

FACTORS ASSOCIATED WITH UNDERNUTRITION AMONG CHILDREN WITH SICKLE CELL DISEASE ATTENDING THE SICKLE CELL CLINIC IN MULAGO NATIONAL REFERRAL HOSPITAL, UGANDA. A CROSS SECTIONAL STUDY.

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Abstract

Background:

Sickle cell disease (SCD) is among the neglected non-communicable diseases, which significantly contributes to early childhood mortality. In Uganda, over 20,000 children are estimated to be sicklers. Undernutrition is common among children with SCD and contributes to increased morbidity and mortality. There is a paucity of data on the prevalence of undernutrition and associated factors in Uganda. **Objective:** To assess the extent of undernutrition and related factors among children aged 5-12 years with SCD attending the sickle cell clinic at Mulago National Referral Hospital (MNRH), Uganda.

Methods:

A hospital-based cross-sectional study was conducted. A total of 270 children with SCD attending the sickle cell clinic at MNRH were recruited consecutively between May and June 2017. The nutritional status of the children was assessed by BMI-for-age (wasting) and height-for-age (stunting) z-scores calculated using STATA in accordance with WHO reference. Binary logistic regression was conducted using odds ratios with 95% CI to measure the strength of association among the predictors.

Results:

About 11.4% were wasted and 13.7% were stunted. Wasting was significantly associated with older age (10-12 years) (AOR=4.27, CI=2.20-8.29) and living in a female-headed household (AOR=0.39, CI=0.16-0.92). Stunting was significantly associated with older age (10-12 years) (AOR=2.90, CI=1.39-6.06).

Conclusion:

Wasting and stunting were prevalent among children with SCD attending MNRH. The factors associated with undernutrition were older age and living in a female-headed household.

Recommendations:

Interventions like skills-based nutrition education integrating older children and enhancement of women's control of household resources by improving the social economic status of caretakers through business training and providing vocational skills can improve undernutrition in children with SCD.

Keywords: Sickle cell disease, Undernutrition, Children, Uganda, Submitted: 2023-03-10 Accepted: 2023-03-16

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1. Introduction

Sickle cell disease (SCD) remains a major neglected tropical disease in Africa (Chakravorty & Williams, 2015). The disease is a genetic disorder that affects the shape of haemoglobin in the red blood cell leading to the formation of a sickle shape (Piel et al., 2013). The sickle shape contributes to co-morbidities throughout the lifetime including pulmonary hypertension, stroke, organ damage, gall bladder disease, and premature mortality (Schnog et al., 2004). Globally, 250,000 out of 300,000 infants born with haemoglobin disorders every year have SCD (Serjeant, 2013). Furthermore, an estimated 240,000 children in low and middle-income countries are born with SCD annually of which 50%-80% die before the age of five years (Aygün & Odame, 2012). In Uganda, about 20,000 children are born with SCD every year (Ndeezi et al., 2016). This could be an underestimate since the majority of the children are not tested in most districts in the country (Okwi et al., 2010).

Several nutrient deficiencies have been reported among children with SCD and this greatly affects their quality of life (Martyres et al., 2016). Undernutrition (stunting, underweight, and wasting) is a common occurrence among children with SCD in Africa and it has a negative impact on the children's quality of life (Barden et al., 2000). However, a few recent studies have reported a low prevalence of undernutrition among children with SCD in developed countries due to better disease management, health care, and macronutrient intake and utilisation (Kuvibidila et al., 2020).

SCD has been known to cause undernutrition by increased metabolic demands (Hyacinth et al., 2010), chronic and acute vaso-occlusions, poor appetite, and compromised absorption. Previous studies on undernutrition in children with SCD have focused on the prevalence of the condition however data on the factors associated in developing countries is scarce (Barden et al., 2000; Hyacinth et al., 2010; Martyres et al., 2016; Okwi et

al., 2010). Factors such as child sex, age of the child (Zemel et al., 2007) maternal or caretakers age, household income (Islam et al., 2021), duration of exclusive breastfeeding, average weight during childhood, the average number of child hospitalization, anaemia severity, geographical location (urban vs. rural), history of hand and foot syndrome, more than two sickle cell crises a year, medical history of severe infections and presence of hepatomegaly have been indicators as key determinants of undernutrition in children with SCD (Acham, 2010; Al-Saqladi et al., 2010; Boadu et al., 2018; Cox et al., 2011; Lukusa Kazadi et al., 2017; Nandanwar & Kamd, 2013; Nikhar et al., 2012; Pryer et al., 2004)

In this study, therefore, we assess the prevalence and factors associated with undernutrition among children with sickle cell disease attending the sickle cell clinic in Mulago National Referral Hospital (MNRH), Uganda. Undernutrition is an important predictor of the morbidity and mortality of children with SCD (Kuvibidila et al., 2020). Therefore, assessing the factors associated with undernutrition can be used by policymakers to make targeted interventions to improve the quality of life of children with SCD. This contributes to the Millennium Development Goal MDG 4, which aims to reduce child mortality.

2. Methods

This was a hospital-based cross-sectional study conducted among 270 children with SCD who were attending the sickle cell clinic in Uganda (MNRH) from May to June 2017. Uganda is located in East Africa and lies across the equator. It is a landlocked country that borders Tanzania south Kenya to the east, Rwanda to the southeast, the Democratic Republic of Congo to the west, and South Sudan to the north. Uganda's economy is predominantly agricultural, with the majority of the population depending on subsistence farming and light agro-based industries. Health services are provided by public and private subsectors; each subsector covers about 50% of the services.

MNRH is a tertiary hospital and serves as a

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national center for managing cases with SCD. On average it manages 800 sickle cell patients from across the country each month. Some of the patients who attend this clinic are referred from other clinics and they come in every month for monitoring. Recruitment of study participants was conducted as they waited for their routine monthly medical care using consecutive sampling.

2.1. Inclusion criteria

We included confirmed cases of SCD, aged 5-12 years, and whose caretakers provided consent for them to participate in the study.

2.2. Exclusion criteria

We excluded very ill cases for example children experiencing acute chest syndrome and vaso-occlusive crises during the time of the study.

3. Sample size

The sample size was determined using the formula for single proportion by Kish Leslie, 1969.

Where: n = sample size; z = z value corresponding to 95% confidence interval = 1.96; p = proportion of malnutrition among SCD children = 22.7% (Cox et al., 2011) = 0.227; (Cox et al., 2011) q = $(1-p)$ = $(1-0.227)$ = 0.773 = absolute precision = 5%. Therefore, from the above formula sample size was 270. We did not consider a non-response rate.

A structured interview administered questionnaire was used to collect child weight, height, socio-demographic, co-morbidities, food intake, and household characteristics information from caretakers.

The weight of the children was measured in kilograms using a calibrated Seca 874

electronic weighing scale. The children were requested to take off their shoes and heavy garments and asked to stand in the middle of the platform to evenly distribute the weight to both feet (Statius, 1995). The weight was recorded to the nearest 0.1kg.

Height was measured in centimeters using a stadiometer. Children were asked to remove their

shoes, and hair ornaments and stand erect with the back to the stadiometer. With the back of the head, upper back, buttocks, back of the legs, and heels in contact with the board, relaxed arms, and the eyes looking horizontally, the headpiece of the stadiometer was lowered so that the hair (if present) was pressed flat, height was recorded to the nearest 0.1cm.

3.1. Study variables

The dependent variable in this study was undernutrition (wasting and stunting) measured by <-2 Z-scores of BMI-for-age and height-for-age WHO reference anthropometric indices respectively.

The independent variables were categorized into child characteristics and caretaker/household characteristics.

The child characteristics included: age (5-9 years and 10-12 years), sex (male, female), birth order (1st, 2nd-3rd, 4th and above), morbidities experienced in the past two weeks before the study (Acute respiratory infection, fever, and diarrhea) and food intake. Food intake was assessed using the validated dietary diversity score which was based on the 10 food groups consumed in the past twenty-four hours prior to the study (Kennedy et al., 2013). For each of the food groups consumed, a child was awarded a score of one or zero if the food group was consumed or not consumed respectively. A dietary diversity score (DDS) cut-off was constructed to describe the dietary diversity with a sum of 0-3 as inadequate DDS and 4-10 as adequate DDS score (Kennedy et al., 2013).

The caretaker/ household characteristics included: Age of the caretaker (20-24, 25-29, 30-34, and above 35 years), marital status (married/living together, not married), the highest level of education (primary, O level, A level, tertiary and university), main occupation (salaried worker, business, labourer, peasant farmer, housewife and other), sex of household head (male-headed, female-headed), number of children (1-2, 3-4, 5 and above), average household size and household wealth index. Household wealth was computed using the principal com-

ponent analysis. The variables considered were obtained using questions in the 2016 Uganda Health Demographic Survey regarding asset and access variables namely: owning: 1) a radio, 2) a television, 3) a mobile phone, 4) a bicycle, 5) a motorcycle, 6) a motor vehicle, 7) a piece of land, 8) large farm animals like cattle, goats, and sheep, 9) small farm animals like poultry, 10) a manufactured bed, and 11) the nature of the house (Statistics (UBOS) & ICF, 2017). The household wealth index was ranked into two quintiles from the lowest to the highest (1=Low and 2=Highest).

3.2. Data analyses

Data was exported from excel to stata14.0 for analysis (StataCorp, 2015). Socio-demographic data were summarized using descriptive statistics like proportions and frequencies for categorical variables and mean and standard deviations for continuous variables as appropriate. Anthropometric measurements of height and weight were used to determine undernutrition. Height and age were converted from centimeters to meters and years to months respectively. Body Mass Index (BMI) was calculated then the BMI for age z-scores and height for age z-scores were computed using the WHO reference (Organization, 2007). Normal nutritional status was defined as z-scores ≥ -2 and undernutrition (wasting and stunting) was defined as z-scores < -2 . The prevalence of stunting and wasting was expressed in percentages.

In order to ascertain the factors that were associated with undernutrition we started with univariable and bivariable analysis. The factors that had a potential for being considered in the multivariable model were variables found to be statistically significant at the bivariable level, factors with a P-value of < 0.2 , and the insignificant variables which were deemed to be important in influencing undernutrition according to literature. We later performed multivariable analysis using a binary logistic regression approach controlling for factors identified under bivariable analysis and literature. The strength of the association between variables was determined using odds ratios, P-

values (α set at < 0.05), and a 95% confidence interval. Models were built using the stepwise regression method. Confounding was checked by observing whether variables included in the model caused a change in the odds ratio of the main exposure by at least 10%. Also confounding was checked by assessing whether variables that were insignificant at the bivariable stage became significant at the multivariable level. Variables in a model that were found consistently insignificant and did not add any value in terms of goodness of fit were eliminated. The model goodness of fit was tested using the Hosmer-Lemeshow goodness of fit test.

3.3. Ethics policies

Ethical approval to conduct the study was sought from the Makerere University School of Public Health Higher Degrees Research and Ethics Committee. Furthermore, permission was also sought from Mulago Hospital Research and Ethics Committee (MREC1152). Details of the study were explained to the Head of the Department and the caretaker's written consent was obtained from the participating caretakers. Caretakers were interviewed individually for privacy and personal information was kept confidential by using identification numbers.

4. Results:

4.1. Characteristics of the study participants

From the total of 270 child care-taker pairs recruited, only 263 child-caretaker pairs were included in the final analysis because some were outliers according to the WHO anthropometric indicator cut-offs. The mean age of the children was eight years ($SD \pm 2$) and the majority 66.5% (175/263) were in the age group 5-9 years (Table 1). A majority of the children had other morbidities in the past 2 weeks including acute respiratory infection 49.1% (129/263), fever 41.4% (109/263), and diarrhea 17.9% (47/263).

4.2. Characteristics of caretaker and their household

The social demographic characteristics of the caretakers are shown in table 2. The mean age of

Table 1: Characteristics of study participants

Child Characteristics	Frequency (n=263)	Percent
Age (Years)		
5-9	175	66.5
10-12	88	33.5
Sex		
Male	126	47.9
Female	137	52.1
Dietary Diversity Score		
Inadequate	134	50.9
Adequate	129	49.1
Birth order		
1 st	74	28.1
2 nd -3 rd	121	46.0
4 th and above	68	25.9
Morbidities in the past two weeks		
Acute respiratory infection (ARI)	129	49.1
Fever	109	41.4
Diarrhea	47	17.9

caretakers was 33 years (SD8 years). The majority 70.3 % (185/263) of the caretakers were married, and about half 45.6% (120/263) had attained secondary education. The majority 73.0 % (193/263) of the respondents came from male-headed households. The average household size was 5 people (SD2 people).

4.3. Prevalence of wasting and stunting

The children's weight ranged from 14.2 - 46.0 kg, height ranged from 100.9 - 157.6 cm, and BMI ranged from 12.1 - 20.1 kg/m². Mean z-scores for wasting and stunting were -1.08 ± 1.07 and -0.81 ± 1.07 respectively. About 11.4% (30/263) were wasted and 13.7% (36/263) were stunted; details are shown in Table 3.

4.4. Factors associated with wasting of study participants.

Wasting was significantly associated with the age of the child and the sex of the household head (Table 4). Children aged 10-12 years were more likely to be wasted compared to their counterparts (AOR=4.27, CI=2.20-8.29). Additionally, children who lived in female-headed households were

less likely to be wasted compared to those born in male-headed households (AOR=0.39, CI=0.16-0.92).

4.5. Factors associated with stunting of study participants

In the present study, stunting was independently associated with the age of the child as shown in Table 5. Children aged 10-12 years were more likely to be stunted compared to their counterparts (AOR=2.90, CI=1.39-6.06).

5. Discussion:

The aim of the study was to assess the prevalence and factors associated with undernutrition in children with SCD aged 5-12 years attending the sickle cell clinic in MNRH. The findings revealed that older age (10-12 years) and living in a female-headed household were significantly associated with undernutrition.

In this study, about 11.4% and 13.7% of the children were wasted and stunted respectively. This shows that undernutrition was prevalent among children with SCD according to the WHO

Table 2: Characteristics of the caretakers and their households

Care taker characteristics	Frequency (n=263)	Percent (%)
Caretaker Age (year)		
20-24	23	8.8
25-29	65	24.7
30-34	75	28.5
≥35	100	38.0
Current marital status		
Married/Living together	185	70.3
Not married	78	29.7
Highest Level of education Primary O' level A' level	92 105 15 51	35.0 39.9 5.7 19.4
More than secondary level		
Main Occupation Salaried worker Business Labourer	40 91 10 20 71	15.2 34.6 3.8 7.6
Peasant farmer Housewife Other	31	27.0 11.8
Sex of household head		
Male headed	193	73.4
Female headed	70	26.6
Number of children		
1-2	76	28.9
3-4	127	48.3
5 and above	60	22.8
Average household size	5 (SD 2)	
Wealth index		
Lowest	87	33.1
Middle Highest	88 88	33.4 33.5

Table 3: Nutrition status of study participants

Variable	Mean ±SD	Frequency (n=263)	Percentage (%)
Weight (kg)	22.75±5.68	-	-
Height (cm)	122.12±12.39	-	-
BMI (kg/m ²)	15.04±1.39	-	-
z-scores for wasting	-1.08 ± 1.07	-	-
z-scores for stunting	-0.80 ± 1.16	-	-
Wasting	-	30	11.4
Stunting	-	36	13.7

Table 4: Factors associated with wasting of study participants

Characteristics	Wasted		Crude OR (95%CI)	P value	Adjusted OR (95%CI)	P value
	No (n=233)	Yes (n=30)				
Age of child (Years)						
5-9	161(92.0)	14(8.0)	1.00		1.00	
10-12	72(81.8)	16(18.2)	2.56(1.18-5.52)	0.017	4.27(2.20- 8.29)	<0.01
Sex of child						
Male	113(89.7)	13(10.3)	1.00			
Female	120(87.6)	17(12.4)	1.23(0.57-2.65)	0.595		
ARI^B co morbidity						
Yes	114(88.4)	15(11.6)	1.00		1.00	
No	119(88.8)	15(11.2)	0.96(0.45-2.05)	0.912	1.37(.699- 2.698)	0.36
Fever^B co morbidity						
Yes	93(85.3)	16(14.7)	1.00		1.00	
No	140(90.9)	14(9.1)	0.58(0.27-1.25)	0.164	.685 (0.34-1.36)	0.28
Diarrhea^B co morbidity						
Yes	41(87.2)	6(12.8)	1.00		1.00	
No	192(88.9)	24(11.1)	0.85(0.33-2.22)	0.747	0.82(0.36-1.85)	0.63
Dietary Diversity Score						
Inadequate	116(86.6)	18(13.4)	1.00			
Adequate	117(90.7)	12(9.3)	0.66(0.30-1.43)	0.295		
Birth order						
1 st	66(89.2)	8(10.8)	1.00			
2 nd to 3 rd	105(86.8)	16(13.2)	1.26(0.51-3.10)	0.619		
4 and above	62(91.2)	6(8.8)	0.80(0.26-2.43)	0.692		
Sex of household head						
Male	171(88.6)	22(11.4)	1.00		1.00	
Female	62(88.6)	8(11.4)	1.00(0.42-2.37)	0.995	0.39(0.16-0.92)	0.03
Marital status of caretaker						
Married	166(89.7)	19(10.3)	1.00			
Not married	67(85.9)	11(14.1)	1.43(0.65-3.18)	0.374		
Number of children by caretaker						
1 to 2	68(89.5)	8(10.5)	1.00			
3 to 4	112(88.2)	15(11.8)	1.14(0.46-2.83)	0.780		
5 and above	53(88.3)	7(11.7)	1.12(0.38-3.29)	0.833		
Family size						
≤5 people	147(90.7)	15(9.3)	1.00		1.00	
>5 people	86(85.2)	15(14.8)	1.71(0.80-3.67)	0.169	1.71(0.89-3.30)	0.109
Wealth index						
Low	112(48.1)	20(66.7)	1.00		1.00	
High	121(51.9)	10(33.3)	0.46(0.21-1.03)	0.060	0.77(0.39-1.54)	0.400

^B=Illnesses experienced by child two weeks prior to study

Table 5: Factors associated with stunting of study participants

Characteristics	Stunted		Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
	No (n=227)	Yes (n=36)				
Age of child						
5-9years	159(90.9)	16(9.1)	1.00		1.00	
10-12years	68(77.3)	20(22.7)	2.92(1.43-5.98)	0.003	2.90(1.39-6.06)	0.005
Sex of child						
Male	111(88.1)	15(11.9)	1.00			
Female	116(84.7)	21(15.3)	1.34(0.66-2.73)	0.420		
Child experienced ARI^B						
Yes	114(88.4)	15(11.6)	1.00			
No	113(84.3)	21(15.7)	1.41(0.69-2.88)	0.342		
Child experienced Fever^B						
Yes	92(84.4)	17(15.6)	1.00			
No	135(88.7)	19(12.3)	0.76(0.38-1.54)	0.450		
Child experienced Diarrhea^B						
Yes	39(83.0)	8(17.0)	1.00			
No	188(87.0)	28(13.0)	0.73(0.31-1.71)	0.465		
Child Dietary Diversity Score						
Inadequate	116(86.6)	18(13.4)	1.00			
Adequate	111(86.1)	18(13.9)	1.05(0.52-2.11)	0.902		
Child birth position						
1 st	64(86.5)	10(13.5)	1.00			
2nd to 3 rd	104(86.0)	17(14.0)	1.05(0.45 - 2.43)	0.916		
4 th and above ^h	59(86.8)	9(13.2)	0.98(0.37-2.57)	0.961		
Sex of household head						
Male	164(85.0)	29(15.0)	1.00		1.00	
Female	63(90.0)	7(10.0)	0.63(0.26-1.51)	0.298	0.41(0.13-1.28)	0.124
Marital status of caretaker						
Married	160(86.5)	25(13.5)	1.00		1.00	
Not married	67(85.9)	11(14.1)	1.05(0.49-2.26)	0.899	1.80(0.66-4.89)	0.254
Number of children by caretaker						
1-2	70(92.1)	6(7.9)	1.00		1.00	
3 to 4	107(84.3)	20(15.7)	2.18(0.83-5.70)	0.112	1.92(0.71-5.19)	0.196
5 and above	50(86.3)	10(13.7)	2.33(0.80-6.84)	0.122	1.85(0.60-5.71)	0.283
Family size						
≤5 people	140(86.4)	22(13.6)	1.00			
>5 people	87(86.1)	14(13.9)	1.02(0.50-2.11)	0.949		
Wealth index						
Low	111(48.9)	21(58.3)	1.00			
High	116(51.1)	15(41.7)	0.80(0.43-1.46)	0.46		

categorisation (Organization, 2007). Undernutrition has a negative impact on the quality of life of children with SCD (Barden et al., 2000).

A prevalence of 11.4% was reported for wasting in this study. According to WHO, this prevalence is categorized to be of serious public health significance (Status, 1995). Wasting is usually caused by frequent infections and reduced food intake. This compromises the body's immunity further increasing the morbidity and mortality rates. Evidence from a cohort study conducted in Tanzania reported an increased risk of hospitalisation with wasting among patients with SCD (Cox et al., 2011).

The prevalence of wasting among children with SCD in other studies ranges between 18.4% to 50.3% (Al-Saqladi et al., 2010; Cox et al., 2011; Lukusa Kazadi et al., 2017). This low prevalence of wasting reported in our study might be explained by the improved management of complications and care of children with SCD. Despite a reduction in the prevalence reported in the study, our results show that wasting is still a significant problem among children with SCD which means that interventions should be put in place to manage it. These include; improving the knowledge of the importance of quick management of complications among the children and caretakers; availing the necessary medicines to manage common illnesses among others.

Height for age (stunting) was low in 13.7% of the children with SCD.

A similar study conducted in the Democratic Republic of Congo among children aged 0-12 years reported stunting at 10.5% (Lukusa Kazadi et al., 2017). This is comparable to the finding of the present study probably because both studies were conducted in the major sickle cell centers in the main cities. Similarly, other studies in the USA have also reported a low prevalence of stunting. This is due to the proper food intake and utilization and excellent care and management of the children (Kuvibidila et al., 2020; Martyres et al., 2016).

5.1. Factors associated with undernutrition

Results of this study showed that older children aged between ten to twelve years were more likely to be wasted and stunted compared to the younger ones. Among children with SCD delay in growth starts early in childhood but becomes more obvious as the child grows up (Nandanwar & Kamd, 2013). This is likely attributed to increased demand for nutrients for growth, fighting off recurrent infections, and a lack of appetite (Martyres et al., 2016). Findings are similar to other studies conducted in Philadelphia and Yemen that have reported the same trend among children with SCD (12,16). For instance evidence from a longitudinal study by Zemel et al (2007) reported that the height status decreased with advancement in age among patients with SCD but more especially during puberty (Zemel et al., 2007). Thus a balanced diet should be emphasized in older children through nutrition education for all family members.

The study also found that household heads influenced undernutrition status as children from female-headed households were less likely to be wasted compared to those from male-headed households. This finding contrasts the theory that being in a male-headed household is more advantageous due to economic security as women are more vulnerable and depend on men (Acham, 2010). However, it is also possible that women might be empowered through obtaining high levels of education and engaging in income-generating activities which enable them to make positive decisions regarding their children like buying nutritious food, taking the child to the hospital when they are sick, and budgeting for other non-food needs (Pryer et al., 2004). Therefore, women's empowerment through the provision of skills, for example, using mother support groups involved in various activities like nutrition counselling, cooking demonstrations, and saving/loan schemes may help to improve the nutrition status of the children. On the other hand, it could also be possible that parents separate after understanding that they are carriers, and probably the sample size of female caretakers in this study was high.

6. Limitations

The study was cross-sectional in nature so no causal relationships can be concluded due to the lack of a temporal relationship between the predictors and nutritional status. Additionally, some predictors related to SCD like the endocrine and metabolic factors, episodes of vasocclusive crises, and a number of hospitalisation were not included in this study.

7. Generalisability

The generalisability of the results in this study is limited to children with SCD attending a health service setting. However, this gives an insight into the factors associated with undernutrition among children with SCD which can be used to improve their management.

8. Conclusion

In conclusion, undernutrition was prevalent among children with SCD. The factors associated with undernutrition were older age (10-12 years) and living in female-headed households. Interventions like skills-based nutrition education integrating older children and enhancement of women's control of household resources by improving the social economic status of caretakers through business training and providing vocational skills can improve undernutrition in children with SCD.

9. List of abbreviations

Table 6: List of abbreviations

ARI	Acute Respiratory Infection
BMI	Body Mass Index
DDS	Dietary Diversity Score Sickle Cell
SCD	Disease
SD	Standard Deviation
WHO	World Health Organisation
MNRH	Mulago National Referral Hospital

10. Data Availability

• The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

11. Author Contributions

• AR, RMK, RK, and AY conceived, designed, and revised the manuscript. AR and AY made the literature search. AR and RMK did the statistical analysis. All authors read and approved the final manuscript.

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