nimeelezwa hatari na faida za ushirikisho kwa utafiti huu. Ninaelewa kuwa nitapewa nakala ya idhini hii nitakapoisahihisha. Ninaelewa kuwa siri za mtoto wangu zitatunzwa vyema. Ninaelewa kuwa ushirika wa mtoto wangu katika utafiti huu ni kwa hiari na ninaweza kukataa kuhusishwa kwa utafiti wakati wowote. Katika kusahihisha idhini hii sijasalimisha haki za sheria za mtoto wangu.

Nimekubali kwa hiari kushirikisha mtoto wangu kwa utafiti huu: Ndio ____ La _____

Nimekubali kumpatia mtafiti nambari ya simu: Ndio _____ La _____

Jina la mzazi _____

Sahihi ya mzazi _____ Tarehe

Kauli ya mtafiti

Mimi niliyesahihisha idhini hii nimeeleza mzazi barabara maelezo muhimu kuhusu utafiti huu na ninaamini kuwa ameelewa na kukubali kushirikishwa katika utafiti huu.

Jina la mtafiti _____ Tarehe

Sahihi

Jina la shahidi _____ Tarehe

Sahihi ya shahidi

APPENDIX 1c: ASSENT FORM

Study title: Prevalence and factors associated with impaired six- minute walk distance in children with sickle cell disease

Name of researcher: Dr Aisha Jahadmy

Supervisors: Dr Diana Marangu and Dr Nyambura Kariuki

Purpose of the form

The purpose of this form is to give you the information you will need to help you decide whether or not to participate in the study.

Purpose of the study: Your participation in this study will help me know what distance you can cover by walking in six-minutes. This will help us to closely follow up your progress so that we can assist as early as possible if there is a problem and to see how well how you respond to treatment.

Procedures: If you agree to participate in the study, I shall ask you a few questions about how you are feeling. I then shall measure your height, weight, length of your leg, how much oxygen you have and how fast your heart is beating and how fast you are breathing. I will also ask you to point on a chart to show me how tired you are feeling before you start walking. I will also examine your heart and chest. You will then be told to walk as fast as you can in six minutes. You can stop and have a rest at any point in time. After the test, I will then measure your heart rate and oxygen level and also answer a few questions about how tired you feel using a chart you will be given. You will then be sent to the bleeding center in clinic 23, to do a haemoglobin level.

Risk, Stress and Discomfort: Walking may cause you to be tired. The haemoglobin test may cause you some pain and swelling at the site you have been pricked. If you require oxygen at any point in time or having a lot of pain in your body or chest, you will be taken to the emergency department for management. If you feel you cannot walk any longer before the time has ended, you will be given a chair to sit until you feel well enough to continue.

Other information

We won't tell anyone you took part in this study. Your name will not be on the charts with the measurement results. You do not have to take part in this study if you don't want to.

Signature of investigator Date

Printed Name of investigator Date

Subject's statement:

This research study has been explained to me. I agree to take part in this study. I have had a chance to ask questions. If I have more questions, I can ask the doctor.

_____ _____

Name and Signature of participant Date

_____ _____

Name and signature of parent/guardian Date

APPENDIX 1d: IDHINI YA KUSHIRIKISHWA KATIKA UTAFITI

Idadi ya watoto wenye upungufu wa utembeaji kwa dakika sita wenye ugonjwa wa sickle cell

Jina la mtafiti: Dr Aisha Jahadmy

Wasimamizi: Dr Diana Marangu na Dr Nyambura Kariuki

Lengo la Fomu

Lengo la fomu hii ni kukupa maelezo unayohitaji kuamua kama utajishirikisha na utafiti wetu.

Lengo la utafiti

Kujinga kwako kwa utafiti huu kutasaidia kukujua unaweza kutembea umbali ngapi kwa dakika sita.Hii itatusaidia kufuatilia kwa karibu maendeleo yako na kuingilia kati mapema kama kuna hitilafu yoyote na pia kuangalia maendeleo ya matibabu.

Utaratibu wa utafiti

Ukikubali kujiunga na huu utafiti,nitakupima kifua na moyo,kisha nitachukua urefu,uzito,urefu wa miguu,kipigo cha moyo,hali ya oxigeni kabla hujaanza kutembea kwa dakika sita.Unaweza kupumzika saa yoyote unayotaka.

Madhara ya utafiti

Unaweza kusikia kuchoka ama kuumwa na miguu baada ya kutemebea.Vipimo hivi havitakuwa na uchungu lakini utatakiwa kupima kiwango chako cha damu baada ya kutembea na hii inaweza kuleta uchungu na kufura sehemu utakayodungwa..Ukisikia kuumwa na roho ama huwezi tena kutembea utahudumiwa saa hiyo hiyo.Utapatiwa kiti iwapo huezi kuendelea kutembea na upumzike mpaka ukiwa tayari kuendelea.

Maelezo zaidi

Utafiti huu utakuwa ni wa siri na hatutamueleza mtu kama umehusishwa nao.Jina lako halitatumiwa kokote na hulazimishwi kujiunga na utafiti huu.Kukataa kwako hakutaleta shida yoyote.

_____ _____

Sahihi ya mshiriki Tarehe

_____ _____

Jina la mshiriki Tarehe

APPENDIX 2a: ASSESSMENT QUESTIONNAIRE

Child's Age _____

Child's Sex: Male_____Female_____ HEMOGLOBIN LEVEL

1.Is your child on hydroxyurea? YES [ ] NO[ ]

2. Was your child admitted into a hospital in the last 4 weeks or had a severe illness within that period? YES [__] NO[_ _]

3. Does your child have any limb, bone or joint problem that can affect walking? YES[__] NO[__]

4. Is your child able to follow and understand instructions? YES [ ] NO[ ]

5. Is your child currently taking any medicine or treatment for any illness apart from SCD? YES[__] NO[__]

6. Does your child have asthma or does he/she usually have noisy breathing such as snoring or wheezing (like a whistling sound) especially at night? YES[__] NO[__]

7. Does your child normally get difficulty in breathing or a cough? YES [ ] NO [ ]

8. Does your child usually complain of chest pain during play or physical activity? YES[__] NO[__]

9. Has a doctor ever said that your child has a heart disease? YES [__] NO[__]

10. Does your child have any confirmed respiratory disease? YES [ ] NO[

If you answered YES to Question 2,3 or 4, your child will not be allowed to participate in this study; If you answered NO to ALL questions (apart from question 1), you can be reasonably sure that your child can safely take part in this study. If answered YES from Question 5-10, will proceed to the cardiorespiratory examination.

Appendix 2b: CARDIORESPIRATORY EXAMINATION

Hands	Pallor Yes No Peripheral cyanosis Yes No Finger clubbing Yes No
Pulses	Irregular radial Yes No Irregular femoral Yes No Radio/radial delay Yes No Radio/femoral Yes No
Inspection of the chest	Normal precordium Yes No
Palpation	Apex beat displaced Yes No
	Thrills Yes No
Percussion	Resonance Yes No
Auscultation(heart)	SI S2 normal Yes No Added sounds Yes No Murmurs Yes No
Auscultation(lungs)	Normal breath sounds Yes No
Leg swelling	Yes No
Heart rate (bpm)	
Respiratory rate	
SPO2	

APPENDIX 2c: ANTHROPOMETRY

Measures	
Weight(kg)	
Height(cms)	
Lower limb length (cms)	
BMI	

APPENDIX 2 d: PRE-SIX MINUTE WALK TEST VITALS

Parameter	
Oxygen saturation (SPO2) %	
Heart rate(bpm)	
RPE SCORE	

APPENDIX 2 e: LAP COUNTER WORKSHEET

TIME OF STARTING THE 6MWT_____

Tick a box for every completed lap of 30m

1	2	3	4	5
6	7	8	9	10
11	12	13	14	15
16	17	18	19	20

LAST UNCOMPLETED LAP (m)_____

Appendix 2f: 6MWD CALCULATOR

No of completed laps walked (N)	
N x 30m	
Last uncompleted lap (m)	
Total distance (6MWD)	

APPENDIX 2 g: POST SIX MINUTE WALK TEST VITALS

Parameter	
Oxygen saturation (SPO2) %	
Heart rate(bpm)	

RPE score	

Stopped or paused before 6 minutes? Yes [___] No [___]

If yes, state reason: _____

Exercise-induced symptoms

Chest pain **Yes [___] No [___]**

Chest tightness **Yes [___] No [___]**

Dizziness **Yes [___] No [___]**

Palpitations **Yes [___] No [___]**

Leg pains **Yes [___] No [___]**

APPENDIX 3: THE 6MWT

a) REQUIRED EQUIPMENT

1. Stop watch or timer

2. Two small cones to mark the lap boundaries

3. Measurement scale for floor measurement

4. Lap counter

5. Resuscitation equipment

6.Chair

7. Pulse oximeter

b) ATS STANDARDISED ENCOURAGEMENT FOR 6MWT

After the first minute: "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining: “You are doing well. You are halfway done.”

When the timer shows 2 minutes remaining: “Keep up the good work. You have only 2 minutes left.”

When the timer shows only 1-minute remaining, “You are doing well. You have only 1 minute to go.”

APPENDIX 4: REFERENCE VALUES

Interpretation of anthropometric indicators

Z-score cut-points	Height-for-age	Weight-for-age	Weight-for-height	BMI-for-age
< -3 SD	Severely stunted	Severely underweight	Severely wasted	N/A
-3 SD to -2 SD	Moderately stunted	Moderately underweight	Moderately wasted	N/A
-2 SD to -1 SD	Mildly stunted	Mildly underweight	Mildly wasted	N/A
-1 SD to +2 SD	Normal height	Normal weight	Normal weight-for-height	Normal BMI
>+2 SD	N/A	Overweight	N/A	Overweight

Heart rate and respiratory reference ranges

PEDIATRIC VITAL SIGNS REFERENCE CHART

Heart Rate (beats/min)			Respiratory Rate (breaths/min)	
Age	**Awake**	**Asleep**	**Age**	**Normal**
Neonate (<28 d)	100-205	90-160	Infant (<1 y)	30-53
Infant (1-12 mos)	100-190			
Toddler (1-2 y)	98-140	80-120	Toddler (1-2 y)	22-37
Preschool (3-5 y)	80-120	65-100	Preschool (3-5 y)	20-28
School-age (6-11 y)	75-118	58-90	School-age (6-11 y)	18-25
Adolescent (12-15 y)	60-100	50-90	Adolescent (12-15 y)	12-20

Reference: PALS Guidelines, 2015

Heart failure is defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues. Signs of heart failure are as follows-

Right-sided (hepatomegaly, ascites, abdominal pain, pleural effusion, lower limb edema)

Left-sided (tachypnea, retractions, nasal flaring or grunting, rales, pulmonary edema)

RPE SCALE

RPE Scale (Rate of Perceived Exertion)	
1	**Very Light Activity** (anything other than complete rest)
2-3	**Light activity** (feels like you can maintain for hours, easy to breath and carry on a conversation)
4-5	**Moderate Activity** (feel like you can exercise for long periods of time, able to talk and hold short conversations)
6-7	**Vigorous Activity** (on the verge of becoming uncomfortable, short of breath, can speak a sentence)
8-9	**Very Hard Activity** (difficult to maintain exercise intensity, hard to speak more than a single word)
10	**Max Effort** (feels impossible to continue, completely out of breath, unable to talk)