BMJ Paediatrics Open

Paediatric sickle cell disease at a tertiary hospital in Malawi: a retrospective cross-sectional study

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ABSTRACT

Introduction Sickle cell disease (SCD) remains a major cause of childhood mortality and morbidity in Malawi. However, literature to comprehensively describe the disease in the paediatric population is lacking.

Methods A retrospective review of clinical files of children with SCD was conducted. Descriptive statistics were performed to summarise the data. χ^2 or Fisher's exact test was used to look for significant associations between predictor variables and outcome variables (case fatality and length of hospital stay). Predictor variables that were significantly associated with outcome variables (p≤0.05) in a χ^2 or Fisher's exact test were carried forward for analysis in a binary logistic regression. A multivariable binary logistic regression was used to identify covariates that independently predicted length of hospital stay.

Results There were 16 333 paediatric hospitalisations during the study period. Of these, 512 were patients with SCD representing 3.1% (95% CI: 2.9%- 3.4%). Sixty-eight of the 512 children (13.3%; 95% CI: 10.5% - 16.5%) were newly diagnosed cases. Of these, only 13.2% (95% CI: 6.2% - 23.6%) were diagnosed in infancy. Anaemia (94.1%), sepsis (79.5%) and painful crisis (54.3%) were the most recorded clinical features. The mean values of haematological parameters were as follows: haemoglobin (g/dL) 6.4 (SD=1.9), platelets ($\times 10^9$/L) 358.8 (SD=200.9) while median value for white cell count ($\times 10^9$/L) was 23.5 (IQR: 18.0–31.2). Case fatality was 1.4% (95% CI: 0.6% - 2.8%)and 15.2% (95% CI: 12.2% -18.6%) of the children had a prolonged hospital stay (>5 days). Patients with painful crisis were 1.7 (95% CI: 1.02 - 2.86) times more likely to have prolonged hospital stay than those without the complication.

Conclusion Anaemia, sepsis and painful crisis were the most common clinical features paediatric patients with SCD presented with. Patients with painful crisis were more likely to have prolonged hospital stay. Delayed diagnosis of SCD is a problem that needs immediate attention in this setting. Although somewhat encouraging, the relatively low in-hospital mortality among SCD children may under-report the true mortality from the disease considering community deaths and deaths occurring before SCD diagnosis is made.

INTRODUCTION

Sickle cell disease (SCD) continues to be a major global public health concern. Data

What is known about the subject?

► Sickle cell disease (SCD) remains a major cause of childhood mortality and morbidity in Malawi but literature to comprehensively describe the disease in the paediatric population is limited. So far, only two small scale single facility-based studies have been conducted.
► One of the studies focused on the progression of the pulmonary complications associated with SCD while the other one focused on the disparity in diagnoses between primary and secondary/tertiary level facilities.

What this study adds?

► Sickle cell disease (SCD) contributes a significant proportion of paediatric admissions in Malawi with anaemia, sepsis and painful crisis as the most common clinical features. Painful crisis is associated with prolonged hospital stay.
► The study further revealed that there is delayed diagnosis of SCD in our setting, and that mortality among hospitalised SCD children is relatively low.

indicate that, globally, an estimate of 400 000 babies are born with SCD annually.[1] Sub-Saharan Africa (SSA) bears the highest burden where up to 90% of the global births of the condition[2] and about 50%–90% of childhood mortality occurs.[3] Despite being one of the major killers for infants and children with high case fatality rates, it remains a condition of low priority in many countries.[3] In an effort to scale up its management and control, SCD has been identified by WHO as an area requiring urgent and increased attention.[4]

In Malawi, particularly in the northern region, SCD is equally a significant cause of childhood morbidity and yet, receives relatively little attention compared with other

childhood conditions.[5] For instance, the country does not have a national repository to explain the burden of the disease. In addition, specific programmes for the prevention and control of SCD remain non-existent. Collectively, these factors have made the disease remain invisible and neglected while affected children continue to suffer from complications of the disease that demand lifelong care and support. Lack of awareness and recognition of SCD by local health authorities continue to make the disease an invisible health problem.[6]

Mzuzu Central Hospital (MCH) which is located in the northern region of Malawi is one of the four referral hospitals in the country. The hospital attends to a large number of patients with SCD, and clinical observations show that, at least five children with SCD are hospitalised weekly with various complications. However, there are no data to explain who these children are and how they fair clinically when admitted. There is lack of knowledge regarding the prevailing pattern of SCD admissions including the age most affected by the disease in Malawi.

Previous literature has described varied age distribution for children most affected by SCD. Studies conducted in Tanzania, Saudi Arabia and South Africa found the median age of admitted children with SCD or those attending clinic to be 6, 7 and 8 years, respectively.[7–9] Other studies conducted in Congo and Tanzania found much older children of median age of 10.5 and 14 years, respectively.[10 11]

Children with SCD often suffer frequent hospitalisations due to various complications of the disease. Earlier studies have revealed varied complications of admitted paediatric patients. However, vaso-occlusive crisis, acute splenic sequestration, haemolytic crises, acute chest syndrome, stroke, pneumonia and severe infection have been reported as common reasons for admission in SCD children.[7 8 10–12] Another study conducted in a paediatric SCD clinic in Malawi reported patient's histories of Malaria (39%), anaemia (72%), jaundice (52%) and pain episodes (50%).[5]

Effective management of these complications revolves around its prompt management. However, this is often compromised in the Malawian setting and other SSA region, due to limited resources.[5 13] For instance, management of painful crises requires that, patients must be given supplemental oxygen, intravenous hydration and level 3 pain relievers such as morphine plus non-opioid and adjuvant.[14] But due to inconsistent supply of medication in SSA, pain management is often restricted to level 2 analgesics.[15]

Similarly, hydroxyurea is not routinely prescribed in Malawi and universal use policy is not available despite documented evidence of its safety and efficacy.[16] Previous studies have attributed under utilisation of hydroxyurea to provider inexperience, cost and inaccessibility.[15 16] With regard to management of severe anaemia, local guidelines recommend supplemental oxygen and blood transfusion although this may be restricted due to limited supply of blood. Equally, monitoring of high-risk

patients with SCD with transcranial Doppler ultrasound and prophylactic exchange transfusions are non-existent in Malawi.[16] Collectively, these management gaps significantly contribute to high morbidity rate.

Furthermore, the haematological pattern of children with SCD appears to demonstrate a comparable trend. Studies conducted in South Africa, Tanzania, Nigeria and Ghana observed higher values of white cell count (WCC) and platelets but lower values of haemoglobin (Hb) and red cell count (RCC).[9 11 17 18] Low Hb has been attributed to chronic haemolysis and shortened red cell lifespan and this further reduces RCCs .[18] On the other hand, the higher platelet count and WCC are attributed to a possible splenic sequestration and serious bacterial infection, respectively.[19 20]

There is paucity of data on the spectrum of SCD among hospitalised Malawian children. The current study seeks to investigate the demographic, clinical and haematological characterisation of admitted paediatric patients at MCH. This information would inevitably have substantial impact as it will provide a better understanding of the disease and facilitate development of specific disease management and control strategies.

METHODS

Study design and setting

This was a retrospective cross-sectional study of children admitted to MCH paediatric ward between July 2016 and June 2019. MCH is a teaching and regional referral hospital with a bed capacity of 410, and serves a population of over 2 289 780 people.[21] The department of paediatrics has a capacity of 60 inpatient beds and admit patients from 7 weeks to 12 years old.

Study population and procedures

Data were collected from clinical files of children with SCD. All files of patients with SCD aged 7 weeks to 12 years admitted to the ward during the study period were included in the study. Patients with other diagnoses other than SCD were not included in the study. First, clinical files of all patients admitted to the ward were screened in order to identify cases of SCD (figure 1). Patients were classified as having SCD if their hospital admission or discharge diagnoses or physician review notes included reference to a diagnosis of SCD.

These patients were further classified into two subgroups: patients already known to have SCD (herein referred to as known cases) and those in whom the diagnosis was made during the course of their hospitalisation (herein referred to as newly diagnosed cases). Patients were identified as known SCD cases based on documented evidence as indicated on admission form or doctors review notes while for newly diagnosed cases it was based on positive SCD laboratory result. The retrieved SCD cases underwent a detailed review to extract relevant data such as age, gender, clinical features, laboratory
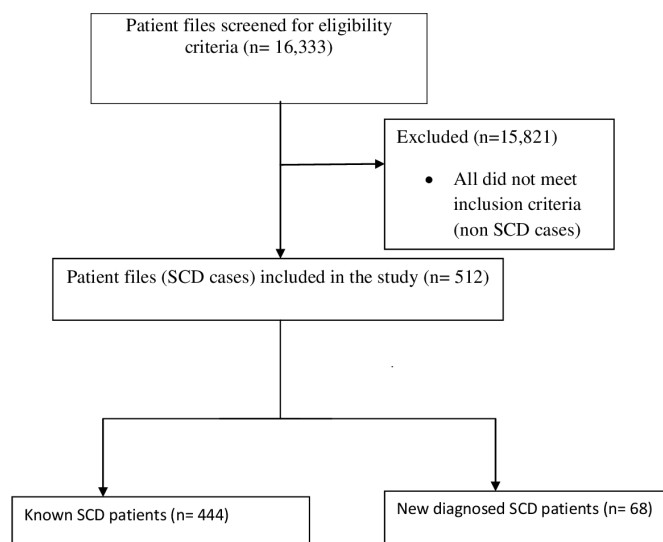
Figure 1 Screening and selection process of SCD clinical files.

investigations, outcome and length of hospital stay using a predesigned data extraction tool.

Development of the data extraction tool was determined by the clinical question and data source (clinical files). A multidisciplinary team including laboratory technologists, SCD medical, nursing and public health experts convened to develop an electronic data extraction tool. This involved formulating clear definitions of variables and coding process.[22] Researchers performed weekly random database reviews against collected data to verify the coded elements.

Data abstractors composed of a medical doctor and professional nurse who had vast experience in SCD. They underwent a 1-day training on study protocol, which included purpose of the study, data extraction tool, screening and coding process, careful review of the variables and their definitions,instructions outlining how to treat incomplete/missing data and location of data in the patient's file.

With regard to SCD diagnosis; sickling tests were conducted using sodium metabisulfite. This test method is a phenotypic procedure which methodically reduces the oxygen tension inducing the typical sickle shape of RCCs.[23] However, due to resource constraints in our setting, genotype confirmation was not conducted. Malaria infection was determined by malaria rapid diagnostic test which detects *Plasmodium falciparum* using Alere SD BIOLINE Malaria Ag P.f/Pan test, which is qualitative and differential test for the detection of antigen of *Plasmodium*.[24] Full blood counts analysis was conducted by Sysmex Hematology Analyzer (Sysmex XP-300 Automated Haematology Analyzer) which uses 50 µL on whole blood[25] (see online supplemental file 1).

Definitions

We applied the following definitions for the purpose of our analysis: vaso-occlusive episode was defined as a new episode of acute pain requiring hospitalisation which results from tissue ischaemia.[26] Acute chest syndrome was defined as acute respiratory illness with fever and/or respiratory symptoms such as cough, dyspnoea, tachypnoea or hypoxia requiring hospitalisation.[26] Dactylitis was defined as a new episode of acute pain and swelling in the fingers or toes due to vaso-occlusion and is usually associated with fever.[27] Priapism was defined as painful, persistent, unwanted erection of the penis.[26] Hepatic sequestration was defined as sequestration of RCCs in hepatic sinusoids, leading to liver enlargement and decreased Hb concentration.[26] Acute splenic sequestration was defined as rapid intrasplenic trapping of sickle cells, which causes a precipitous fall in Hb level and spleen enlargement.[26] Leg ulcers was defined as the ulceration of the skin of the legs with prolonged wound healing requiring medical attention for wound treatment, debridement or dressings.[26] Jaundice was defined as yellowish pigmentation of the skin and sclera[27] while Arthritis was defined as acute or chronic inflammation of a joint, often accompanied by pain, stiffness, warmth, swelling and redness.[26] Clinically, anaemia was defined as the presence of pallor conjunctivae, mucous membranes, nail beds and palms.[28] The laboratory definition of anaemia was acute lowering of the Hb level below normal reference ranges[27] while severe anaemia was defined as Hb level of less than 4 g/dL.[14] Sepsis was considered to be the presence of fever with a negative malaria parasite test, and/or raised WCC.[27]

Patient and public involvement

This study did not involve patients nor the public as it was a retrospective cross-sectional study and data were obtained from medical case files.

Data analysis

Data were entered in Microsoft excel 2016, validated and cleaned before importing into Stata, V.13.0 (StataCorp) for analysis. Descriptive statistics were performed to summarise patients' demographic, clinical and haematological characteristics. χ^2 or Fisher's exact test was performed to explore associations between predictor variables and outcome variables (case fatality and length of hospital stay). A χ^2 test was performed for all crosstabulations where the sample size (n) was greater than the number of cells multiplied by 5 and where the expected value in 80% of the contingency cells was greater than 5 and no cell had the expected value of less than 3. Where this condition was not met, a Fisher's exact test was performed instead. A p value of 0.05 or less was considered statistically significant. Only those predictor variables which had a statistically significant association with outcome variables (painful crisis, splenic sequestration and hepatic sequestration) were carried forward for analysis in a binary logistic regression and adjusted for, in a multivariable binary logistic regression. Length of hospital stay was dichotomised into ≤5 days and >5 days because children presenting with sepsis are often put on a 5-day course of parenteral antibiotics. These children

Table 1 Demographic characteristics of patients with SCD

Characteristic	Frequency (%)
Sex	
Male	298 (58.2)
Female	214 (41.8)
Age (months)	
<12	25 (4.9)
12–59	227 (44.3)
≥60	260 (50.8)
SCD History	
Known cases	444 (86.7)
Newly diagnosed cases	68 (13.3)
Age (months) for newly diagnosed cases during study period (n=68)	
<12	9 (13.2)
12–59	40 (58.8)
≥60	19 (27.9)
Length of hospital stay	
≤5 days	434 (84.8)
>5 days	78 (15.2)
Case fatality	7 (1.4)

Median age=60 months (IQR: 30.5–108 months); median length of stay=3 days (IQR: 2–5 days).

cannot be discharged from hospital before they complete their treatment course even if their condition improves substantially before day 5 that they qualify for discharge. Therefore, putting the cut point at day 5 took care of the prolonged hospital stay which was due to treatment

being received and allowed us to explore hospital stay which was purely due to the condition of the patient.

RESULTS

Of the 16 333 paediatric hospitalisations, 512 were SCD children, representing 3.1%. There were more males (58%) than females. Out of 512 patients, 68 (13.3%) were newly diagnosed SCD cases. Nine (13.2%) of these were diagnosed in infancy (before 12 months of life), while 19 (27.9%) after their fifth birthday. Seventy-eight children (15.2%) were hospitalised for more than 5 days. Seven children (1.4%) died (table 1).

The most recorded clinical features were anaemia (94.1%), sepsis (79.5%) and painful crisis (54.3%). Leg ulcers, priapism and dactylitis were the least common clinical features representing 0.6%, 1.0% and 0.6%, respectively. In addition, 68 (16.4%) patients had malaria, diagnosed using rapid diagnostic test (table 2).

Routine full blood counts showed that the mean Hb count was 6.4 g/dL (SD=1.9). Forty-four children had Hb concentration of <4 g/dL. The mean count for RCCs, WCCs and platelets were 2.4 (SD=0.6), 26.4 (SD=14.6) and 358.8 (SD=200.9), respectively (table 3). These parameters were compared against the normal reference limits of the haematology analyser (Sysmex XP 300).

There were no statistically significant associations between clinical features and case fatality. Significant associations were, however, observed between length of hospital stay and painful crisis (p=0.03), hepatic sequestration (p=0.01) and splenic sequestration (p=0.03) (table 4). In a univariable logistic regression patients with painful crisis, splenic and hepatic sequestration were 1.7,

Table 2 Common clinical features of patients with SCD

Clinical feature	<12 months (n=25) n (%)	12–59 months (n=227) n (%)	≥60 months (n=260) n (%)	Total (n=512) n (%)
Anaemia	23 (92.0)	212 (93.4)	247 (95.0)	482 (94.1)
Severe anaemia*	0 (0.0)	17 (8.6)	27 (12.0)	44 (9.9)
Sepsis	22 (88.0)	191 (84.1)	194 (74.6)	407 (79.5)
Painful crisis	12 (48.0)	89 (39.2)	177 (68.1)	278 (54.3)
Jaundice	11 (44.0)	62 (27.3)	106 (40.8)	179 (35.0)
Pneumonia	10 (40.0)	65 (28.6)	40 (15.4)	115 (22.5)
Acute chest syndrome	3 (12.0)	14 (6.2)	16 (6.2)	17 (6.6)
Arthritis	4 (16.0)	32 (14.1)	44 (16.9)	80 (15.6)
Splenic sequestration	3 (12.0)	30 (13.2)	27 (10.4)	60 (11.7)
Hepatic sequestration	3 (12.0)	18 (7.9)	21 (8.1)	42 (8.2)
Leg ulcers	0 (0.0)	1 (0.4)	2 (0.8)	3 (0.6)
Priapism (n/N (%)†	0/12 (0.0)	1/127 (0.8)	2/159 (1.3)	3/298 (1.0)
Dactylitis	3 (12.0)	0 (0.0)	0 (0.0)	3 (0.6)
Malaria (n/N(%)‡	0/23 (0.0%)	33/184 (17.9)	35/207 (16.1)	68/414 (16.4%)

*Severe anaemia (Hb level <4 g/dL).
†n/N is included where the symptom is applicable to males only.
‡n/N is included where not everyone was tested for malaria.

Table 3 Haematological parameters of SCD children admitted at MCH

Parameter (unit)	n	Mean (SD)	Median (IQR)	Range	Reference range
RCC (×10^{12}/L)	322	2.4 (0.8)		0.6–6.3	4–6
Hb (g/dL)	445	6.4 (1.9)		1.4–12	10.9–17.3
MCV (fL)	310	82.8 (10.3)		43.1–121.6	71–95
MCHC (g/dL)	303	33.2 (2.7)		22.3–51.0	33–36
WCC (×10^9/L)	407	–	23.5 (18.0–31.2)	2.7–145.4	4–10
Platelets (×10^9/L)	380	358.8 (200.9)		11–1424	122–330

One child had WCC of 338.6 and was excluded from the WCC analysis because was considered as an extreme outlier. Other conditions might have been responsible for such an elevated WCC. The mean for RCC, platelets and the median for WCC are all outside the reference ranges. Different n's for different FBC parameters are due to missing data.
MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Haemoglobin Concentration.
Hb, haemoglobin; RCC, red cell count; WCC, white cell count.

2.1 and 2.4 times, respectively, more likely to be hospitalised for more than 5 days than those without these complications. However, in multivariable analysis, only painful crisis (OR=1.7; 95% CI: 1.02- 2.86) was significantly associated with length of hospital stay (table 4).

DISCUSSION
Our study provides a description of paediatric SCD in Malawi. There has been relatively limited information about the spectrum of paediatric SCD in our setting when compared with information available from other African countries and beyond. Our study has established that SCD contributes a considerable proportion of paediatric admission in our setting. It has further revealed delayed SCD diagnosis, common clinical features (anaemia, sepsis, painful crisis) and low haematological parameters and case fatality rate in our study population.

Our study has revealed that, SCD contributed a significant proportion (3.1%) among the admitted children. These results are slightly higher compared with findings documented in Kuwait,Kenya, Sudan and Uganda where SCD contributed to about 0.6%, 0.8%, 1.5% and 0.7%, respectively.[12 29–31]

Findings from our study have further revealed that, only 13.2% of the patients were diagnosed with SCD during infancy, up to 58.8% between the ages of 12 and 59 months, and more than a quarter (26.5%) got diagnosed after their fifth birthday. These findings provide evidence of delayed diagnosis in Malawi. This is not surprising given that routine new-born screening programmes are non-existent. As a result, diagnosis is often made late and follow-up of suspected cases are rarely done.[5 32] There is no specific age for diagnosis of SCD in Malawi, a situation which is similar to other African countries.[33]

The case fatality of 1.4% in our study is slightly lower compared with previous studies conducted in Tanzania, Malawi, Kenya and Brazil which reported varied mortality frequencies of 1.9%, 3.8%, 4.5% and 7.4%, respectively.[32 34–36] However, our in-hospital mortality is more likely an underestimate of the total mortality from SCD as many children may have died at home before diagnosis of

SCD was made.[9] These results must, therefore, be interpreted with caution. A substantial proportion (15.2%) of the children had a prolonged hospital stay (>5 days) which is known to be associated with increased mortality and economic burden on the health system and families.[37]

In our study, anaemia was the most recorded clinical feature in patients with SCD followed by sepsis and painful crisis, representing 94.1%, 79.5% and 54.3%, respectively. These features were based on clinical presentation at the time of admission. However, the mean Hb of our patients was 6.4 g/dL, which was similar to those recorded in a steady state paediatric population in Nigeria (6.9 g/dL).[38 39] This suggests that, most of our hospitalised children had Hb levels that were normal for children with SCD. It is, therefore, not surprising to note that only 9.9% of the patients had severe anaemia (Hb <4 g/dL) requiring blood transfusion according to Malawian treatment guidelines.[14] This emphasises the need to verify clinical and subjective diagnoses of anaemia with laboratory investigation in patients with SCD so as to confirm the severity of anaemia and institute appropriate management for the patients.

Painful crisis was the third common clinical feature observed in our study, contrary to previous studies where it was the top most complication for children with SCD.[7 8 12] This could likely be as a result of positive efforts by the hospital in educating parents on the prevention of pain triggers at home which includes maintaining adequate oral hydration, avoiding strenuous exercises, keeping the child warm when it is cold but also to avoid getting too hot. These educational sessions are facility-based initiatives, which are conducted quarterly through a parent support group programme.

The frequency of leg ulcers (0.6%), priapism (1%) and dactylitis (0.6%) in our study was low which is consistent with previous studies conducted in Congo and Saudi Arabia.[10 40] The prevalence of leg ulcers and dactylitis is generally low in younger children.[41] In addition, the low frequency could be due to a small sample for this age group in our study. On the other hand, some studies indicate that the prevalence of priapism is usually low due

Table 4 Association between clinical features and case fatality, and length of hospital stay

| | Case fatality | | | Length of hospital stay | | | | |
Variable	Died n (%)	Discharged n (%)	P value*	≤5days n (%)	>5days n (%)	P value*	Unadjusted OR (95% CI)†	Adjusted OR (95% CI)†
Gender								
Male	4 (1.3)	294 (98.7)	(0.62)	248 (83.2)	50 (16.8)	0.25		
Female	3 (1.4)	211 (98.6)		186 (86.9)	28 (13.1)			
Age								
≤12	0 (0.0)	25 (100.0)	0.79	23 (92.0)	2 (8.)	0.58		
12–59	4 (1.8)	223 (98.2)		191 (84.1)	36 (15.9)			
≥60	3 (1.2)	257 (98.8)		220 (84.6)	40 (15.4)			
Anaemia								
Yes	7 (1.5)	475 (98.5)	0.65	410 (85.1)	72 (14.9)	0.45		
No	0 (0.0)	30 (100.0)		24 (80.0)	6 (20.0)			
Sepsis								
Yes	7 (1.7)	400 (98.3)	0.34	342 (84.0)	65 (16.0)	0.36		
No	0 (0.0)	105 (100.0)		92 (87.6)	13 (12.4)			
Painful crisis								
Yes	5 (1.8)	273 (98.2)	0.47	227 (81.60)	51 (18.4)	0.03	1.7 (1.04 to 2.85)	1.7 (1.02 to 2.86)
No (reference)	2 (0.9)	232 (99.1)		207 (88.5)	27 (11.5)		–	–
Hepatic sequestration								
Yes	1 (2.4)	41 (97.6)	0.45	30 (71.4)	12 (28.6)	0.01	2.4 (1.19 to 5.02)	1.9 (0.89 to 4.24)
No (reference)	6 (1.3)	464 (98.7)		404 (86.0)	66 (14.0)		–	–
Splenic sequestration								
Yes	1 (1.7)	59 (98.3)	0.58	45 (75.0)	15 (25.0)	0.03	2.1 (1.08 to 3.91)	1.9 (0.92 to 3.73)
No (reference)	6 (1.3)	446 (98.7)		389 (86.1)	63 (13.9)		–	–
Acute chest syndrome								
Yes	2 (5.9)	32 (94.1)	0.07	25 (73.5)	9 (26.5)	0.06		
No	5 (1.1)	473 (98.9)		409 (85.6)	69 (14.4)			
Pneumonia								
yes	1 (0.9)	114 (99.1)	1.00	96 (83.5)	19 (16.5)	0.66		
No	6 (1.5)	391 (98.5)		338 (85.1)	59 (14.9)			
Arthritis								
Yes	1 (1.3)	79 (98.7)	1.00	64 (80.0)	16 (20.0)	0.20		
No	6 (1.4)	426 (98.6)		370 (85.6)	62 (14.4)			

Table 4 Continued

| Case fatality | | | | Length of hospital stay | | | | |
Variable	Died n (%)	Discharged n (%)	P value*	≤5 days n (%)	>5 days n (%)	P value*	Unadjusted OR (95% CI)†	Adjusted OR (95% CI)†
Leg ulcer								
Yes	0 (0.0)	3 (100.0)	1.00	3 (100.0)	0 (0.0)	1.00*	1.00*	
No	7 (1.4)	502 (98.6)		431 (84.7)	78 (15.3)			
Malaria								
Yes	0 (0.0)	68 (100.0)	0.49	57 (83.8)	11 (16.2)	0.95		
No	4 (1.2)	342 (98.8)		291 (84.1)	55 (15.9)			

χ^2 or Fisher's exact test was performed to explore associations between predictor variables and outcome variables (case fatality and length of hospital stay). A p value of 0.05 or less was considered statistically significant. Only those predictor variables which had a statistically significant association with outcome variables (painful crisis, splenic sequestration and hepatic sequestration) were carried forward for analysis in a binary logistic regression and adjusted for, in a multivariable binary logistic r.
*Statistical testing by χ^2 or Fisher's exact.
†Binary logistic regression.

to lack of awareness by physicians and under-reporting by patients.[42] This could be true in this study given the young age of patients under the study.

Malaria was diagnosed in 68 (16.4%) patients. Unfortunately, our study does not have comparative data to determine how these findings compare with those in children without SCD. Nonetheless, our findings are relatively higher than previous studies conducted in Tanzania and Kenya which recorded 11.6% and 15.6%, respectively.[11 34] We are unable to determine the cause for such a high frequency because according to Malawian guidelines, all patients with SCD are given antimalaria prophylaxis (sulfadoxine pyrimethamine) every month.[14] This calls for more research to understand the role of the antimalaria prophylaxis in patients with SCD.

As expected, the mean for RCC, WCC and platelets were all outside the normal reference ranges. Previous studies observed similar findings[17 18] and this is attributed to chronic haemolysis, higher risk of infections and chronic pain in patients with SCD.[17]

We did not find any significant associations between case fatality and clinical features unlike previous studies which found significantly higher mortality in patients with infection.[43] The discrepancy may be due to the fact that there were very few events (deaths) in our study (see online supplemental file 2). On the other hand, our study found that painful crisis, splenic and hepatic sequestrations were the complications that lead to longer (>5 days) hospital stay. Another previous study also observed longer hospital stay for painful crisis.[44] In our setting, this might be as a result of inadequate use of clinical guidelines to manage these complications. Enforcing adherence to clinical guidelines may help in proper management of these complications which will ultimately lead to quick recovery.

Limitations and recommendations

Our study had some limitations. The most critical one being missing data as it was collected from clinical files. Due to lack of diagnostic capacity in our setting, some of the patients' diagnoses were often determined on clinical basis. In addition, the test which was conducted to diagnose SCD has a low specificity given that it cannot distinguish sickle cell trait from SCD. Furthermore, there is a possibility that some children may have been admitted more than once, but this may not critically affect the interpretation of our results given that the focus of this study was to understand the clinical presentation of all paediatric SCD hospitalisations.

Despite these limitations, our study has provided a description of the clinical picture of paediatric SCD in Malawi, highlighting the need for diagnostic newborn screening and SCD registries in Malawi. The authors further recommend the need for low-cost life-saving interventions for SCD management in low-resource settings. Although we have provided data that will inform policy regarding paediatric SCD in Malawi, the study has also highlighted areas for further research. We

propose that priority should be given to a study seeking to describe the management of hospitalised SCD children in order to identify gaps in the care process so that measures to improve survival and reduce hospital stay can be instituted.

CONCLUSION

SCD contributes a significant proportion in paediatric hospitalisations, with anaemia, sepsis and painful crisis being the most common clinical presentations of hospitalised children. Painful crisis was associated with longer hospital stay. Delayed diagnosis of SCD is a problem that needs immediate redress in this setting. Although the relatively low in-hospital mortality among SCD children is somewhat encouraging, this estimate may under-report the true mortality from the disease considering community deaths and deaths occurring before SCD diagnosis is made.

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Laboratory methods

Sickling Testing

Sickling test was conducted among patients suspected of having a sickle cell syndrome. The sickling tests were conducted using Sodium metabisulphite. The Sodium metabisulphite reduces the oxygen tension inducing the typical sickle-shape of red blood cells. This test uses fresh blood in any anticoagulant. To prepare regents for this method, 0.2 g of sodium metabisulphite in 10 ml of distilled water. Stir until dissolved. Prepare fresh each time. You normally, Mix 1 drop of blood with 1 drop of 2% sodium metabisulphite solution on a microscope slide. Then you cover with a cover slip and seal the edge with wax/vaseline mixture or with nail varnish. Allow to stand at room temperature for 1 to 4 hours. Thereafter, examine under a microscope with the dry objective. In positive samples, the typical sickle-shaped red blood cells will appear Occasionally the preparation may need to stand for up to 24 hours. In this case put the slides in a moist Petri dish. False negative results may be obtained if the metabilsulphite has deteriorated or if the cover slip is not sealed properly(23).

Malaria testing

Whole blood was used to do Malaria Rapid Diagnostic Test (MRDT) using The Alere SD BIOLINE Malaria Ag P.f/Pan test which is a rapid, qualitative and differential test for the detection of histidine-rich protein II (HRP-II) antigen of *Plasmodium falciparum* and common *Plasmodium* lactate dehydrogenase (pLDH) of *Plasmodium* species in human whole blood. It detects HRP2 Ag specific to *P. falciparum* and pLDH specific to *Plasmodium* species with a fast test result (15-30 minutes) and not beyond. This is a lateral flow technology with a very high sensitivity and specificity of 99.7% (P.f), 95.5% (non-P.f) 99.5% (251,252) respectively. Malawi has a high prevalence of *Plasmodium falciparum* and hence a need to use such a diagnostic tool(24).

FBC Analysis

FBC analysis was done by Syesmex Haematology analyser (Sysmex XP-300™ Automated Haematology Analyzer) which uses 50μL on whole blood. Using this analyser, WBCs, RBCs and PLTs were counted using the direct current detection method with coincidence correction. Automatic discriminators separate the cell populations based on complex algorithms. The intensity of the electronic pulse from each analysed cell was proportional to the cell volume. The haematocrit (HCT) was directly determined based on the red cell count and volume detection of each individual RBC. Even with samples at extremely low or

unusually high concentrations, the Sysmex cell counters analyse WBCs, RBCs and PLTs with uncompromised precision and accuracy(25).

LIST OF CASES T

Age (months)	Sex	Painful crisis	Anaemia	Jaundice	Pneumonia	
16	2	1	1	2	1	
44	2	2	1	2	2	
41	1	1	1	1	2	
60	1	1	1	2	2	
24	2	2	1	2	2	
96	1	1	1	2	2	
60	1	1	1	2	2	

NOTE: 1=Yes/Discharged/positive/Male
2= No/Died/negative/Female
3=Unknown

ΓHAT DIED

Acute Chest Syndrome	Sepsis	Convulsions	Coma	Stroke	Psychosis	
1	1	2	2	2	2	
2	1	2	2	2	2	
1	1	2	2	2	2	
2	1	2	2	2	2	
2	1	2	2	2	2	
2	1	2	2	2	2	
2	1	2	2	2	2	

Splenic sequestration	Hepatic sequestration	Leg ulcer	Arthritis	MRDT
2	2	2	2	2
2	2	2	2	2
2	1	2	2	2
2	2	2	2	2
2	2	2	2	3
2	2	2	1	2
1	2	2	2	2

WBC	HB	RBC	MCV	MCHC	PLATELETS	HIV status
						3
27.8	5.2				560	3
18.6	7.3	2.91	72.5	34.6	539	3
24	6.9	2.46	78.5	35.8	117	3
14.7	3.3	1.18	99.2	28.2	177	3
33	7.5	2.73	81.3	33.8	388	3
16.7	5.2	2.35	79.1	34.4	11	2

Length of hospital stay	Admission outcome
1	2
2	2
1	2
3	2
1	2
2	2
8	2