ORIGINAL ARTICLE

Prevalence and Clinical Characteristics of Acute Stroke among Children with Sickle Cell Disease Admitted to the University Teaching Hospitals-Children's Hospital: A Retrospective Study

Derby Tembo[1,2,4, ID], Uzima Chirwa[2, ID], Nfwama Kawatu[2, ID], Dalitso Ng'wane[3], Peter Kabemba[2], Catherine Chunda-Liyoka[2], Gretchen L. Birbeck[2,4,5, ID]

[1]*Chipata Central Hospital, Department. of Pediatrics and Child Health, Chipata, Zambia.*
[2]*University Teaching Hospitals-Children's Hospital, Lusaka, Zambia.*
[3]*Kitwe Teaching Hospital, Kitwe, Zambia.*
[4]*University Teaching Hospitals Neurology Research Office, Lusaka, Zambia.*
[5]*University of Rochester, Department of Neurology, Rochester, NY, USA.*

ABSTRACT

Background: Sickle cell disease (SCD) is a major public health concern, with Sub-Saharan Africa accounting for approximately 75% of the global burden. Approximately 10% of SCD patients experience symptomatic stroke within the first two decades of life. Epidemiological data on SCD-associated stroke in Zambia is limited.

Methods: This retrospective study reviewed records for 2022 calendar year of children with SCD, and acute stroke admitted to the University Teaching Hospitals-Children's Hospital (UTHs-CH) in Lusaka, Zambia. It aimed to identify cases, describe their demographic and clinical characteristics and assess inpatient mortality outcomes.

Results: Among 971 children admitted with SCD, 35 (3.6%) presented with acute strokes; 17 cases had complete records. Mean age at presentation was **7 years (**IQR: 3.8), 77% females. The average age at SCD diagnosis was 32 months (IQR: 31.5). Most patients (65%) were from Lusaka district, and 59% were caregiver-initiated admissions. Common stroke symptoms included: motor deficits 50%, seizures 24%, speech deficits 21% and headache 5%. Notably, 29% of patients did not receive blood transfusions, and among those transfused, 50% experienced >48-hour delays. Vaso-occlusive crises in the past year and prior strokes had occurred in 65 and 47%, respectively. Only 18% were on hydroxyurea. The inpatient mortality rate was 14%.

Corresponding author:
Derby Tembo
Private Bag RW 1X, Ridgeway, Lusaka, Zambia, Tele: +260974908880 Email: debby.tembo.uthnro@gmail.com

Keywords: Paediatric stroke, Sub-Saharan Africa**,** Sickle Cell Disease, Hydroxyurea, Zambia, Epidemiology.

This article is available online at: http://www.mjz.co.zm, http://ajol.info/index.php/mjz, doi: https://doi.org/10.55320/mjz.52.3.707

The Medical Journal of Zambia, ISSN 0047-651X, is published by the Zambia Medical Association

Conclusion: This study highlights a 3.6% prevalence of acute stroke among children with SCD admitted to UTHs-CH and identifies gaps in acute care, particularly delays in blood transfusions highlighting health system gaps. Future research should address barriers to timely intervention and optimize management protocols for SCD-associated strokes in Zambia.

INTRODUCTION

Sickle cell disease (SCD) is a haemoglobinopathy caused by the inheritance of two abnormal genes coding for the formation of haemoglobin (Hb), one of which must be haemoglobin S (HbS). This condition arises from a genetic mutation in the beta globin chain, leading to the formation of sickle-shaped red blood cells. The resultant pathophysiology is a shortened lifespan of sickle-red blood cells and a tendency to obstruct blood vessels, causing chronic endothelial dysfunction and end organ damage.

Globally, approximately 300,000 children are born with SCD annually, with sub-Saharan Africa (SSA) accounting for over 75% of cases.[1, 2] Without intervention, 50-90% of children in the region die before their fifth birthday.[1] There is limited data on the epidemiology of SCD in Africa, including Zambia due to various factors which include; inadequate newborn screening programs, underreporting of cases, lack of large epidemiological studies; many deaths occurring before diagnosis and many births occurring outside the hospital. Available data estimate a prevalence of SCD trait and SCD to be around 18% and 1-2% respectively, in Zambia.3

Children with SCD face a significant higher risk of stroke compared to the general population. It is estimated that 11% of individuals with SCD experience a clinically apparent stroke before the age of 20 year, and 10-30% develop silent strokes identifiable on imaging.[4] Studies in Africa have reported SCD stroke prevalence rates between 2.9-16.9%.[2] Among children with abnormal transcranial dopplers (TCDs), a Tanzanian study identified 43% prevalence of subclinical strokes.[5] SCD-related stroke has a high recurrence rate of 60-92%,[6] with a greatest risk during the two to three years after the initial stroke.[7, 8] A Nigerian study reported a recurrence rate of 17.4 events per person years of observation after the initial event.[9]

Stroke in SCD is attributed to ischaemic reperfusion injury and endothelial dysfunction and injury caused by adhesion of sickle cells to each other and to the vascular endothelium.[10] Stroke can lead to significant morbidity and mortality in the paediatric population with SCD, with increased socioeconomic burden on the health system for the acute care and rehabilitation.

Despite the significant concern regarding the burden of SCD-associated strokes, epidemiological data is lacking in Zambia. To better understand this knowledge gap and help inform a planned prospective study, we conducted a retrospective review of acute strokes in children with SCD admitted to UTHs- CH.

METHODS

This retrospective study reviewed medical records of children aged 1- 16 years old with SCD, who were admitted to the UTHs-CH in 2022 with acute stroke. The UTHs- children's hospital is the largest paediatric referral centre in Zambia, serving more than 6,000 registered patients with SCD as of 2019. The study aimed to identify acute stroke cases, describe their demographic and clinical characteristics including laboratory and neuroimaging findings, where available, and determine their inpatient mortality outcomes.

Definition of Stroke

Stroke was defined based on the diagnosis of stroke as given by the clinical team or by criteria adopted from prior research. An acute stroke was classified as a rapidly developing clinical syndrome of focal (or global in some cases) disturbances of cerebral function lasting more than 24 hours or leading to death, without an apparent cause other than a vascular origin based upon chart review.(11) Cases

were categorized as acute if stroke symptoms developed within 14 days before or during hospital admission. The lack of standardized stroke imaging protocols may have introduced the potential for clinical misclassification.

Case Identification and Data Collection

Potential cases were identified through a systematic review of admission and death registries for the 2022 calendar year. This period coincided with transcranial Doppler ultrasound screening for stroke risk in SCD patients admitted to the hospital. Efforts were made to locate inpatient records stored in the hospital archive. Since some families may have retained patient files, additional research was conducted at the Haematology Clinic to cross-check records for potential missed cases. In March- April 2024, a secondary review of outpatient records for SCD patients receiving care was conducted to identify any cases that should have been captured in the initial search.

To determine the total number of SCD admissions for prevalence calculations, hospital information management system (HIMS) data were obtained. HMIS records, compiled from ward admissions and updated by data clerks, included SCD diagnoses but did not specify secondary conditions like stroke.

Inclusion Criteria

Inpatient files from identified SCD admissions were reviewed. A case was included if it met the following criteria:

1. A confirmed diagnosis of SCD or documented history of SCD.
2. Age between 1 and 16 years.
3. A diagnosis of acute stroke was made during admission or documentation of stroke symptoms that developed within 14 days before admission.
4. Evidence of stroke in the absence of an alternative explanation.
5. A death certificate indicating SCD or stroke (e.g., hemiparesis) as a cause of death.

Data Extraction and Analysis

For identified acute SCD-associated stroke cases, data were extracted on:

1. Demographics: Age, gender, age at diagnosis of SCD, address of patient and referral clinic.
2. Past medical history including SCD- related complications in the past year.
3. Clinical findings: Neurological symptoms, comorbid conditions, relevant laboratory values (e.g. haemoglobin distribution).
4. Stroke- specific treatments: Blood transfusions, hydroxyurea use.
5. Neuroimaging findings: If available, brain imaging results were recorded.
6. Outcomes: Inpatient mortality and length of hospital stay.

A structured data abstraction tool was used to directly enter collected data into REDCap for analysis. Descriptive statistics were applied using Epi Info to estimate stroke prevalence among all SCD admissions, explore factors associated with mortality, and assess missing data patterns. Results are reported as mean or percentage values as appropriate.

Ethical approval

This study was approved by the University of Zambia Biomedical Research Ethics Committee (Ref: 4891-2024).

RESULTS

The HIMS records indicated a total of 1,872 admissions for SCD of unspecified age in 2022. Among all UTHs-CH admissions with SCD, 5.8% were under one year old, aligning with the HIMS-based estimate of 1,763 SCD admissions for children aged 1-16 years in 2022.

Our search strategy outcomes are outlined in figure 1 (Patient Flow Diagram). We identified five death records where SCD and stroke was listed as the cause. None of these cases survived long enough for

hospital admission (they were brought in dead or died during triage). Screening admission records presented challenges due to missing or incomplete data, approximately three months of haematology unit admission were missing entirely (i.e. admission books were misplaced).

Despite these challenges, we reviewed available records and identified 1,031 admissions where SCD was documented. Only 31 (3%) of these admissions explicitly noted stroke in the records. A separate screening of 132 outpatient records from Haematology outpatient Clinic in 2024 did not reveal additional admissions with stroke, which should have been captured in our initial search.

Among 17 available patient files for children with both SCD and stroke diagnoses on admission, 2/17 (11.8%) had a documented history of stroke symptoms prior to admission. These symptoms had occurred more than 14 days before admission, indicating an old stroke rather than an acute SCD crisis. Among 995 SCD admissions without documented stroke, 282 cases from the traced record identified two additional strokes where symptoms developed after admission.

Assuming that 5.8% of the 1,031 SCD admissions we identified in our search involved children under one year old, we estimate that 971 SCD admissions met our inclusion criteria. Additionally, 14 children had stroke diagnosis at admission but no corresponding file for review. Among these, 11.8% of stroke cases may have been misdiagnosed as chronic rather than acute. In total, we identified 35 acute strokes:

- 5 confirmed via death certificate.
- 15 with stroke recognized on admission and confirmed upon inpatient record review.
- 13 with stroke recognized at admission but lacking full inpatient records for review.
- 2 additional strokes identified during admission.

Assuming missingness of data was random, we estimate that 3.6% (35/971) of children with SCD admitted to UTHs-CH in 2022 experienced an acute stroke.

Demographic and clinical data for these patients are summarized in Table 1(Patient demographic and clinical characteristics). Among the 17 acute stroke cases with inpatient records available, the mean age was 7 years (IQR: 3.8), with 13 (77%) being female. The mean age at the initial SCD diagnosis was 32 months (IQR: 31.5). More than half (59%) were caregiver-initiated admissions, while 65% were from Lusaka district. The most frequently observed stroke symptoms were motor deficits 9/17 (50%), seizure 4/17 (24%), and speech deficits 3/17 (21%). Additionally, headaches were reported in 1/7 (5%) of cases.

Blood transfusions were not administered to 5/17 (29%) and were delayed beyond 48 hours after admission in 6/12 (50%). Vaso-occlusive crises and acute chest syndrome requiring admission occurred in the past year in 11/17 (65%) and 1/17 (6%), respectively. The history of a previous stroke was noted in 8/17 (47%). While 9/17 (53%) had been on hydroxyurea in the past year, only 18% were on it at the time of their stroke.

The overall inpatient mortality rate for SCD admissions was 14%. However, none of the children with stroke who survived to admission died. Risk factor evaluation was limited due to incomplete admission data.

DISCUSSION

This retrospective patient chart review has several limitations, primarily due to missing admission records and inpatient files that could not be traced for detailed reviews. The validity of our findings relies on the assumption that data loss was random. Despite these limitations, our initial, relatively low-cost exploratory study provides valuable insights into SCD-related stroke in Zambian children admitted to UTHs-CH. These findings can guide future research.

We estimate that 3.6% of SCD admissions to UTH-CH among children 1-16 years of age involved acute stroke. This prevalence aligns with the 2.9-16.9% range reported in a systematic review and meta- analysis of 10 cross-sectional studies on children with SCD in sub- Saharan Africa.[2] In this Zambian study, stroke prevalence was higher in females, like findings from Tanzania and Saudi-Arabia.[12, 13] However, a study from Cameroon and another in Uganda found no significant sex differences in SCD- associated stroke prevalence.[14, 15]

The mean age at stroke presentation in our study was 7 years (IQR: 3.8), comparable with findings from Nigeria and Uganda.[15, 16, 17] Most studies in SSA indicate that strokes are more common in SCD children within the first decade of life,[2] particularly between the ages 2 to 10 years.[8] Unlike North America and Europe where SCD-strokes are more commonly reported after the age of two.[4] However, studies in SSA have identified strokes in children younger than two years.[2] Our study also observed acute strokes in children under the age of 2, emphasizing the importance to including younger children in future research. The earlier stroke onset in SSA may be linked to delayed SCD diagnosis, as observed in our study where the mean age of SCD diagnosis was 32 months (IQR: 31.5). Additionally, African children with SCD are reported to develop cerebral vasculopathy at an earlier age, increasing their susceptibility to stroke.[18] Several other factors may contribute to acute strokes in young children with SCD in SSA. The increased burden of infection in the region may elevate the risk for SCD-associated stroke through increased blood viscosity, often linked to increased white cell count, fever and dehydration.[19] TCD velocities are influenced by the severity of anaemia, and high prevalence of severe anaemia and hypoxia in SSA, may also play a significant role in the pathogenesis of SCD-associated stroke.[20, 21, 22] Furthermore, nutritional deficiencies, such as inadequate folate levels, can contribute to low haemoglobin levels, further exacerbating stroke risk.[23]

Another critical challenge in many African healthcare systems is lack of routine stroke prevention programs, such as TCD screening, which leads to missed opportunities for timely intervention.[24] Routine TCD screening in children with SCD is an important tool for identifying those at high risk of stroke,[24] enabling timely intervention through preventive strategies such as regular blood transfusions or hydroxyurea therapy.[25] A recent regional study reported that approximately 17% of SCD children exhibited conditional risk in TCD examinations, indicative of increased stroke risk.[18, 26] Notably, about 36% of these children with conditional risk were under the age of four, suggesting that SCD-associated vasculopathy begins at an early age in this population.[18] This highlights the urgent need to implement and prioritize national TCD screening programs to enhance stroke prevention efforts in this vulnerable population. These measures are integral to reducing the burden of stroke in children with SCD.

Despite correct diagnoses of SCD and acute stroke symptoms at presentation, critical therapies such as blood transfusions were often delayed or not administered. Several barriers contribute to delays in blood transfusion for children with acute stroke in Zambia. Limited blood availability remains a significant challenge, as shortages in many African settings can prevent timely intervention.[27] Additionally, stroke symptoms in young children with SCD are often misinterpreted, leading to delays in diagnosis and treatment.[25] Frequent transfusions also increase the risk of alloimmunization and iron overload, making subsequent transfusions more difficult.[28] Furthermore, the absence of standardized emergency stroke protocols in Zambia exacerbates these challenges, as access to exchange transfusion or even simple transfusion is often delayed. In high-income countries such interventions are initiated promptly, with resultant good outcomes.[29]

These findings underscore the need for further studies that track “time in motion” to identify barriers to care. All deaths we identified occurred within 48 hours of hospital admission. However,

because this was a retrospective study, we could not determine whether these deaths were due to severe un-survivable strokes or preventable complications that could have been mitigated with earlier recognition and intervention. Prospective multi-site studies are needed to address these questions.

Limitations:

- Incomplete inpatient records: Some admission books were missing, and key haematology records were unavailable. This may have led to underreporting of cases.
- Single-site study: The study was conducted at UTHs-CH, and its findings may not be representative of the broader paediatric sickle cell disease population in Zambia. Multi-site studies would provide more comprehensive data.
- Potential confounding factors: The COVID-19 pandemic, a known risk factor for stroke, may have influenced the prevalence of acute strokes in children with sickle cell during the study period.(30)

CONCLUSION

This study reports a 3.6% prevalence of acute stroke among children with SCD admitted to UTHs-CH and a 14% inpatient mortality rate for SCD-associated stroke. Although stroke recognition at admission was adequate, delays in critical interventions, such as blood transfusions, were observed. Developing a national SCD registry and conducting prospective multi-site studies could generate more generalizable data, addressing existing gaps and strengthening the evidence base for informed decision making and interventions.

What is already known on this topic:

- Sickle cell disease significantly increases the risk of stroke in children.
- The prevalence of stroke in children with SCD varies widely across different regions.
- There is a lack of epidemiological data on SCD associated strokes in Zambia.

What this study adds:

- This study estimates a 3.6% prevalence of acute strokes among children with SCD admitted to UTHs-CH.
- Stroke-related mortality occurred early after presentation.
- The findings emphasize the need for improved acute care therapies for children with SCD and acute stroke.

Acknowledgement: We thank the management of UTHs- CH for supporting us in conducting this study.

Conflicts of interest: The authors declare no conflicts of interest.

Authors contribution:

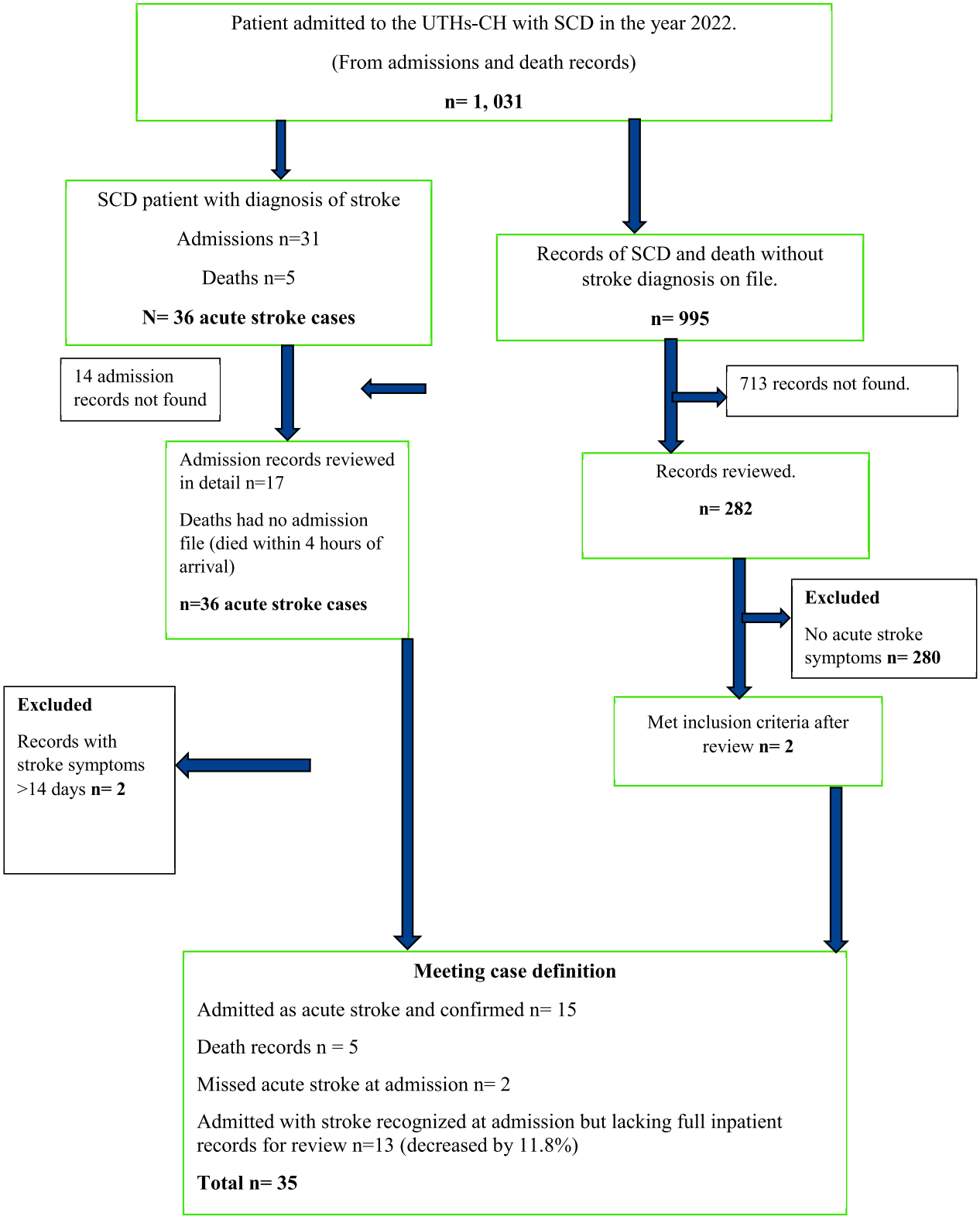
All authors contributed to the study design and preparation of the manual script.

Funding: This work was supported by a grant from the National Institute of Neurological Disorders and Stroke (R35NS122265). The content is solely the responsibility of the authors and does not necessarily represent that of the US National Institutes of Health.

Table 1: Demographic and Clinical Date for Children with SCD and Stroke whose Inpatient Records were available for review (n=17)

Patient characteristic	
Age at admission in years, mean (interquartile range)	7 (3.8)
Age in months at SCD diagnosis, mean (interquartile range)	32 (31.5)
Sex (Female), n (%)	13 (77)
Referral, (%) - Caregiver initiated - Hospitals within Lusaka district - Hospital outside Lusaka district	 10 (59) 2 (12) 5 (35)
Residence in Lusaka district, n (%)	11 (65)
Stroke symptoms, n (%) - Motor deficit - Seizure - Speech deficit - Headache	 9 (50) 4 (24) 3 (21) 1 (5)
Had a blood transfusion n (%)	n=12 (70.6)
Time to initial blood transfusion (n=12), n (%) - >48 hours - 24 to 48 hours - 12 to 24 hours - 6 to 12 hours - <6 hours	 6 (50) 2 (17) 1 (8) 1 (8) 2 (17)
History of vaso-occlusive crisis in past year, n (%)	11 (65)
History of acute chest syndrome in the last one year, n (%)	1 (6)
History of previous stroke, n (%)	8 (47)
History of treatment with hydroxyurea, n (%)	9 (53)
On hydroxyurea therapy at presentation, n (%)	3 (18)
Length of stay, n (%) - More than 7 days - 4 to 7 days - 1 to 3 days	 12 (70) 2 (18) 2 (12)
Haemoglobin concentration (g/dl)	7.6 (1.8)
White cell count (k/ul)	18.5 (8.2)
Platelet count (k/ul)	365 (147)

Figure 1: Patient Flow Diagram



ORCID iD

- Derby Tembo, orcid.org/0000-0001-5220-5735
- Uzima Chirwa, orcid.org/0000-0003-1872-6240
- Nfwama Kawatu, orcid.org/0000-0002-3056-673X
- Gretchen Birbeck, orcid.org/0000-0002-0735-3461

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