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Clinical Features and Outcome of Sickle Cell Patients in Pediatric Emergency Departments in Lubumbashi, Democratic Republic of Congo

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Authors' contributions

This work was carried out in collaboration among all authors. Author SNL designed the study, wrote the protocol, and wrote the first draft of the manuscript in French. Authors JNM and ANN managed the study's analyses, performed statistical analysis, and reviewed the manuscript. Author DMB Translated, revised, and edited the manuscript into English. Authors AYA, JMK, and TK writing – review & editing. Author DAD is writing and reviewing the first draft, conceptualization, and editing. The author, PBM, managed the literature searches, conceptualization, writing, reviewing, and editing. Author SWO conceptualization, supervision, reviewing, and editing. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To describe the epidemiology clinical outcome, and therapeutic aspects of sickle cell patients admitted to pediatric emergency departments, and to identify the risk factors associated with the clinical outcome.
Study Design: Descriptive cross-sectional study.
Place and Duration of Study: University of Lubumbashi teaching hospital, pediatric emergency departments and Jason Sendwe Referral Hospital from 10 February 2020 to 30 April 2022.
Methodology: 105 children with sickle cell disease aged 6 months to 16 years were admitted and recruited in the study. The Kaplan-Meier method was used to analyze survival to D22, the log-rank test to compare survival curves, and Cox regression to identify mortality risk factors, at a significance level of $p < 0.05$.
Results: The main reasons for admission were infection (83.8%), hyperalgesic vasoocclusive crisis (73.3%) and severe anemia (36.2%). According to the Adegoke severity score, 60% of the children had a severe clinical profile, 32.4% were moderate and 7.6% were mild. Median survival was 5.9 days. Survival decreased from 80% on day 2 to 67.6% on day 22. Survival was significantly shorter for moderate and severe clinical profiles (P = 0.001), transfer from a peripheral hospital (P = 0.006), and diagnosis of an infectious syndrome (P = 0.002). The critical period was the first 2 days of hospitalization, with a mortality rate at 20% compared with an all-cause mortality rate at 12.4%. In the adjusted multivariate analyses, death risk factors were transfer (P=0.04), severe clinical profile (P=0.033), hospital stay >2 days (P=0.04), infectious syndrome (P=0.01) and suspected hepatocellular failure (P=0.009).
Conclusion: Sickle cell morbidity and mortality in Lubumbashi are high and associated with mostly controllable risk factors. The prognosis for sickle cell disease can be improved by training health workers in sickle cell disease and by better organizing specific care at all levels of the health pyramid.

Keywords: Epidemioclinic; survival factors; sickle cell disease; pediatric emergencies.

1. INTRODUCTION

Sickle cell anemia is the most common hereditary disease in the world [1]. It is caused by a mutation at position 6 of the gene encoding hemoglobin. This leads to the substitution of valine by glutamic acid in the molecular structure of the ß-globin subunit, resulting in the production of hemoglobin S [2]. The polymerization of hemoglobin S is the starting point of a cascade of biological events that, from the first months of life, lead to acute and chronic complications with a high vital and/or functional risk [3–5]. In northern countries, the establishment of reference centres for sickle cell disease over the last few years has enabled the organization of sickle cell care and the development of research programs that have shed light on the natural history of sickle cell disease. This has led to the development of treatment strategies, including neonatal screening, which have undeniably reduced the negative impact of complications on the survival of sickle cell patients. In fact, the life expectancy of people with sickle cell disease has increased from around 10 years in 1972 to over 50 years in

2022 [6]. In sub-Saharan Africa in general and in the Democratic Republic of Congo in particular, the situation remains worrying, as the disease is still associated with severe morbidity and very high mortality [7–9]. The health context is characterized by failing health systems, with almost all indicators of access to care in red. There is a chronic shortage of health workers and very little basic training in sickle cell disease [10]. However, efforts are being made to improve care, including the establishment of hematopoietic stem cell transplant centres in countries such as Nigeria and Tanzania [11,12]. In the Democratic Republic of Congo, despite the high incidence of the disease and its morbidity, which is characterized by a severe form associated with a high mortality rate of up to 50% before the age of 5, there is a lack of comprehensive care for patients and no prevention policy has been implemented. In addition, access to essential treatments such as hydroxyurea, morphine analgesics, and labile blood products is difficult [13–16]. However, in pediatrics, there is little research on sickle cell emergencies and the factors associated with their development. The aim of this study was to describe the epidemiology, clinical outcome, and therapeutic aspects of sickle cell patients presenting with a sickle cell complication in the pediatric emergency departments of the main referral hospitals in Lubumbashi, as well as identify risk factors associated with poor outcome.

2. MATERIALS AND METHODS

This was a descriptive cross-sectional study conducted in the pediatric emergency departments of the University of Lubumbashi Teaching Hospital and Jason Sendwe Provincial Referral General Hospital from February 10, 2020, to April 30, 2022. Children aged 6 months to 16 years admitted for sickle cell disease, confirmed by the Sickle Scan® rapid diagnostic test, were included in this study.

2.1 Sample Size Calculation

Non-probability and convenience sampling with a single entry were used. The study sample consisted of 105 patients with sickle cell disease. The minimum sample size for meaningful results was calculated using the following formula:

$$n = \frac{z^2 x\, p(1-p)}{\varepsilon^2}$$

Where:

n = minimum sample size
z2 = 1.96 (standard normal deviation of the statistical significance level),
p : hospital prevalence of sickle cell disease (6%)
Ɛ: margin of error (95% confidence level and 5% margin of error).

In the literature available at the time of research protocol development, a hospital prevalence of sickle cell anaemia of 2.3% was observed in a study conducted in Kindu, North Kivu [17], while a Pierre Fabre Foundation advocacy document in favour of the Monkole Centre referred to a prevalence of 6% [18]. Thus, for the two prevalences, we obtained minimum sample sizes of 35 and 86.68 (i.e. 87 individuals), respectively. To obtain the 105 patients included, we used the larger sample, to which we added 20% of the necessary individuals (18 patients).

2.2 Data Collection

2.2.1 Sociodemographic and clinical data

A semi-closed questionnaire was used to collect anamnestic data from the patients' relatives, followed by data from the physical examination. Each data collection form had a patient identification code. The following data were collected:

- Sociodemographic data : age, sex and place of origin
- Clinical anamnestic data : major antecedents (number of transfusions/year, hospitalisations/year, severe CVO/year, hip, hepatobiliary, neurological or renal complications), use of hydrea, specific vaccinations, antibiotic prophylaxis and folic acid.)

Medical records were kept of where the patients came from, the reasons for their consultations, the diagnoses made, the treatments administered, the patient's progress or outcome, and the length of hospitalisation.

2.2.2 Biological data

2.2.2.1 Blood sample collection

Blood samples were collected by a team of trained physicians and nurses. Using a Vacutainer needle, four milliliters of blood were collected via phlebotomy into tubes containing

ethylenediaminetetraacetic acid (EDTA). The sample was transported to the analysis laboratory in an Elite Bags insulated bag, certified UN3373 for the transport of biological material, or stored in a cool place at 4°C for less than 72 hours after collection before being sent to the laboratory. The patient identification code was written on both the EDTA tube and the test request form.

2.2.2.2 Analytical techniques

2.2.2.2.1 Hematological analyses

Haematological parameters were obtained using the CYANHemato® automatic analyzer in accordance with standard procedures and reference values with in-house quality control. This instrument employs the "Coulter" method, which involves counting the cells passing through an aperture and measuring the hemoglobin content of the red blood cells by photometry. It analyses 20 haematological parameters using 25 µl of whole blood: WBC total white blood cell count, LYM lymphocyte count, MON monocyte count, GRA granulocyte count, LYM % lymphocyte percentage, MON % monocyte percentage, GRA % granulocyte percentage, HB haemoglobin, GR erythrocyte count, H haematocrit, CMV mean corpuscular volume, TCMH mean corpuscular haemoglobin content, MCHC mean corpuscular haemoglobin concentration, IDR erythrocyte distribution index, PLT platelet count, THT thrombocrit, VMP mean platelet volume, PDI platelet distribution index, P-LCC platelet count, P-LCR platelet ratio. For each sample, an analysis report was generated and included with the result sent by the laboratory.

2.2.2.2.2 Chemistry analyses

Chemistry analyses were performed using the Selectra ProM® multiparameter analyzer. This instrument performs analyses of clinical biochemistry, specific proteins, electrolytes, etc. It operates in automatic wavelength selection mode, as well as mono-, bi-, and tri-reactive analysis modes. Its measurements are in kinetics with linearity control, but also in bichromatic endpoint. It has been used to measure transaminases, LDH, CRP, creatinine, and urea.

2.3 Definition of Terms

2.3.1 The patient's clinical profile

A patient's clinical profile is a classification that determines the severity of sickle cell disease. It is determined by the Adegoke method [19] (Fig. 1). This method uses 15 parameters to assess the patient's condition over the last 12 months and lifetime complications. Each item was given a score between 0 and 5. The total score is the sum of the scores for each item and ranges from 0 to 34. This allowed three categories of disease severity to be distinguished: mild (total score < 8), moderate (8-17) and severe (>17).

The Adekoge method uses clinical and laboratory parameters to assess the severity of sickle cell disease. These parameters look at the child's current condition, the frequency of severe pain episodes, blood transfusions, and hospitalizations over the last 12 months, and the cumulative incidence of complications over a lifetime.

2.3.2 True emergency

An emergency was considered 'true' if the patient's situation required immediate care [20]. In fact, the initial functional and lesional assessment made it possible to identify those patients who showed signs of deterioration in their general condition (fever with temperature above 38°C, disorders of consciousness, deterioration in respiratory function, shock, severe pain from the outset, etc.) or who were referred with a severe, painful Vaso occlusive crisis, in a state of acute worsening anemia, or with a history of blood transfusion during the current episode.

2.3.3 Microcytosis

The mean corpuscular volume (MCV) was used to determine whether or not each patient had microcytosis. In fact, microcytosis was determined according to the age of each patient, following the reference values maintained by the French National Agency for Health Accreditation and Evaluation [21]. Therefore, microcytosis was present in the following case:

- Age <2 years: MCV <70 fl
- Age ≥ 2 years and < 6 years: MCV <73 fl
- Age ≥ 6 years and < 14 years: MCV <80 fl
- Age ≥ 14 years: MCV <83 fl

2.3.4 Suspicion of hepatocellular failure

Suspicion of hepatocellular failure was based on severe asthenia, jaundice, hypouricemia, severe thrombocytopenia (<100000/mm3) and a marked increase in transaminases.

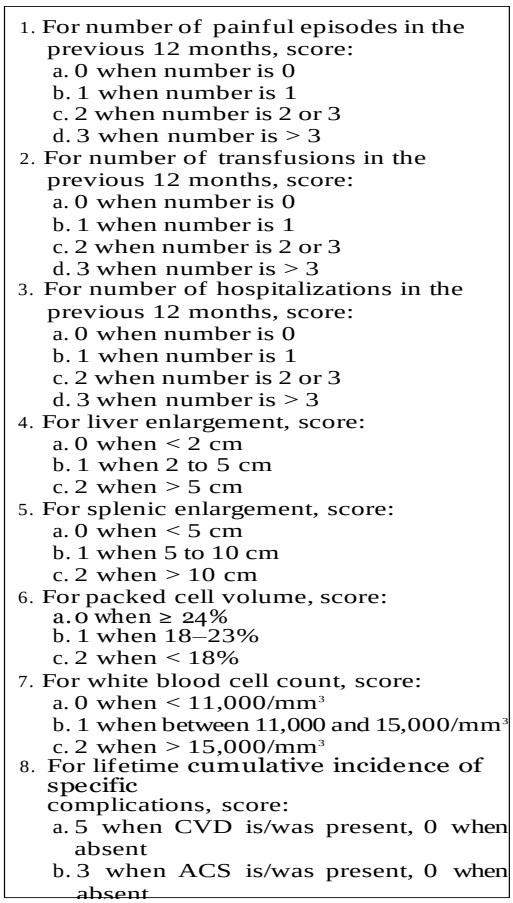
1. For number of painful episodes in the previous 12 months, score:
   a. 0 when number is 0
   b. 1 when number is 1
   c. 2 when number is 2 or 3
   d. 3 when number is > 3
2. For number of transfusions in the previous 12 months, score:
   a. 0 when number is 0
   b. 1 when number is 1
   c. 2 when number is 2 or 3
   d. 3 when number is > 3
3. For number of hospitalizations in the previous 12 months, score:
   a. 0 when number is 0
   b. 1 when number is 1
   c. 2 when number is 2 or 3
   d. 3 when number is > 3
4. For liver enlargement, score:
   a. 0 when < 2 cm
   b. 1 when 2 to 5 cm
   c. 2 when > 5 cm
5. For splenic enlargement, score:
   a. 0 when < 5 cm
   b. 1 when 5 to 10 cm
   c. 2 when > 10 cm
6. For packed cell volume, score:
   a. 0 when ≥ 24%
   b. 1 when 18–23%
   c. 2 when < 18%
7. For white blood cell count, score:
   a. 0 when < 11,000/mm³
   b. 1 when between 11,000 and 15,000/mm³
   c. 2 when > 15,000/mm³
8. For lifetime cumulative incidence of specific complications, score:
   a. 5 when CVD is/was present, 0 when absent
   b. 3 when ACS is/was present, 0 when absent

Fig. 1. Sickle Celle Anemia Scoring System

2.4 Data Processing and Analysis

Data were compiled in a database using Excel 2016 and analyses were performed using SPSS for Windows version 26. Descriptive statistics were presented as mean (plus or minus standard deviation) for continuous variables with a normal distribution and median (IQR: interquartile range) for continuous data with a non-Gaussian distribution. The normality test (Kolmogorov-Smirnov or Shapiro-Wilk) was used to distinguish between normally and non-normally distributed quantitative variables. Absolute (n) and relative (%) frequencies were reported for categorical variables. Several tests were used to compare between groups: the student's t-test and ANOVA (normally distributed quantitative variables) to compare two means; Mann-Whitney U test and H Kruskall Wallis (non-normally distributed variables); Chi-square test or Fisher's exact test for categorical (qualitative) variables. The Kaplan-Meier method was used to describe survival or death in the study population. The log-rank test was used to compare survival curves. Patients discharged at the request of the family were left-censored. The proportional hazards model (Cox regression) was used to investigate independent risk factors for mortality in children with sickle cell disease. For all these tests, a significance level of $p < 0.05$ was maintained. All patients discharged against medical advice were censored to the left (i.e. towards death).

3. RESULTS

3.1 The study's recruitment and demographic characteristics of patients

Of 2036 admissions during the study period, 219 were clinically suggestive of sickle cell disease (SCD) and 1817 were not suggestive of SCD. Of the 219 potentially eligible patients, 32 were AS and 187 were SS homozygous. Of these, 18 did not agree to participate in the study, and 44 were readmissions (Fig. 1). Males predominated (54.3%), with a sex ratio of 1.18. The age group 6-13 years was the most represented, with 40%. The patient itinerary showed that 41% of patients were transferred from another health facility (Table 1).

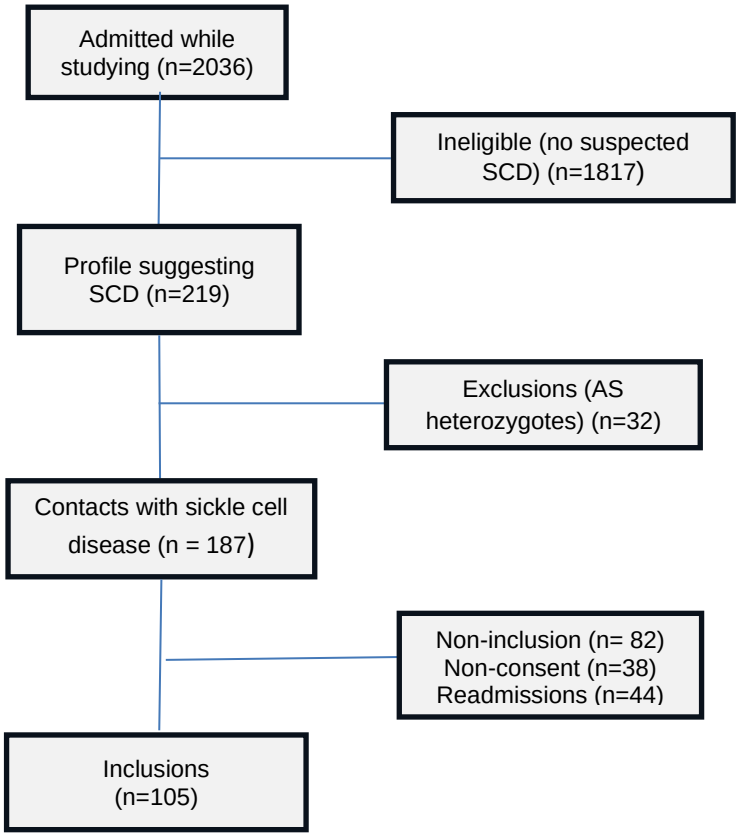

Fig. 2. Flow chart of patient enrolment

Table 1. Sociodemographic characteristics

Variables	Headcount (n=105)	Percent
Age		
< 2 years (from 6 months)	17	16,2
2-5 years old	37	35,2
6-13 years old	42	40,0
14-16 years old	9	8,6
Gender		
Male	57	54,3
Female	48	45,7
Patient Itinerary		
From home	62	59,0
Transferred	43	41,0

Of the 2036 admissions collected at the two sites during the study period, 219 had profiles suggestive of sickle cell disease, and 1817 were not suggestive of SCD. Of the 219 potentially eligible patients, 32 were AS and 187 were SS homozygous. Of these, 18 did not agree to participate in the study, and 44 were readmissions.

3.2 The Patient's Main Clinical Features and Basic Management

According to the Adegoke severity score, 60% of the children had a severe clinical profile, 32.4% had a moderate clinical profile, and 7.6% had a mild clinical profile. The mean severity score was 8.8±3.8 with extremes ranging from 2 to 19 (Fig.

3). As part of the basic management and background treatment of patients, 92.4% of patients did not receive hydroxyurea, and infection prevention was not ensured as 99% of patients had never received specific vaccinations and 82.9% did not have access to oral penicillin antibiotic prophylaxis. Only 39% of patients took folic acid regularly (Table 2). Pain (32.2%), fever (25.9%), pallor (15.9%), cough (5.0%) and unconsciousness (4.2%) were the main reasons for consultation in children with sickle cell disease (Table 3). Among the causes of admission, infectious syndrome was the most common, with a frequency of 83.8%, followed by hyperalgesic CVO (73.3%), worsening anaemia (36.2%), suspected hepatocellular failure (10.5%) and stroke (5.7%). The most common infections were pneumonia (30.7%) and malaria (23.9%), followed by meningitis (11.4%) and urinary tract infections (11.4%). The most described topographies in hyperalgesic VOC cases were osteoarticular (43.4%) and generalized (31.3%) (Table 4).

According to the results of the sickle cell disease severity score, most patients had a severe (60%) or moderate (32.4%) clinical profile. Only 7.6% had a mild profile.

3.3 The Most Important Biological characteristics of the Patients in the Study

3.3.1 Biological characteristics according to disease clinical profile

According to the results of the biological workup, the mean hematocrit value was significantly lower in patients with severe disease (*P*=0.047). Conversely, mean white blood cell (WBC) (*P*=0.01) and lactate dehydrogenase (LDH) (*P*=0.01) values were significantly higher in patients with a severe clinical profile (Table 5).

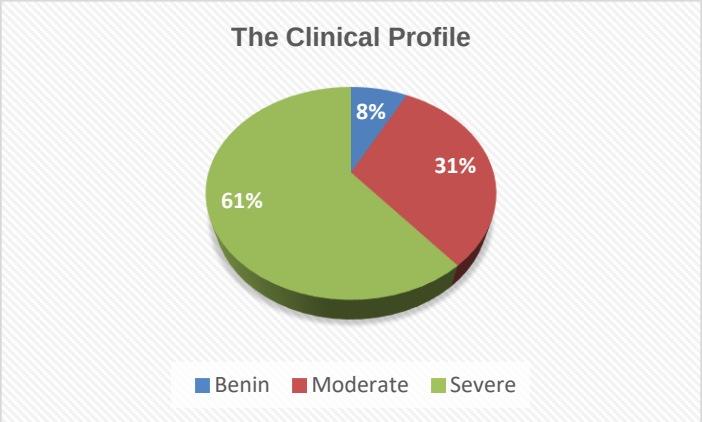

Fig. 3. The distribution of patients according to their clinical profile, as determined by the Adegoke score

Table 2. Patients' basic and primary care

Variables	Headcount (n=105)	Percent
Regular hydroxyurea intake		
No	97	92,4
Yes	8	7,6
Penicillin therapy		
No	87	82,9
Yes	18	17,1
Specific vaccination		
No	104	99,0
Yes	1	1,0
Regular intake of folic acid		
No	64	61,0
Yes	41	39,0

Table 3. The main reasons for the consultation

Reasons for consultation	Frequency	Percent
Pains	77	32,2
fever	62	25,9
Paleness	38	15,9
Coughing	12	5,0
Unconsciousness	7	4,2
Difficulty breathing	7	2,9
jaundice	5	2,9
Convulsions	4	2,1
vomiting	4	2,1
swelling of the feet and hands	10	1,7
diarrhoea	3	1,7
very dark urine	5	1,3
tiredness	2	0,8
lameness	1	0,8
Swelling of the head	2	0,4

Table 4. Children by admission cause

Admission cause	Headcount (n=105)	Percent
Infectious syndromes	88	83,8
Type of infection (n=88)		
Pneumonia	27	30,7
Malaria	21	23,9
Meningitis	10	11,4
Urinary tract infection	10	11,4
Sepsis	6	6,8
Osteomyelitis	4	4,6
Unspecified infections	10	11,4
Hyperalgesic vasoocclusive crisis	77	73,3
Topography		
Cerebral	6	7,2
Thoracic	4	4,8
Abdominal	11	13,3
Osteoarticular	36	43,4
General	26	31,3
Severe anemia	38	36,2
Suspicion of hepatocellular insufficiency	11	10,5
Stroke	6	5,7
Renal insufficiency	4	3,8
Acute chest syndrome	3	2,9
Femoral head osteonecrosis	1	1 ,0

Table 5. Patients' biological characteristics according to the disease's clinical profile

Variable	Total n=105	Benin n=8	Moderate n=34	Severe n=63	*P*
Hb g/dl	7,2±1,9	8,0±2,7	7,7±1,4	6,8±2,0	0,05
H (%)	22,9±7,7	25,7±9,3	25,1±6,3	21,4±8,0	**0,047**
MCV fl	75,7±10,1	73,6±7,7	76,1±7,7	75,8±11,6	0,82
MCHC	32,5±5,5	32,1±3,4	31,1±3,7	33,3±6,4	0,19
WBC x10^3/mm^3	14,7(13,5-16,5)	9,0(5,5-14,5)	12,7(7,8-16,0)	16,5(14,7-20,0)	**0,01**
LRP x10^3/mm^3	246(223-307)	308(97-410)	247(194-340)	239(218-331)	0,61
LDH IU/L	764(671-867)	857(443-1408)	641(563-760)	867(761-967)	**0,01**
AST IU/L	61,4(56,4-74,6)	45,4(40,0-128,0)	59,4(42,0-82,1)	64,5(57,0-81,6)	0,51

Variable	Total n=105	Benin n=8	Moderate n=34	Severe n=63	*P*
ALT IU/L	57,1(49,7-67,0)	51,4(45,1-61,3)	56,1(44,5-70,0)	59,0(48,7-70,0)	0,47
Creatinine mg/dl	0,47(0,40-0,50)	0,31(0,20-0,57)	0,39(0,27-0,49)	0,49(0,45-0,53)	0,29
Uremia mg/dl	16,0(14,6-18,0)	19,4(12,4-25,7)	16,9(14,3-21,3)	16,0(14,5-18,0)	0,97
CRP mg/dl	68,2(47,8-86,7)	30,8(16,5-47,8)	65,3(27,1-99,6)	76,0(54,7-96,0)	0,28

Hb: Hemoglobin, H: Hematocrit, MCV: Mean corpuscular volume, MCHC: Mean corpuscular haemoglobin concentration, WBC: White blood cell, LRP: Platelets, LDH: lactodehydrogenase, AST: Aspartate-Aminotransferase, ALT: Alanine-Aminotransferase

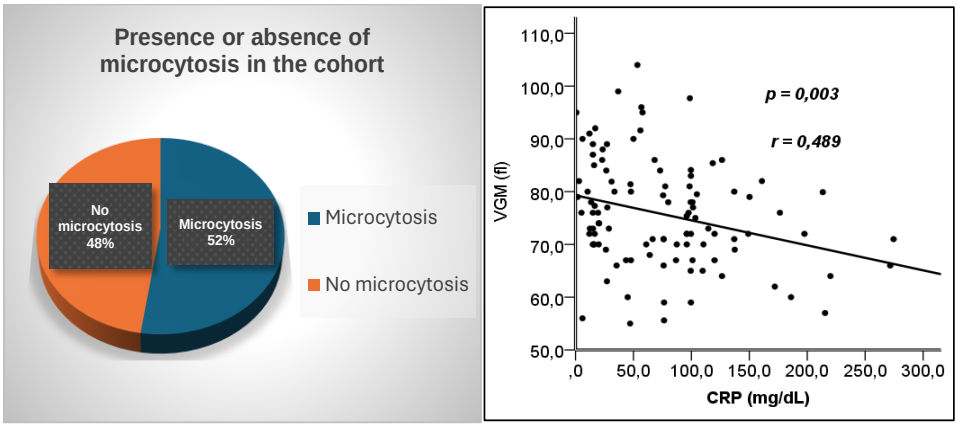

Fig. 4. shows the frequency of microcytosis in the study population.
In sickle cell patients, anemia is typically normocytic and normochromic. The presence of microcytosis in more than half of the patients highlighted the need for further analysis.

3.3.2 Analyzing the microcytosis observed in the cohort.

It was found that more than half of the sickle cell children included in the study had microcytosis, with a frequency of 52.4% (Fig. 4A). A simple linear correlation was found between MCV and CRP (Fig. 4B). This correlation was negative and statistically significant (p=0.003). This means that the increase in CRP significantly explains 49% of the reduction in MCV in patients (r = 0.489). In other words, 49% of the microcytosis is due to the infectious/inflammatory syndrome.

3.4 Study of Survival of Children with Sickle Cell Disease in Pediatric Emergency Departments

3.4.1 Length of hospital stay and Vital outcomes.

The median length of hospital stay was 6 days, with extremes of 0 and 22 days. The majority of children spent between 7 and 13 days in the hospital (Table 6). The mortality rate observed during the study was 12.4%. All patients discharged against medical advice were censored to the left (i.e. to death). More patients had a good outcome (67.6%) (Table 6).

Table 6. Children hospitalized according to length of stay.

Length of stay in hospital	Headcount	Percent
0-2 days	24	22,9
3-6 days	33	31,4
7-13 days	37	35,2
14-20 days	7	6,7
≥21 days	4	3,8
Total	105	100,0

Table 7. Classification of patients according to their vital outcomes

Outcomes	Headcount	Percent
Deaths	13	12,4
Survived	71	67,6
Discharged against medical advice	21	20,0
Total	105	100,0

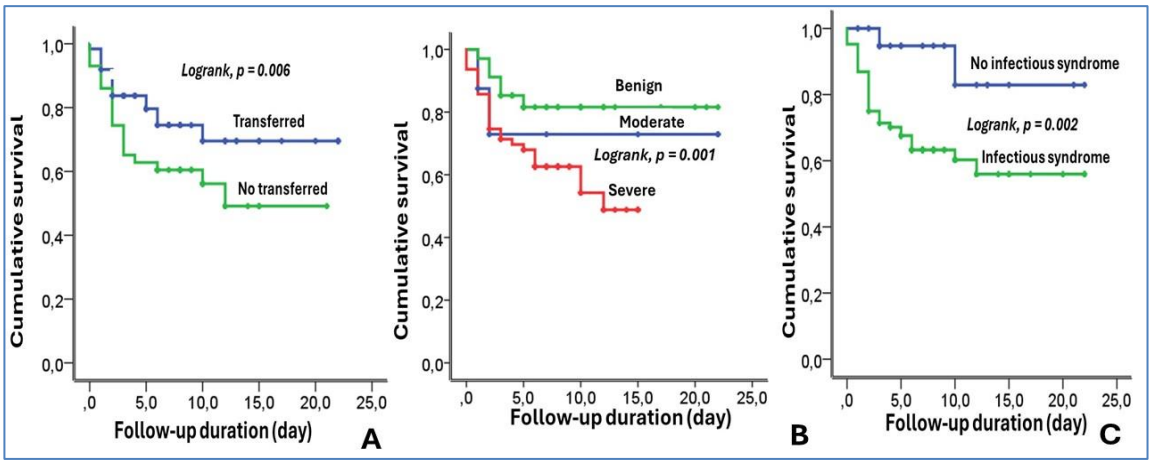

Fig. 5. Cumulative proportions of surviving patients (Kaplan-Meier) by origin, clinical profile, and infectious syndrome

Referral from peripheral care structures, severe clinical profile and diagnosis of an infectious syndrome significantly influenced patient survival.

Table 8. Factors Predictive of Mortality in Patients: Univariate and Multivariate Analysis Using Cox's Regression

Variables	Univariate Analysis		Mulitivariate Analysis	
	P	HR (IC95%)	*P*	HRa (IC95%)
Transfer				
None		1		1
Yes	0,008	2,83(1,30-3,61)	0,04	2,41(1,68-2,95)
Hospitalisation				
≤2		1		1
>2	0,002	1,395(1,13-1,73)	0,04	1,72(1,08-2,72)
Severe anemia				
None		1		1
Yes	0,007	2,84(1,94-3,63)	0,67	1,10(0,70-1,75)
Infectious syndrome				
None		1		1
Yes	0,04	4,42(2,05-8,69)	0,01	3,18(1,69-4,70)
Susp hepatocellular insufficiency				
None		1		1
Yes	0,001	4,94(2,31-10,59)	0,009	3,27(2,34-7,98)
Clinical profile				
Mild		1		1
Moderate	0,57	1,63(0,13-3,11)	0,22	1,33(0,59-1,90)
Severe	0,02	3,60(1,38-6,77)	0,03	3,40(2,06-5,53)

3.4.3 Survival rate of patients

The median survival time for children with sickle cell disease was 6 days. Survival varied according to the length of the hospital stay. At two, seven, and 14 days, it was 80%, 70.5% and 67.6% respectively; it remained at 67.6% until the 22nd day of hospitalization of the last child. The critical period was the first 2 days of hospitalization, with a mortality rate of 20%. This survival was also influenced by the patient's origin at admission, the clinical profile, and whether or not an infectious syndrome had been diagnosed. The median survival of patients admitted from home was 11 [9-14] days, whereas that of patients transferred from other care structures was 5.5 [5-7] days. Trans-in patients had a significantly shorter survival (*P* = 0.006) compared to those admitted from home (Fig. 5A). Depending on the clinical profile, survival was significantly (*P*=0.001) shorter in patients with moderate and severe profiles (Fig. 5B). Similarly, survival was significantly (*P*=0.002) shorter in patients with an infectious syndrome (Fig. 5C).

3.4.4 Predictive factors for mortality

In univariate analysis, transfer in, length of hospital stay >2 days, severe anemia, infectious syndrome, suspicion of hepatocellular failure, and severe clinical profile were predictors of mortality in sickle cell patients. After adjustment, multivariate analysis showed that transfer [(HRa: 2.41; IC95%: 1.68-2.95); *P* = 0.036], number of hospitalizations >2 [(HRa: 1.72; IC95%: 1.08-2.72); *P* = 0.042], infectious syndrome [(HRa: 3.18; IC95% : 1.69-4.70); *P* = 0. 014], severe clinical profile [(HRa: 3.40; IC95%: 2.06-5.53); *P* = 0.033] and hepatocellular failure [HRa: 3.27; IC95%: 2.34-7.98); *P* = 0.009] were independently and significantly associated with the risk of death in sickle cell patients (Table 8).

4. DISCUSSION

The aim of this study was to evaluate the epidemiology, clinical outcome, and therapeutic aspects of sickle cell disease patients admitted to pediatric emergency departments in two hospitals in Lubumbashi and identify factors associated with poor outcome. In terms of epidemiology and clinical aspects, this cohort study included sickle cell patients with a median age of 5.9 years (IQR: 2.9 - 8.8 years) with a slight male predominance (54.3%). This male predominance in admissions has been reported by other authors in North Kivu, DRC (17), Ghana [22] and Saudi Arabia [23,24]. The male predominance in critically ill children is thought to be due to genetics and rheological disorders. Genetic variation in the production of F-cells has been shown to allow female sickle cell patients to have more HbF than their male counterparts [25,26]. In addition, HbF levels are associated with the clinical severity of sickle cell disease, according to two studies conducted in the Democratic Republic of the Congo [27–29]. A Nigerian study also found a significant inverse correlation between sickle cell disease severity and HbF levels. Sickle-cell children with moderate disease had significantly lower mean fetal hemoglobin levels than those with mild disease (7.7 ± 5.6% versus 10.8 ± 6.0%; p = 0.013). In contrast, more children with a mild disease profile (43.8%) had elevated HbF levels (HbF ≥ 10%) than those with moderate disease (21.9%) [30]. This implies that female sickle cell patients would have less severe morbidity, leading to fewer emergency admissions. Other studies attribute this male predominance to an inadequate response to repetitive vascular injury, which disrupts nitric oxide (NO) production [22].

In this study, the results of the Sickle Cell Disease Severity Score were characterized by a mean value of 8.8 ± 3.8 with extremes of 2 and 19. Of the patients, 60% had a severe clinical profile, while 32.4% and 7.6% had a moderate and mild profile, respectively. We did not find any studies that determined these profiles in the acute care setting. Other studies should confirm the results because of their prognostic value in managing patients admitted to the emergency department. This is important because in our setting, patients do not have a follow-up diary in which their basic characteristics, such as basal Hb level and clinical profile, are recorded. In Mbayabo et al.'s study [26] in the Central Province of the Democratic Republic of the Congo (DRC) and in Adegoke et al.'s study [19] in Nigeria, respectively, a moderate clinical profile prevailed in the inpatient phase, with a low proportion of severe profiles. In a study conducted in Kisantu, the mean severity score was 8.21 ± 5.30 (range 0 - 23); 45.6% were in the moderate range, 43.4% had a mild clinical profile, and 11% had a severe profile [26]. In southwest Nigeria, the mean severity score was 9.85 ± 5.22, with only 0.4% of children having a severe clinical profile, while 55.7% had a moderate severity score and 33.9% had a mild profile [19].

Hyperalgesic vasoocclusive crisis, observed in 77 patients (73.3%), was the main cause of admission, followed by infection (67 cases or 63.8%) and severe anemia (38 cases or 36.2%). In DRC, Mashako et al. found that all patients in their series (100%) had VOC, and 73.9% of them had severe anemia. They were associated with infections such as malaria (31.9%), septicemia (26.1%), salmonellosis (20.3%), pneumonia (11.6%), and osteomyelitis (10.1%) [17]. In Brazzaville, Mpemba-Loufoua et al. reported infection as the main cause of hospitalization in 58.6% of sickle cell patients, acute anemia in 33.3%, VOC in 31.4% and malaria in 21.6% [31]. In Sikasso, Mali, Keita reports that the main diagnoses observed in sickle cell children admitted to pediatric wards were VOC (56.2%), infection (25%) and acute anemia (12.5%) [32]. In the Oppong-Mensah series, VOC (39.8%), acute chest syndrome (ACS) (25.9%) and infection (12.4%) were the main causes of admission [22]. In Saudi Arabia, El-Ghany et al. reported VOC (64.9%), infection (24.5%), ACS (18.1%) and acute hemolytic crisis (12.8%) in one region [23], while in another region, Elmoneim et al. observed that VOC (49%) was followed by ACS (20.9%), infection (17.5%) and acute anemia (8.1%) [24]. In India, Patel et al. identified VOC (59.01%) and severe anemia (39.34%) as the leading causes of hospitalization in children with sickle cell disease [33]. These observed differences may indicate the heterogeneity of the clinical presentation of sickle cell disease, but they may also be related to differences in management quality. Among the patients included in our study, specific vaccination, regular folic acid intake, or treatment with hydroxyurea were found in only 1%, 39% and 7%, respectively. This finding clearly highlights the urgent need to organize specific sickle cell care in our context. The biological profile of the patients in this cohort was characterized by low levels of Hb, H, and CMV, but with quite significant hyperleukocytosis. This trend was also reported in a study of sickle cell children admitted to a tertiary hospital in India. Indeed, Patel et al. reported a mean Hb level of 8.08 ± 2.40 g/dl with H of 23.34 ± 6.40% and CMV of 75.99 ± 2.12 μ^3 [33]. In Saudi Arabia, El-Ghany et al. found a mean Hb level of 8.2 ± 1.5 g/dl (23), whereas we found a mean Hb level of 7.2 ± 1.9 g/dl, an H of 22.9 ± 7.7% and a CMV of 75.7 ± 10.1μ^3. The worsening of anemia was therefore constant in all these studies carried out in the critical phase; however, our study shows a deterioration, but more pronounced, with a hemoglobin level one unit lower than in the others. A significant proportion of our patients had microcytic anemia. This observation has also been reported by authors in India, who associate it with martial deficiency, in a population of sickle cell children from tribes and castes with a low socioeconomic level [33,34]. In our study, two findings support a more inflammatory origin: i) the demonstration of a statistically significant association between very high CRP levels and microcytosis; ii) the observation of a simple negative linear correlation, statistically significant (P = 0.003), between CRP levels and CMV. However, we did not investigate martial status, nor did we look for an associated thalassemic syndrome.

A survival study on hospitalized children with sickle cell disease found a mortality rate of 12.4%. This mortality rate is similar to that observed in the Van-Dunem et al. cohort of children in Angola in 2007, i.e., 12.9% [35]; it is twice as high as that observed by Onubogu et al. in Nigeria in 2023, i.e., 5.9% [36]. In the study by Boma et al. in Lubumbashi, the mortality rate was 19.83% [37]. We can therefore conclude that sickle cell disease is still associated with a high mortality rate in our context, although this is only a partial assessment. This in-hospital mortality rate reflects mortality during hospitalization and considers the mortality specific to sickle cell disease in children admitted as an emergency. Patients' deaths after discharge from the hospital are not taken into account. This mortality rate does not include patients with sickle cell anemia who were admitted to other health facilities during the same period, or even those who did not present for consultation. As a result, it is not intended to reflect the overall mortality associated with sickle cell disease, which would be best assessed by a cohort study involving only sickle cell patients who have been followed since birth. When looking at patient outcomes, 67.6% of children had a positive outcome. The median length of hospital stay was 6 days, with extremes of 0 and 22 days. This length of hospital stay is similar to that reported by Colombatti et al., which was 6.42 days [38], and longer than that observed in the El Ghany series, which was 4 days [23]. In this study, the mean and median survival times for children with sickle cell disease were 5.9 and 6 days, respectively (extremes = 5 and 7). Survival varied according to the length of hospitalization and was 80%, 70.5% and 67.6% on days 2, 7 and 14 respectively. The critical period corresponded to the first 2 days of hospitalization, with a mortality rate of 20%. In this study, the clinical severity

score of sickle cell disease was another factor associated with patient survival. Survival was significantly shorter in patients with a moderate or severe profile (*P*=0.001). This finding highlights the need for systematic assessment of disease severity in all children with sickle cell disease to identify those most at risk of adverse outcomes and to provide appropriate and prompt treatment. Compared with patients transferred from home, patients transferred from other care settings had significantly shorter survival (*P* = 0.006). This reflects the pre-admission pathway's impact on the vital prognosis of patients admitted to tertiary care facilities as emergencies. Finally, the survival curve for patients was influenced by the presence or absence of an infectious syndrome influenced the patient's survival curve. The results of this study showed that survival was significantly shorter (*P*=0.002) in patients diagnosed with an infectious syndrome. This confirms the important role of infections in the mortality associated with sickle cell disease in the pediatric population, but also highlights the variability in the expression of sickle cell disease in different geographical contexts, particularly due to differences in the spectrum of infections [7,37]. This high mortality finding led us to identify associated risk factors. In a univariate analysis, we found that referral from other care settings, length of hospital stay > 2 days, worsening anemia, infectious syndrome, suspected hepatocellular failure, and the patient's severe clinical profile were all associated with the observed mortality. This suggests that inadequate pain management may have prolonged hospital stays, and that inappropriate and ineffective transfusion practices may have contributed to anemia deaths. In this cohort, none of the patients received morphine therapy, and transfusions, which accounted for 39% of deaths, were performed with whole blood in 95% of cases. In a study conducted in Lubumbashi, Boma et al. [37] also identified referral from another health care facility, a severe clinical profile (determined by the Mikobi method), severe infection, and a low Hb level as determinants of mortality in sickle cell children admitted to emergency care. However, in their cohort, age between 12 and 16 years, multiple organ failure, stroke, and very high LDH were the other predictors of death that we did not find in this study. Similarly, length of hospital stay > 2 days and suspected hepatocellular failure were not identified as predictors of mortality in their cohort but were in ours. In a multivariate analysis, we were able to show, after adjustment, that transfer from an institution, length of hospital stay > 2 days, infectious syndrome, severe clinical profile of the patient, and suspected hepatocellular failure were independently and significantly associated with the risk of death in sickle cell patients. The main limitation of this study is the study population's non-representativeness in relation to the population of sickle cell patients in Lubumbashi. A hospital cohort that failed to capture sickle cell children who did not attend the study facilities during the recruitment period may not accurately reflect the overall sickle cell population in the region. Despite this limitation, the study's results provide valuable information that is needed to improve the care of children with sickle cell disease in our context.

5. CONCLUSION

This study shows high sickle cell morbidity and mortality in two pediatric emergency departments in Lubumbashi. Mortality was associated with mostly controllable risk factors, including length of hospital stay >2 days, probably related to inadequate management of sickle cell pain, transfer of the patient from another care facility, clinical status suspicious for hepatocellular failure, and severe clinical profile of the patient. These results suggest that the prognosis of sickle cell disease in this context can be improved by training health workers in sickle cell disease and by better organizing specific sickle cell care at all levels of the health care pyramid.

CONSENT AND ETHICAL APPROVAL

The study was approved by the Medical Ethics Committee of the University of Lubumbashi under number UNILU/CEM/053/2021. The medical ethics rules were followed. Written informed consent was obtained from the parents or guardians of each child before enrollment, and data were anonymized.

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

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