

Improvement of Sickle Cell Disease Morbimortality in Children: Experience in a Remote Area of an African Country

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Abstract

Background: Sickle cell disease (SCD) is a public health problem in the Democratic Republic of Congo. While reference sickle cell centers have been implemented in capital cities of African countries and have proven to be beneficial for SCD patients, they have never been set up in rural areas for families with very low sources of income.

Method: A cohort of 143 children with SCD aged 10 years old (IQR (interquartile range): 6–15 years) (sex ratio male/female = 1.3) were clinically followed for 12 months without any specific intervention aside from the management of acute events, and then for 12 months with a monthly medical visit, biological follow-up, and regular prophylaxis.

Results: The median age of patients at the diagnosis of SCD was 2 years (IQR: 1–5). The implementation of standardized and regular follow-ups in a new sickle cell referral center in a remote city showed an increase in the annual mean hemoglobin level from 50 to 70 g/L ($p = 0.001$), and a decrease in the lymphocyte count and spleen size ($p < 0.001$). A significant decrease ($p < 0.001$) in the average annual number of hospitalizations and episodes of vaso-occlusive crises, blood transfusions, infections, and acute chest syndromes were also observed.

Conclusions: Creation of a sickle cell referral center and the regular follow-up of children with SCD are possible and applicable in the context of a remote city of an African country and represent simple and accessible measures that can reduce the morbimortality of children with sickle cell disease.

Author Summary

Sickle cell disease (SCD) is one of the most prevalent genetic diseases in the world. More than 300,000 newborns with SCD are born each year. The majority of them are in sub-Saharan Africa, where access to medical care and public health strategies to reduce mortality and morbidity are not uniformly available. It is a debilitating chronic disease responsible for more than 50% of the deaths of children under 5 years of age if they do not receive regular medical follow-up. In Sub-Saharan Africa, most sickle cell disease management centres are in large cities and capitals. There is very little data on this disease in remote city in a low- and middle-income country. In this study the authors demonstrate the feasibility and affordability of comprehensive follow-up care for children with sickle cell disease based on the creation of a reference center in a rural city of the Democratic Republic of Congo for families with very low income. Simple and accessible measures included in conventional recommendations can reduce the morbimortality of these patients in remote areas if applied rigorously with regular follow-ups.

1. Background

The world's leading genetic disease, sickle cell disease (SCD), was declared a public health priority by the United Nations in 2008 during the 63rd session of the UN General Assembly. According to the study conducted by Piel et al. in 2017, Africa had more than 250,000 births of children with a severe form of

this disease [1]. In the absence of early and appropriate care, 50–90% of these newborns will die before the age of five [2]. In Central Africa, the incidence of SCD at birth is estimated to be 1–2%—the highest in the world. After Nigeria, the Democratic Republic of Congo (DRC) contributes the highest number of SCD patients in sub-Saharan Africa [3].

Of the estimated general population of 91,994,000, the DRC has 25–30% carriers of the disease gene (heterozygous AS) and 2–3% of SS homozygotic newborns, with the annual number of newborns with SCD estimated to be 40,000 [4,5]. Without major changes in the expansion of the endemic disease, the number of affected people is growing at an uncontrolled rate [6,7]. While these figures are significant from an epidemiological point of view, the disease remains little recognized and can be overlooked or leading to underdiagnosis”, etc. resulting in high mortality and morbidity [6,8]. Despite significant progress in reducing the under-five mortality rate in the DRC between 2014 and 2018 [9,10], SCD is still characterized by a very high rate of morbidity and mortality [2,11]. In the absence of routine neonatal screening for SCD, diagnosis is often made in the presence of complications of the disease [5]. Work describing this mortality in cohorts of sickle cell patients followed from birth or with regular medical follow-up is rare in the DRC. Since 1988, it has been demonstrated in high-income countries that neonatal screening can identify affected children and medical care can be started early, i.e., before the age of three months, with the introduction of anti-pneumococcal antibiotic prophylaxis. This strategy has been demonstrated to significantly improve the mortality and morbidity of the disease [12]. Sectoral studies of neonatal screening and a large clinical trial on the safety and feasibility of hydroxyurea treatment in sickle cell children by Tshilolo et al. in 2009 and 2018 give the proportions of 16.9% of heterozygous AS and 1.4% of SS [5]; however, neonatal screening is only useful when it is part of an organized care system for affected children [13]. Treatment with hydroxyurea is feasible and safe in children with sickle cell disease living in sub-Saharan Africa. This treatment not only reduces mortality but also reduces various complications like vaso-occlusive events [14]. However, this hydroxyurea remains scarcely available and is too expensive to be feasible in sub-Saharan Africa [15].

SCD is a major public health concern in the DRC, and the basic resources for its management have remained insufficient with most of initiatives that have been conducted in Kinshasa. While some projects have been set up in Kisangani and Lubumbashi, remote cities, such as Mbuji-Mayi and Kananga, have never received support for improving management of SCD. On the other hand, the DRC has had the National SCD Control Program (PNLCD) since December 2001, which covers a complete protocol: treatment protocol, national policy, standards, and guidelines, etc. Unfortunately, due to the lack of necessary resources, this program cannot efficiently carry out its role. For example, the PNLCD integrated its protocol in 4 of 26 provinces in the DRC (Kwilu, Congo Central, Haut-Katanga, and Kinshasa). This explains the little attention paid to the fight against SCD, especially in remote areas like the city of Mbuji-Mayi in the center of the country. In the DRC, the existing initiatives are mainly derived or driven by civil society organizations and are most often located in large cities where specialized centers for the management of SCD can be found. Private impulses are needed to raise awareness and improve the management of this disease for patients living in remote areas. Given the burden of this disease, it is therefore vital to intensify the fight against SCD in the remote cities of sub-Saharan Africa by creating

specialized centers for care and setting up regular follow-up of patients at a reduced cost in the absence of completely free care.

The application of simple, accessible, and less expensive measures accompanied by regular medical monitoring would improve the health of SCD patients in sub-Saharan Africa if applied rigorously [16]. In high-income countries, the increase in survival and better life quality of SCD patients are less due to sophisticated therapeutics, such as stem cell transplantation, and more so to organized systems of early and adequate patient management [17,18]. The considerable improvement in the prognosis of SCD achieved by the teams of Serjeant in Jamaica, a country with limited resources, is a remarkable example showing that the prognosis of SCD can be improved in Africa if suitable strategies are in place [18]. These strategies should include the creation of sickle cell referral centers and integrated care structures within health facilities, the establishment of sickle cell care networks, and the early diagnosis of associated complications by regular medical follow-up. Studies reported on SCD in Africa are mainly retrospective hospital studies conducted in large cities and capitals. In Africa, prospective studies on the optimal follow-up of SCD patients with the rigorous application of management recommendations are rare [16].

A preliminary investigation conducted in 2015 on the knowledge and behaviors of 50 families affected by SCD in Mbuji mayi in the DRC showed that sickle cell children were very ill and there was no referral center specializing in the management of SCD in Mbuji mayi. The majority (96%) of families affected by SCD want a referral center for care to be created, and 94% of them agreed to subscribe to it for medical follow-up of their affected children. The level of knowledge in families affected by SCD in Mbuji mayi is low. Thus, the creation of a referral center and the possibility of a fixed annual amount for the care of patients is a strategy that could be implemented in Mbuji mayi to improve the care of sickle cell patients [19].

The objective of the present study is to demonstrate the feasibility and affordability of comprehensive follow-up care for children with sickle cell disease based on the creation of a reference center in a rural city of the DRC for families with very low income.

2. Methods

2.1. Study Context

This study was conducted in Mbuji mayi, which is the capital city of the province of Eastern Kasai in the DRC (Figure 1). It is the third-largest city in terms of population. Mbuji mayi's 2020 population is now estimated to be 2,525,263 (Mbuji mayi population data 2020), covering an area of 135.12 km² and corresponding to a population density of 12,441 inhabitants/km².

In the DRC, SCD management is devoted to the PNLCD. In line with the strategy for strengthening the health system, the PNLCD recommendations have not integrated SCD control activities in primary healthcare structures. The PNLCD is also not present in Mbuji mayi.

The study was carried out in the Mbujimayi Pediatric Clinic—one of the largest specialized pediatric structures. Currently, it is the structure that organizes the management of SCD with regular follow-ups at no cost to patients in Mbujimayi and is also one of the referral pediatric structure for the city of Mbujimayi, which is an Eastern Kasai province. It includes a pediatric ward with a capacity of 20 beds that are constantly occupied, neonatology ward, maternity ward, and semi-automated laboratory. However, it is important to note that the city of Mbujimayi has two large old hospitals (Bonzola General Reference Hospital and Dipumba General Reference Hospital). These two hospitals are owned by the Société Minière de Bakwanga (MIBA), the first industrial diamond production company in the DRC. Due to the fall of MIBA more than 15 years ago, the company is facing very serious financial difficulties. These hospitals have been abandoned and are in an advanced state of disrepair, requiring rehabilitation. This has a significant impact on the quality of care to patients, including sickle cell patients. In the case of acute complications, sickle cell patients are treated at their own expense, and there is generally no follow-up. With the opening of the Mbujimayi pediatric clinic and the organization of free care, the influx of sickle cell patients has increased significantly.

2.2. Study Type and Inclusion Criteria

From January 2017 to December 2018, we conducted a prospective cohort study including SCD children. These children had never been followed up or treated with hydroxyurea prior to their inclusion in the study. The cohort was followed up for 2 years, consisting of a simple follow-up in the first-year (2017) without the application of recommendations for the management of SCD, and in the second year (2018), with a classic regular follow-up of the same cohort with the application of simple, classic, and locally accessible recommendations (Table 2).

Patients diagnosed with SCD (i.e., sickle cell anemia or sickle cell/beta-thalassemia) who were older than 3 months and younger than 18 years were eligible for this study. Children under 3 months of age were excluded because of the lack of routinely organized neonatal screening to identify newborns with pre-symptoms. The diagnosis of SCD was made using an isoelectrofocusing technique (Perkin Elmer, Massachusetts, USA). Blood samples were collected on blotting paper and taken from the laboratory of the Monkole Hospital in Kinshasa, located at the cape of the DRC. Monkole Hospital is a large center of sickle cell disease in Kinshasa, the DRC. In addition, patients considered for inclusion had to reside in Mbujimayi during the study period. We excluded all SCD children whose primary guardian refused to sign to indicate informed consent as well as those who were heterozygous AS.

2.3. Data Collection

Data were collected during follow-up consultations using a data collection sheet for each patient. Then, these data were transcribed into a common database (Excel file).

2.4. Study Parameters and Operational Definitions

Sociodemographic parameters were age, sex, and age at the first diagnosis of SCD (recorded by a healthcare provider).

Clinical parameters were the origin of diagnosis (clinical and/or biological), weight (kg), height (cm), weight-for-height Z-score (WHO) assigned by sex and age, symptoms, and palpable size of the spleen. The splenomegaly was classified according to Hackett (WHO, 1963). Study Parameters and Operational Definitions (see table 1).

Table 1
Study Parameters and Operational Definitions

Parameters	Operational Definitions
Anemia	The decrease in whole-blood hemoglobin concentration of more than 2 standard deviations below the mean of age- and sex-matched reference range [21].
VOC	Any painful episode requiring intake of an analgesic (e.g., paracetamol, ibuprofen, or tramadol) or leading to a medical consultation in a healthcare structure.
Infectious episode	Any noted increase in the body temperature beyond 38.5 °C that needed to be managed in a healthcare facility.
Red blood cell transfusion	Any administration of labile blood products (in particular, packed red blood cells or whole blood) that occurred in a healthcare facility.
Acute chest syndrome	Presence of fever, cough, chest pain, difficulty breathing ± performance of chest X-ray.
Jaundice	A clinical observation, i.e., the presence of yellow coloration of the bulbar conjunctiva.
Hospitalization	Admission to hospital for treatment lasting at least 24 hours.
Adherence to care	Assessed as excellent, fair, or poor depending on the clinical follow-up as observed.
Large city	A city with an urban landscape and an international airport that is directly connected to foreign countries.
Remote city	Urban–rural town in the country with no direct contact with foreign countries.
VOC: vaso-occlusive crisis	

Biological parameters were obtained by testing patients using an isoelectric focusing technique and a hemogram (excluding information related to reticulocyte counts). The biological parameters, especially hemoglobin, were used to evaluate the severity of the disease.

Therapeutic parameters consisted of medications taken. The criteria for prescribing hydroxyurea comprised three or more severe vaso-occlusive crisis occurring in the last 12 months, SCD-related pain, or chronic anemia interfering with daily activities and severe or recurrent episodes of acute chest syndrome [22,23].

2.5. Medical Monitoring

Patients were subjected to a 2-year follow-up process comprising a monthly planned medical visit with clinical and hematological assessment. During the first year (2017), medical staff (doctors, nurses) and community relays received training on diagnosis, management of sickle cell disease, and the implementation of standardized follow-up in year 2. The first year passed without the application of any recommendations, while for the second year (2018), the systematic application of standardized and regular follow-ups was organized (see Table 2).

Table 2
Follow-up of sickle cell patients and the applied strategy.

Parameters of medical monitoring	Year 1	Year 2
Parental Counseling and Education [22,24–26]	<ul style="list-style-type: none"> · Early identification of fever, VOC, anemia, broad spleen, and urgent consultation for management. · Report any acute events (VOC, acute anemia, fever, etc.). 	<ul style="list-style-type: none"> · Education on the need for adequate nutrition, hydration, and regular hospital follow-ups. · Early identification of fever and its urgent treatment, and of a large spleen. · Use of prophylactic medications such as penicillin V, folic acid, antimalarial drugs (sulfadoxine–pyrimethamine every two weeks), and deworming with mebendazole (once every six months).
Immunization [27]	<ul style="list-style-type: none"> · Checking the vaccine schedule. · No stimulation to get full vaccination coverage. 	<p>Immunization against infections according to the vaccines recommended in the DRC:</p> <ul style="list-style-type: none"> · Bacillus Calmette–Guérin vaccines against tuberculosis. · Diphtheria, tetanus, and whooping cough. · Oral polio. · Measles. · Yellow fever. · Tetanus. · <i>Haemophilus influenzae</i> type b; <p>Pneumococcus (Prevenar 13).</p>
Strategy	<ul style="list-style-type: none"> · Setting up of a notification book of acute complications (fever, pain, acute anemia, etc.) that contains the contact number. · Organize free-of-charge emergency treatment for all SCD patients. 	<ul style="list-style-type: none"> · Establishment of an appointment book to be given to parents or the patient: this book contained the dates of the appointments and the contact numbers. · Organize free-of-charge consultations for all SCD patients. · Set up a system of SMS and/or phone calls to remind people about appointments. · Organization of listening and information sessions for parents and patients every 3 months. · Monthly distribution of folic acid and oral penicillin. Mebendazole and antimalarial treatments were dependent on the patient.

Year 1: Follow-up of acute complications and biological parameters without application of conventional recommendations. Emergency support only.

Year 2: Standardized and regular follow-up with the implementation of recommendations for the management of sickle cell disease [26] adapted to local conditions.

VOC: vaso-occlusive crisis; SCD: sickle cell disease; SMS: short message service. NB: No patients were treated with hydroxyurea because of the drug's low availability and high cost.

** The minimum vaccine coverage proposed/funded in the DRC includes the Bacillus Calmette–Guérin (BCG) vaccine against tuberculosis; vaccine against diphtheria, pertussis (whooping cough), and tetanus (DPT); oral polio vaccine (OPV) against polio; measles vaccine against measles; the Admiral vaccine against yellow fever; and the tetanus vaccine against maternal and neonatal tetanus [27].*

2.6. Statistical Analysis

To analyze blood parameters of patients from children through to adulthood, data were reported as the percentage of the lower normal limit for corresponding age. Because no criteria are defined for our area in Congo, normal values were compiled from neighboring regions [28–35]. Normal distribution was tested with the D'Agostino and Pearson normality test. A paired t-test (Gaussian data) or Wilcoxon matched-pairs signed-rank test (no Gaussian data) were used to compare data for each patient. Data were plotted within boxplots (2.5%–97.5% range). Rate size evolution was analyzed with the Chi-square test and the relation between platelet count and rate size was analyzed by dividing platelet counts by a re-encoded rate size ($h_0 = 1, h_1 = 2, \dots$).

$p < 0.05$ was considered to indicate statistical significance (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Statistical analyses were performed using Prism 8.0.1. (GraphPad Software Inc, San Diego, CA) software.

2.7. Ethical Approval

All parents or legal respondents of patients provided their written informed consent for participation in the study. The study protocol had been reviewed and approved by the Ethics Committee of the Medical Faculty at the University of Mbuji-Mayi (N/Réf.: 012/VD-RSCU/Fac-Méd/UM/DMT/2019) and the Head Board of the Public Health Division of Eastern Kasai Province (DPSPN°71/204/C.N.E.S/DPS/NTK/K.OR/2019). The study was conducted in agreement with the

principles of the Helsinki Declaration II. The aim and procedures of the study were explained to the participants and legal respondents. The participants were informed that they could withdraw at any time without further obligation. The anonymity of the participants was guaranteed, and no personal details were recorded. The results of this study were presented to parents and legal respondents during a discussion session at the end of the study.

3. Results

The process of the study and the recruited cohort of 143 SCD children are described in Figures 2 and 3, respectively. The losses during follow-ups and the deaths rates during the first-year period were 41% (104/251) and 1.6% (4/251), respectively.

The demographic and clinical characteristics of SCD children at 12 months of follow-up (FU) before the implementation of international recommendations are reported in Table 3. The diagnostic means initially used were predominantly based on clinical features (43%, 62/143). The circumstances of the diagnosis were mostly VOC (66%) and anemia (18%), and none were diagnosed during the neonatal period. The Z-score weight for height less than $-2DS$ was observed in 47% of the patients.

Table 3

Demographic and clinical characteristics of sickle cell children at 12 months of follow-up, before the implementation of sickle cell management recommendations (n = 143).

Variable	Median (IQR 25%–75%)	n	%
Age	10 (IQR: 6–15 years)		
Age at diagnosis	2 (IQR: 1–5 years)		
	Before 1 year	53	37
	Between 1 and 5 years old	55	39
	Between 5 and 10 years old	22	15
	After 10 years	13	9
Sex	Female	62	43
Schooling	Yes	99	69
Z-score weight-for-height less than -2SD	Yes	67	47
Mode of the first diagnosis	Clinical	62	43
	Electrophoresis of Hb	44	31
	Emmel test	37	26
Circumstances of the first diagnosis			
	Vaso-occlusive crisis	94	66
	Anemia	25	18
	Screening at the time of inclusion	14	10
	Fever	8	6
	Jaundice	2	1
	Neonatal screening	0	0
Confirmation of diagnosis by isoelectrofocusing	Yes	143	100
Chronic complications	Yes	31	22
Type of complications	Hip arthritis	13	11
	Stroke	7	5
	Right eye blindness	1	1
	Osteomyelitis	4	3
	Leg ulcer	3	2

	Other	3	2
Reasons for hospitalizations	Vaso-occlusive crisis	45	31
	Infectious episodes	34	24
	Anemia/blood transfusion	24	17
	Other causes	40	28
Presence of hepatomegaly	Yes	86	60
Presence of jaundice	Yes	126	88
Presence of splenomegaly	Yes	98	69
Spleen measurement (according to Hackett)	H0	45	31
	H1	16	11
	H2	34	24
	H3	24	17
	H4	15	10
	H5	9	6
IQR: interquartile range; H0: Hackett stage 0 (no splenomegaly); H1: splenomegaly stage 1 of Hackett; H2: splenomegaly stage 2 of Hackett; H3: splenomegaly stage 3 of Hackett; H4: splenomegaly stage 4 of Hackett; H5: splenomegaly stage 5 of Hackett.			

Comparison of Data before and after the Implementation of Standardized and Regular Follow-Ups

After one year of implementation of standardized and regular follow-ups, an overall reduction in the annual average of clinical complications was observed, i.e., VOC, infectious episodes, acute chest syndrome, blood transfusions, and hospitalizations (Table 4a). To evaluate the evolution of these parameters, the results were expressed as the percentage of the lower limit of the reference range due to the variation in reference ranges with age for the considered biological parameters. A significant increase in hemoglobin level and platelet count was observed as well as a decrease in lymphocyte count. We did not observe statistical differences for the other hematological parameters. Anemia was observed in 100% of our cohort and was severe and normocytic for 115 patients (80%).

Table 4a

Comparison of acute complications of sickle cell disease before and after the Implementation of Standardized and Regular Follow-Ups

	Year 1	Year 2	p-value
Clinical Parameters	Follow-up without any intervention n = 143	Standardized and regular follow-up n = 143	
	Annual average [IQR]	Annual average [IQR]	
Vaso-Occlusive Crisis	3.9 [1–6]	1.1 [0–2]	<0.001 (***)
Infectious episode	4.0 [2–6]	1.1 [0–1]	<0.001 (***)
Hospitalization	3.8 [2–5]	1.2 [0–2]	<0.001 (***)
Acute Chest Syndrome	1.0 [0–1]	0.0 [0–0]	<0.001 (***)
Blood Transfusion	1.9 [1–3]	0.0 [0–1]	<0.001 (***)
IQR: interquartile range (25%–75%). Significant p-values (≤ 0.05) appear in bold.			

Table 4b

Comparison of biological parameters for sickle cell patients before and after the Implementation of Standardized and Regular Follow-Ups

	Year 1	Year 2	p-value
Biological Parameters	Follow-up without any intervention	Standardized and regular follow-up	
	Median (+/- SD)	Median (+/- SD)	
HB (g/L)	50 (54 ± 20)	76 (76 ± 14)	<0.001
RBC (× 10 ⁶ /mm ³)	2.0 (64 ± 25)	2.9 (86 ± 19)	<0.001
HCT (%)	15 (61 ± 21)	23 (84 ± 15)	<0.00
MCV (fL)	81 (129 ± 20)	82 (125 ± 13)	0.176
WBC (× 10 ³ /mm ³)	9.6 (374 ± 201)	8.4 (270 ± 109)	<0.001
Lymphocytes (× 10 ³ /mm ³)	4.1 (364 ± 293)	3.2 (239 ± 145)	<0.001
Neutrophils (× 10 ³ /mm ³)	4.7 (375 ± 205)	4.4 (369 ± 137)	0.554
Platelets (× 10 ³ /mm ³)	260 (248 ± 131)	328 (317 ± 108)	<0.001
<i>HB: hemoglobin; RBC: red blood cells; HCT: hematocrit; MCV: mean corpuscular volume; WBC: white blood cells. The averages of biological parameters represent the percentage of the normal lower limit of the reference range (% LLN) ± SD of the evolution of each patient in relation to themselves.</i>			

The therapeutic characteristics before the implementation of a regular follow-up are described in Table 5. None of the SCD children had been treated with hydroxyurea in the past. Applying the criteria for consensual indications of hydroxyurea treatment (≥ 2 acute chest syndromes per year, vaso-occlusive crisis ≥ 3 per year, severe anemia $< 70\text{g/L}$) in the management of SCD, 94% of SCD children in the studied cohort required introduction of hydroxyurea treatment.

Table 5
Therapeutic characteristics before regular follow-up applying sickle cell management recommendations (n = 143).

Variable	n	%
Prophylaxis		
Folic acid and oral penicillin	21	15
Routine vaccine	81	57
Pneumococcal vaccination (23 valent)	0	0
Antimalarial	0	0
Dewormers	0	0
Hydroxyurea treatment	0	0
Traditional treatment	96	67
Indicated for hydroxyurea treatment	134	94

Comparison of the evolution of splenomegaly one year before and one year after the implementation of standardized and regular follow-ups showed a statistically significant difference (p -value < 0.001) (see Figure 4).

4. Discussion

This current study took place at the support center for SCD created in the remote city of Mbuji mayi in Kasai Oriental province in the DRC (around 2.5 million inhabitants) [36]. It aimed to establish a reference center of sickle cell disease that would offer comprehensive outpatient and inpatient care to establish regular and standardized medical follow-ups of patients and to estimate whether this is feasible and affordable in a remote city. Additional goals were to observe the results after one year of implementation of a regular medical follow-up, to estimate the need for the introduction of treatment by hydroxyurea, and to determine if all the tools would be in place to ensure adequate medical follow-up for those who would be treated with hydroxyurea. A cohort of 143 SCD children with a median age of 10 years was followed for 2 years. In the first year, follow-up was limited to the management of acute complications of the disease (VOC, acute anemia, infection episodes, acute chest syndrome, etc.) without other specific interventions, and the second year included the implementation of standardized and regular follow-ups. Results after 12 months of regular, standardized medical follow-ups and parental education, without treatment introduction by hydroxyurea, showed an overall reduction in acute complications, i.e., vaso-occlusive crises, infectious episodes, acute chest syndrome, episodes of blood transfusions and hospitalizations, and improvement of anemia. The results show that the intervention of a newly

established sickle cell referral center with evidence-based guidelines had a positive impact in reducing morbimortality. Regular follow-ups of SCD patients, including a hematological follow-up, are possible and applicable both before the introduction of hydroxyurea treatment and in the context of a remote city in the DRC.

Creating a support center located close to patients that organizes free-of-charge care allowed the current study to be conducted. This is one of the recommended strategies for effectively reducing the burden of SCD morbimortality [8]. In the context of poverty, the goal of equal access to healthcare can only be achieved if health policies guarantee effective care for all patients. As described in Mali, providing centers and units of competence is vital [37]. These structures, whose missions focus primarily on diagnosis and management, should be local community centers. They are steppingstones necessary to promote access to timely care for a great number of SCD patients at an affordable cost. As reported by the Human Development Index, the majority of patients affected by SCD are those with a limited income [38], and in most African countries, only rich patients have access to basic treatments such as prophylactic oral penicillin; for example, in the DRC, the cost of SCD management is not affordable for approximately 95% of patients [37,39].

There are very few referral centers for the management of sickle cell disease in sub-Saharan Africa [16]. The few centers of reference for sickle cell disease, if they exist, are in the capitals and large cities of these countries and not in remote areas. In the DRC, the sickle cell referral centers are in Kinshasa (Monkole Hospital and the SS Centre for Mixed Medicine and Anaemia (CMMASS) and Lubumbashi (SCD referral center at Nsendwe Hospital).

In sub-Saharan Africa, models of sickle cell disease management programs have been proposed in the capitals of some countries. Of note are the Center for Research and control for SCD (CRLD) in Bamako au Mali [40], the National Reference Centre for Sickle Cell Disease (CNRD) in Brazzaville, Republic of Congo [41], National Sickle Cell Disease Center in Cotonou, Benin [42]. All these centers are almost entirely privately funded (including in the DRC). The model implemented was based on neonatal screening for SCD as part of a project and follow-up with long-term sickle cell patients. The cost of care for patient-dependent follow-up can be prohibitive. Although these projects have received government support in their implementation, these programs remain limited at the capital level, and the positive impetus for neonatal screening stops with the end of funding and/or remains non-systematic at the expense of patients and at a high cost to families. This model has not been integrated into the primary healthcare system, such as is the case with the treatment of malaria, tuberculosis, or HIV that are properly managed at health center levels even in remote areas of sub-Saharan Africa. A major barrier to progress has been the absence of large-scale early-life screening [43], the high cost of screening with conventional methods (hemoglobin electrophoresis) as well as the lack of standardized and systematic medical follow-up for all screened patients [16]. In the last few years, novel inexpensive SCD point-of-care test kits have become widely available and have been successfully deployed in African field settings. These kits could potentially enable universal early SCD screening. Other recent developments are the expansion of the pneumococcal conjugate vaccine towards near-universal coverage and the demonstrated safety, efficacy,

and increasing availability and affordability of hydroxyurea across the African continent. Most elements of standard healthcare for SCD children that are already proven to work in the West could—and should—now be implemented at a large scale in Africa countries [43].

Outside the capitals, care centers are rare and can be found only in some large cities in sub-Saharan African countries. For example, in Senegal, an SCD center can be found at the Peace Hospital in Ziguinchor, a town in southern Senegal [44], but the model of the program remains the same as the one described above in the capitals. To date, these centers serve only sickle cell patients living in capitals and large cities and a few patients transferred from remote provinces with financial means. As rural areas in sub-Saharan Africa are destitute, many sickle cell patients in these areas are financially unable to travel to large cities for treatment. The solution that can be envisaged to take care of all patients is to open new centers for the management of sickle cell disease throughout these countries [45] and implement a model of integration into primary healthcare. However, a few questions are worth asking: What should the status be of a Sickle Cell Reference Center in Africa? What should its missions be? What should the policies for access of sickle cell patients to specific care in Africa be? How should the African States be involved in the design and implementation of these policies? How should the management of cases in poor rural areas with limited access to basic health structures be organized?[46]. Sickle cell disease has been recognized to have global health significance by key institutions, including the World Health Organization in 2006 and the United Nations in 2008. In 2010, the WHO released national healthcare management goals and set targets for the control and management of SCD to be met by the countries of sub-Saharan Africa. These are yet to be translated into action. To do this would require active and sustainable public-private partnerships for sustainable program development in these regions. Effective interventions should be integrated into existing health systems, with the best examples linking primary healthcare facilities to specialized SCD centers in regional and tertiary healthcare institutions [8]. However, multiple constraints necessitate an organization based on a network of health professionals working in sickle cell referral centers with specific missions of research, communication, and teaching; the establishment of guidelines for diagnosis, treatment, and prevention; and centers of competence that focus primarily on the screening, diagnosis, and management of SCD patients while favoring equity in access to care [37]. Despite the remaining challenges, several high-SCD-burden African countries have the political will and infrastructure for the rapid implementation and scale-up of comprehensive SCD childcare programs. A globally funded effort starting with these countries and expanding elsewhere in Africa and to other high-burden countries, including India, could transform the lives of SCD children worldwide and help countries to meet the requirements of the Sustainable Development Goals. This endeavor would also require ongoing research focused on the unique needs and challenges of SCD patients and children, particularly in regions of high prevalence [43].

This study included SCD children for whom the initial diagnosis was not reported at birth. This initial diagnosis was mainly made based on only clinical features, especially the presence of VOC or anemia. These results are consistent with those of other authors who reported an average age of around 10 years in SCD patients and a first diagnosis at the age of 2 years or later [45,47–51]. VOC was also reported as the most frequent mode of first diagnosis [44,47,50,52].

In this study, patients were subjected to a 2-year follow-up process comprising a monthly planned medical visit with a clinical and hematological assessment. The first-year period (2017) passed without the application of any intervention, apart from the regulation and treatment of acute complications, while in the second year (2018), the systematic application of standardized and regular follow-ups at monthly medical visits was organized and included folic acid and daily oral penicillin prophylaxis, deworming, and antimalarial treatments as well as a hematological assessment at each visit. In addition, an enhanced adherence process and education to prevent crises were implemented. The results of the first year of follow-up showed that sickle cell children without any specific medical intervention presented severe clinical and hematological pictures with an annual average of four VOCs, four infectious episodes, one acute thoracic syndrome, and four hospitalizations, demonstrating the severity of the disease in a remote area of a developing country. Annual averages of acute events and degradation of biological parameters similar to the results of this study among SCD patients who have not been followed-up with in the past have been reported in the literature [47,50,53–55]; however, there were no reports on the impact of regular follow-ups in those studies.

The application of standardized and regular follow-ups for 12 months showed encouraging results, with a significant reduction in acute events of the disease, i.e., a reduction in episodes of VOC, infectious episodes, blood transfusions, acute thoracic syndromes, hospitalizations and an increase in the hemoglobin level from 50 to 70 g/L. The steady-state hemoglobin level of 50 g/L before regular follow-up was lower than that previously reported for large cities of the DRC or other African countries (70 g/L) [45,47,50,56]. This could be explained by the lack of optimal management of the disease in the past but, also, by other factors that should be explored. The study also showed a decrease in the number of white blood cells that occurred due to affected lymphocytes.

The results of this study provide important baseline data for a new referral center in a remote area of the DRC and how such a center can fill gaps to ensure comprehensive management of sickle cell patients. Similar results were observed during the implementation of a sickle cell disease management program in a tertiary hospital in a remote area of India. Indeed, a recent study conducted in a remote region of West India by a non-governmental organization reported the implementation of a comprehensive SCD program in a secondary level hospital. They registered 404 SCD patients between December 2015 and June 2017 and compared the uptake of proven interventions and indicators of disease severity from one year prior to registration until the end of the study (June 2018). After the introduction of standardized and regular monitoring, they observed a statistically significant decrease in VOC (277 vs. 53.4), hospitalizations number (49.8 vs. 42.2), and blood transfusions (27.4 vs. 17.8) [57]. As for our results, they demonstrate that the implementation of a comprehensive SCD management program can significantly reduce the severity of the disease. This shows that it is possible to set up sickle cell disease centers in remote areas and to organize optimal management.

Studies carried out in high-income countries have sufficiently demonstrated the benefits of standardized and regular medical follow-up of sickle cell patients with a reduction in acute and chronic complications of the disease and improvement in the quality of life [58–66]. Prospective cohort studies of SCD patients

are rare in Africa due to barriers to medical monitoring [37]. However, a cohort study conducted in Benin in 2015 showed that the frequency of VOC was reduced to about once every two years, and some of the patients were crisis-free for as long as five years after implementing comprehensive healthcare management [67]. In Jamaica, the establishment of early diagnosis and simple prophylactic measures, i.e., oral penicillin and diagnosis of splenic sequestration, led to a significant reduction in SCD-associated deaths [68].

No children enrolled in the new center and followed in this study were treated with hydroxyurea in the past; however, 94% of SCD patients included in this study were indicated for HU treatment. Indications of hydroxyurea treatment are common in Africa [15]. In a Nigerian study, 65% of 206 SCD patients were indicated for hydroxyurea treatment [69]. The use of hydroxyurea in the treatment of SCD is very low in low- and middle-income countries [14,15]. The efficacy and therapeutic benefits of hydroxyurea have been widely documented; it remains the appropriate basic treatment in the management of SCD for African countries and this study demonstrates that its side effects can be monitored [8,15,15,58,63,70–72]. However, in low- and middle-income countries, there are many barriers to hydroxyurea treatment. These barriers include ignorance, the non-prescription of the drug by doctors, and the cost of the drug [73,74]. The creation of care centers is needed to facilitate awareness and advocacy. The creation of referral centers and the organization of optimal management of SCD by doctors trained in major sickle cell syndrome would certainly increase the knowledge, prescription, and awareness of the drug. In a study in India, the number of SCD patients on hydroxyurea increased from 4% to 98% after the implementation of a comprehensive program of sickle cell disease management in a remote tribal area [57].

The creation of a new sickle cell referral center and its positive results is a new model for providing follow-up care and optimal treatment in remote areas. It represents the awareness and ongoing response to the management of SCD for the families concerned. However, in this study, the large number of patients lost during follow-up is worrying. Addressing this requires strong local strategies to strengthen adherence to care. The referral center must establish early detection and management of the disease. Neonatal screening provides many benefits such as in the prevention of infection through early implementation of antibiotic prophylaxis, folic acid, deworming, proper management of malaria, and immunizations against pneumococcal infections; this is feasible in Africa but requires political support [75]. For this reason, our suggested strategies are to continue the offer of regular and standardized care, plan future research projects to study SCD screening of pregnant women during antenatal consultations, organize routine neonatal screening of all newborns for at-risk pregnancies (AS and SS women) and children under five years of age with indications (transfusion history, anemia, notions of pain or repeated fever, etc.), and introduction of hydroxyurea treatment to all eligible patients. The use of rapid sickle cell tests coupled with those for malaria and equipping reference centers with a confirmation technique, i.e., isoelectrofocusing, could also be a strategy to consider for remote areas of low- and middle-income countries. A final perspective is to advocate, at the government level, for free care for all sickle cell children to guarantee regular follow-ups.

The size as well as the severity of the disease of our cohort could be the result of selection bias. Data must be interpreted considering these two aspects. Even if treatment is free of charge, if the clinical expression is mild, families are unlikely to come to a medical center. A longer-term study would undoubtedly make it possible to approach these patients and to make known the benefits of a comprehensive care program among this patient population.

5. Conclusions

This study showed that the creation of a sickle cell referral center for the regular follow-up of children with SCD and the application of SCD management recommendations are possible and applicable in the context of a remote city in a low- and middle-income country. Simple and accessible measures included in conventional recommendations can reduce the morbimortality of these patients in remote areas if applied rigorously with regular follow-ups. In addition, future challenges include the implementation of neonatal screening of newborns from at-risk pregnant women (SS and AS women), screening children under five years of age with indications, and the introduction of hydroxyurea treatment. Implementing this comprehensive care plan in its entirety requires strong public and private partnerships to ensure quality of care for SCD patients in poor settings.

6. List Of Abbreviations

BCG: Bacillus Calmette–Guérin

CMMASS : SS Centre for mixed medicine and anaemia

CNRD : National reference centre for sickle cell disease

CRLD : Center for research and control for SCD

DRC : Democratic Republic of Congo

DPT: Diphtheria, Pertussis (whooping cough), and Tetanus

FU : follow-up

HB: Hemoglobin.

HCT: Hematocrit.

HIV : human immunodeficiency viruses

IQR : Interquartile range

LLN: normal lower limit

MCV: mean corpuscular volume.

MIBA : Bakwanga mining (Minière de bakwanga)

OPV: Oral polio vaccine

PNLCD: National SCD control program (Programme National de Lutte Contre la Drépanocytose)

RBC: Red blood cells.

SCD : Sickle cell disease

SD: Standard deviation

SMS: Short message service

UN General Assembly : United Nations General Assembly

USA : United State of America

VOC : vaso-occlusive crisis

WBC: white blood

WHO : World health organization

7. Declarations

• Ethics approval and consent to participate :

All parents or legal respondents of patients provided their written informed consent for participation in the study. The study protocol had been reviewed and approved by the Ethics Committee of the Medical Faculty at the University of Mbuji mayi (N/Réf. : 012/VD-RSCU/Fac-Méd/UM/DMT/2019) and the Head Board of the Public Health Division of Eastern Kasai Province (DPSPN°71/204/C.N.E. S/DPS/NTK/K.OR/2019). The study was conducted in agreement with the principles of the Helsinki Declaration II. The aim and procedures of the study were explained to the participants and legal respondents. The participants were informed that they could withdraw at any time without further obligation. The anonymity of the participants was guaranteed, and no personal details were recorded. The results of this study were presented to parents and legal respondents during a discussion session at the end of the study.

• Consent for publication:

Informed consent was obtained from the legal parents of all children who participated in the study. A copy of the document is available for review by the publisher of this journal.

• **Availability of data and materials:**

All data generated and/or analyzed during this study is available in a database from the corresponding author on reasonable request.

• **Competing interests:**

The authors declare no conflicts of interest.

• **Funding:**

This research received no external funding.

• **Authors' contributions:**

Conceptualization, B.M.M. and B.G.; Methodology, B.M.M., G.T.D. V.D. and B.G.; Validation, B.M.M., G.T.D. and B.G.; Formal Analysis, V.D.; Investigation, D.K.K., J.K.M., Y.N.M. and B.M.M.; Resources, P.M.B.; Data Curation, V.D., P.M.B. and B.M.M.; Writing – Original Draft Preparation, B.M.M.; Writing – Review & Editing, B.M.M., and B.G.; Visualization, B.M.M.; Supervision, G.T.D and B.G.; Project Administration, B.G. All authors have read and approved the manuscript.

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Figures



Figure 1

Location of the city of Mbuji-Mayi on the map of the Democratic Republic of Congo (DRC) [20].

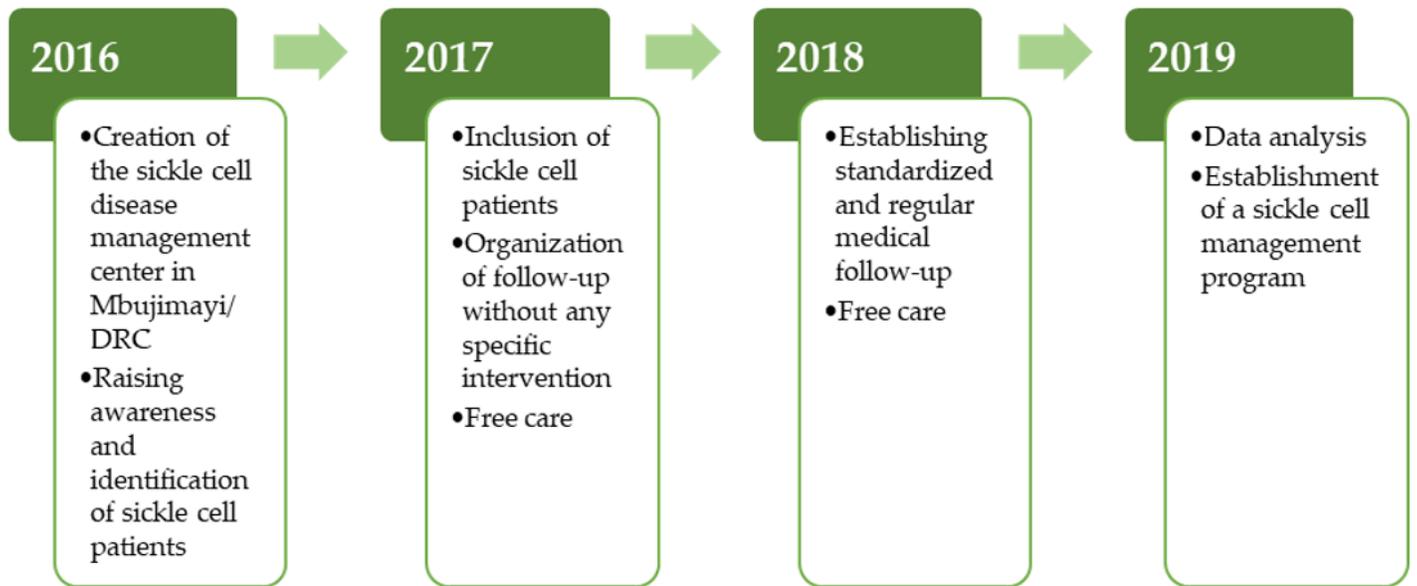


Figure 2

The overall evolution of the study on the application of standardized and regular follow-ups at Mbuji mayi in the DRC.

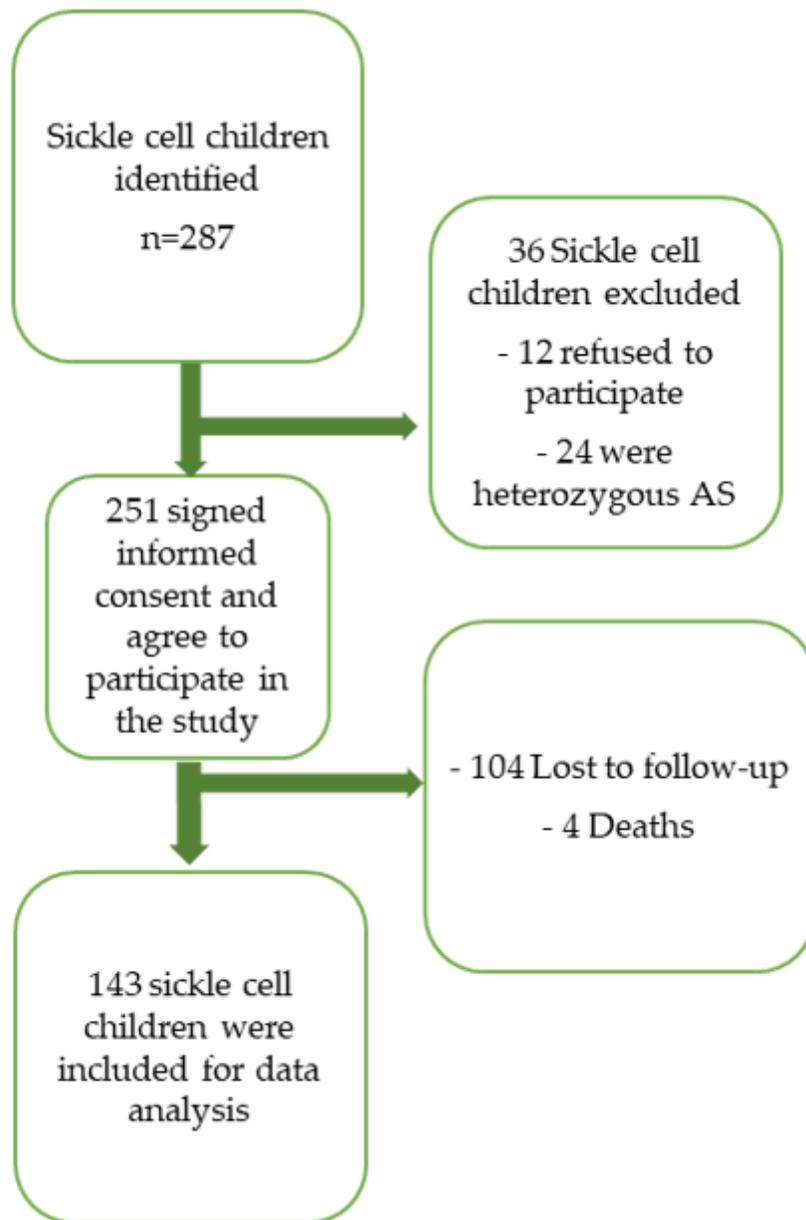


Figure 3

Inclusion of sickle cell children in the study.

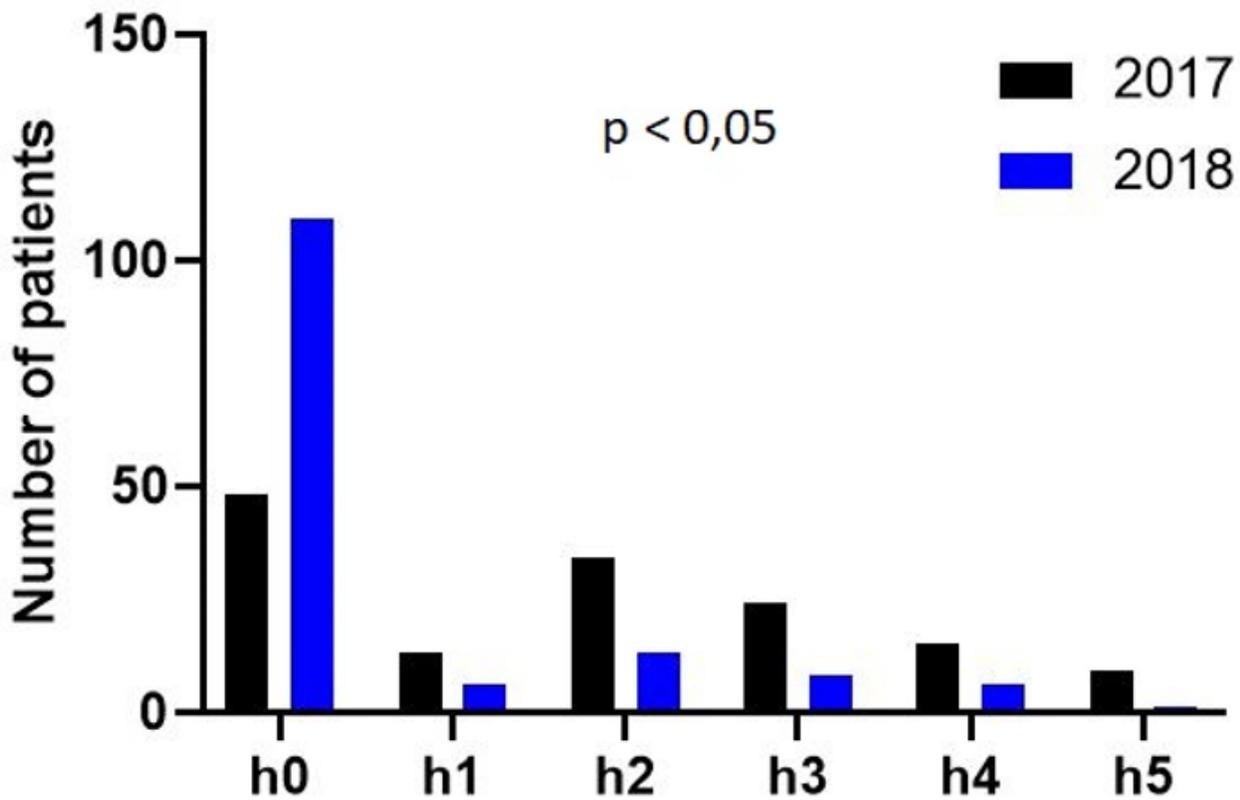


Figure 4

Comparison of splenomegaly before and after the implementation of standardized and regular follow-ups Changes in spleen status in sickle cell patients in 2017 (followed without any medical intervention) and 2018 (standardized and regular follow-ups). Figure shows statistically significant difference between 2017 and 2018 ($p < 0.0001$). The clinical classification of splenomegaly according to Hackett (WHO, 1963) includes five categories ranging from 0 to 5: from non-palpable spleen, even in deep inspiration (category 0; H0) to spleen descending well below the navel, exceeding the line passing between the umbilicus and the pubic symphysis (category 5; H5).