Original Article *Iran J Ped Hematol Oncol. 2025, Vol 15, No 2, 440-455*

Prevalence, Disease Manifestations and Outcomes of Paediatric Sickle Cell Anaemia in Calabar, Nigeria: A Single Center 6-Year Review

Anthony Nlemadim FWACP[1*], Jacintha Okoi-obuli FMCPaed[1], Elizabeth Nkanga FMCOph[2], Chimaeze Torty FWACP[3], Kingsley Akaba FMCPath[4], Juliet Venn FWACP[5], Kelechi Uhegbu FWACP[6], Sunday Okonkwo FMCOph[7], Grace Nwankwo FWACP[1], Ofonime Essien FMCPath[4], Glory Bassey FWACP[8], Friday Odey FMCPaed[1], Martin Meremikwu FMCPaed, FRCPCH[1]

1. Haematology-Oncology unit, Department of Paediatrics, University of Calabar Teaching Hospital (UCTH), Calabar, Nigeria
2. Calabar Children's Eye Centre, Department of Ophthalmology, University of Calabar, Calabar, Nigeria
3. Neurology unit, Department of Paediatrics, University of Calabar, Calabar, Nigeria
4. Department of Haematology, University of Calabar, Calabar, Nigeria
5. Children emergency room, Department of Paediatrics, UCTH, Calabar, Nigeria
6. Gastroenterology unit, Department of Paediatrics, University of Calabar, Calabar, Nigeria
7. Department of Ophthalmology, University of Calabar, Calabar, Nigeria
8. Respiratory unit, Department of Paediatrics, University of Calabar, Calabar, Nigeria

*Corresponding author: Dr. Anthony Chibueze Nlemadim, Haematology-Oncology Unit, Department of Paediatrics, UCTH, Calabar, Cross River State, Nigeria. Email: tonynlemas@yahoo.com. ORCID ID: 0000-0003-0095-8975.

Received: 13 October 2024 **Accepted:** 09 January 2025

Abstract

Background: The burden of sickle cell anaemia (SCA) is worsening globally. Recognition of paediatric SCA burden is vital to comprehending the overall SCA burden. Aim was to determine the prevalence, disease manifestations and outcomes of paediatric SCA.

Materials and Methods: It was a retrospective study of all children with SCA, 0.5 year (6months) - 17 years old, managed from 2018 through 2023. Data obtained were sex, age at first visit per year, diagnoses and date per visit, location (clinics or emergency-room) of visit, intervals between visits, and death. Disease manifestations per subject were summarized into diagnosis while default was defined as >3 months visit interval.

Results: Of the 532 subjects, 55.6% were males with overall median (interquartile [IQR]) age on first visit of 9 (5 - 13) years. On average, paediatric SCA constituted 4% of first visits per year. There were 252 sick visits per year, 544 diagnoses per year and 146 hospitalisations per year. Commonest diagnosis in emergency-room and clinics were bone pain crises (46.2%) and steady-state (48.5%), respectively. The 11 - 17-year-olds were more likely to have bone pain crises than 0.5 - 4-year-olds (Odds Ratio [OR] 0.381; 95%CI: 0.487-0.787) and 5 - 9-year-olds (OR 0.298; 95%CI: 0.573-0.861). They were also more likely to have avascular necrosis than the 0.5 - 4-year-olds (OR 0.789; 95%CI: 0.047-0.938) and 5 - 9-year-olds (OR 0.777; 95%CI: 0.064-0.781). Overall median (IQR) default time was 6 (5 - 7) months with more defaults (85.1%) than compliants (14.9%) ($p<0.001$) while 0.56% died.

Conclusion: The overall prevalence of Paediatric SCA in the region is 4% with approximately one hospitalisation per sick visit and more than one diagnoses per visit. There is a high default rate but a low mortality rate (0.56%). Sustained improvement in the management of SCA, from childhood through adulthood, may help alleviate the increasing burden of the condition.

Keywords: Morbidity; Mortality; Paediatric; Prevalence; Sickle cell

[DOI: 10.18502/ijpho.v15i2.18174]

Introduction

Sickle cell anaemia (SCA) is the most common haemoglobinopathy whereby a child inherits two haemoglobin S (HbS) (1). The HbS arises from point mutation on position 6 of the deoxyribonucleic acid (DNA) of the β-globin gene located in chromosome 11p15.5 (1). This implies Cytosine/Thymine/Cytosine (CTC) – to – Cytosine/Adenine/Cytosine (CAC) substitution in the DNA which in turn results in a Guanine/Adenine/Guanine (GAG) – to – Guanine/Uracil/Guanine (GUG) change in the mRNA (1). It is the most prevalent Hb disorder which the World Health Assembly has noted to be a

public health burden especially in sub-Sahara Africa with majority of cases emanating from Nigeria (2, 3). This burden entails its prevalence, morbidity (including disease manifestations), and outcome (mortality and survival) (4). The prevalence of SCA in Nigeria is about 20 per 1,000 births (2%) with that in Calabar being 2.14% (5, 6). These values were largely obtained from adult patients with SCA. Since year 2000, Nigeria has persistently exceeded more than 2,000 per 100,000 live births of SCA incidence largely due to increase in population and survival in childhood (4). Its prevalence in children varies across different regions in Nigeria: 11.9% in Benin, 10.1% in Zaria, 5% in Imo, 3.7% in Port Harcourt and 2.69% in Jos (7-11). They are obviously higher than the predominantly adult derived prevalent values. The disease manifestations arise due to the mutation which results in the substitution of glutamate for valine in the β-globin chain of the Hb resulting in the formation of Hb sticky points during stressful conditions, Hb polymerization and subsequent erythrocyte sickling (12). The sickling further results in acute episodic events (crises) and complications of SCA (12). The crises include vaso-occlusive crises (VOC), aplastic crises, splenic sequestration and hyper-haemolytic crises. The VOC includes stroke, seizures, sickle cell retinopathy, bone pain crises, acute chest syndrome, abdominal crises, among others (13). Most of the complications are infective like osteomyelitis, septic arthritis; structural like vertebral collapse, kyphosis; severe anaemia with or without heart failure, among others (13). These crises and complications constitute the morbidity in SCA and are the main reasons for their high mortality rate. The mortality rate of SCA has been noted to be higher in adults than in children (14). This has been attributed to factors notably faulty transition to adult SCA care, lower medication adherence since they are independent from their parents, fear of leaving familiar health care providers, increasing treatment cost and progressive disease severity (15, 16). This may also be the reason childhood prevalence of SCA is higher than that in adulthood. Earlier studies have assumed high paediatric SCA mortality but the childhood SCA mortality trend has been shown to be reducing over the decades (17, 18). The magnitude of the morbidity, mortality and survival of children with SCA is unknown in various regions of Nigeria despite having the highest global burden of SCA. The population of Nigeria has grown over the past two decades and it may contribute to the rising burden (4). Efforts have been made over this period to improve survival of persons with SCA especially in the development of treatment guidelines (19-21). Some of these efforts include regular counselling during routine clinic visits and intake of medications like hydroxyurea. Therefore, elucidation of the frequency, disease manifestations and survival of children with SCA in locations with high prevalence in Africa will aid in the understanding of how best to tackle the trend of the burden by relevant stakeholders. Hence, this study aimed to determine the prevalence, morbidity and outcomes of paediatric SCA in a hospital centre of a low- and middle-income country.

Materials and Methods

This was a retrospective study that reviewed medical records of children with SCA seen in the Paediatric out-patient and Haematology-Oncology clinics as well as the Children Emergency Room (CHER) of the Department of Paediatrics in a tertiary hospital in south-south Nigeria. The clinics and CHER are the portals of entry of all children into the hospital.

[DOI: 10.18502/ijpho.v15i2.18174]

Study period: January 2018 through December 2023.

Sample size: all children with SCA managed during the study period were enrolled.

Inclusion criteria: all children, 6 months to 17 years old, diagnosed and treated of SCA (i.e., HbSS) in the hospital.

Exclusion criteria: children less than 6 months of age, any child who is not SCA and any child with SCA, identified in the nurses' register, whose medical case file could not be found.

In the Paediatric out-patient clinic and CHER, Registrars are the first contact doctors that see patients. These doctors summarize the patients' clinical (disease) manifestations into diagnoses. These patients are then reviewed by one of the three Consultant Paediatricians in CHER who make final diagnosis of the disease manifestations of each patient. Similarly, the Paediatric Haematology-Oncology clinic has four Consultants who manage children with SCA and they make their final diagnoses in each visit of the patients. After review by the Consultant Paediatrician, the patient may either be hospitalized or managed on an out-patient basis. Transition of children to adult SCA care is done between 17 and < 18 years of age.

Names and hospital numbers of all children with SCA (insured and uninsured), obtained from the nurses' registers, were used in getting their medical case folders, where the required information was drawn.

The information included sex, age and date on first visit in each of the years, diagnoses and date in each of the visits, location of each visit: clinic or CHER, intervals between visits, age and date at transition to adult care, age and diagnosis at death. For the purpose of this study, there were three age group categories: Pre-school age (0.5 to 4 years), primary school age (5 to 9 years) and secondary school age (10 to 17 years). The intervals between visits were used to obtain the default time. In addition, the first time visit in the clinic and CHER, in each of the years, of all non-SCA children was obtained and used in calculating the prevalences. These data were entered into collection forms.

The date of first-time clinic visit of each subject in each year was gotten by noting the initial fee paid for that year, in the nurses' registration booklet, which is always higher than the routine consultation fees. In the CHER, the nurses' emergency room register was similarly used to obtain initial visits. Patients' data were then transferred to Microsoft Excel where duplicated names and hospital numbers were removed to avoid repetition.

Outcomes: paediatric SCA prevalence, diagnoses, frequent hospitalisation, compliants, compliant time, defaults, default time, transition to adult SCA care and death.

Definition of terms:

a. Overall prevalence of SCA is average annual prevalence of SCA. For the purpose of this study, annual prevalence of SCA is number of first visits by the SCA patients in that year divided by the total number of first visits of all children in the same year, multiplied by hundred.

b. Diagnosis is symptoms, signs and laboratory investigations in each patient summarized into medical term(s) by a Consultant Paediatrician.

c. Frequent hospitalisation is > 2 hospitalisations per patient per year.

d. Infrequent hospitalisation is 1 to 2 hospitalisations per patient per year.

e. Compliant is any child with SCA with hospital visits interval of ≤ 3 months. Routine clinic visits of children with SCA are performed up to 3 monthly hence there should be at least 4 visits in a year.

f. Default is any child with SCA with > 3 months of no hospital visit.

[DOI: 10.18502/ijpho.v15i2.18174]

g. Compliant time or visit compliance per subject was cumulative ≤ 3 months intervals of visits or treatment
h. Default time per subject was time from first ever visit in the study period to the end of 2023 minus compliant time. It is the total time of no hospital visit of > 3 months per patient.
i. A sick visit is hospital visit that results in non-steady state diagnosis. It may lead to hospitalisation.
j. Steady-state is that point in time when there is no acute painful crisis, infection, inflammation or hospital admission for at least 4 weeks and no blood transfusion for at least 4 months (22).

Statistical analysis

Information extracted from the collection forms were collated using Microsoft Excel worksheet. Some data in the worksheet were exported and analysed using Statistical Package for the Social Sciences (SPSS) version 23.0 software (https://www.ibm.com/analytics/spss-statisticssoftware).

All numerical data were skewed and were presented as median (interquartile range). Categorical variables (age groups, sex, diagnoses, hospitalisations and default time) were compared with appropriate Chi-square tests. To avoid type 1 error, Bonferroni correction of the adjusted residuals, derived from post-hoc analyses of the association between age groups, sex and diagnoses, was utilized to derive the adjusted p-values (p-value_adj). Multinomial logistic regression was conducted to measure the relationship between significant diagnoses (outcomes), obtained from the post-hoc analyses; and the predictors (age group and sex). Default analyses (default time and annual overall default) were calculated using Kaplan-Meier method and the differences in the default curves compared with Log Rank (Mantel-Cox) Chi-square test. Alpha level < 0.05 was set as statistical significance at 95% confidence interval.

Results

A total of 532 (97.3%) out of the 547 children with SCA observed over the 6-year period were included in the study. The medical case files of the remaining 15 children with SCA were not found. Males were 296 (55.6%) while 236 (44.4%) were females with male: female ratio of 1.3: 1. The overall median (IQR) age on first visit of the children with SCA was 9 (5 - 13) years with range of 0.5 year (6 months) to 17 years. There were 2,696 hospital visits and 879 hospitalisations while 3,263 diagnoses were made during the period giving a ratio of 1.2 diagnoses per visit and 544 diagnoses per year. Furthermore, there were 252 sick visits per year, 56 sick visits per 100 visits per year, 348 non-steady-state diagnoses per year, 146 hospitalisations per year and approximately 1 hospitalisation per sick visit per year. Overall prevalence of childhood SCA was 3.99% with the highest annual prevalence (4.95%) occurring in 2020. Table I.

There were 52 (8.3%) > 2 hospitalisations per year while 1 to 2 hospitalisations per year were 578 (91.7%) and the difference among the age groups and sex of these 2 groups of hospitalisations was not statistically significant (Chi-square 0.898; p=0.970). Furthermore, males had more hospitalisations than the females (357 versus 273). Figure 1.

Pattern of diagnoses in the emergency room and clinics

Thirty-two types of diagnoses were made during the study period out of which 25 types were in the emergency room while 30 types were observed in the clinics. Seizures and meningitis were observed only in the emergency room while steady-state, aplastic crises, sickle cell

[DOI: 10.18502/ijpho.v15i2.18174]

retinopathy, Pott's disease, otitis media, vertebral collapse and nephrotic syndrome were observed only in the clinics. Bone pain crises were more frequently seen in the clinics with highest in 2023 and least in 2020. There were 1,248 non-steady-state clinic diagnoses unlike the 842 diagnoses in the emergency room. Table II.

Yearly outcomes of the clinical management of children with SCA

Three (0.56%) subjects died during the period in review while 47 (8.83%) transited to adult care. The first death occurred in 2018, at the age of 13 years, following acute chest syndrome while the others occurred in 2021 and 2023, at the ages of 10 and 15 years, due to hyperhaemolytic crisis and severe anaemia with heart failure, respectively. Majority of the transitions to adult care [18 (38.3%)] occurred in 2022. Figure 2. Of the 482 subjects that neither died nor transited to adult care, 410 (85.1%) of them defaulted to clinical management. Overall median (IQR) default time was 0.5 (0.43 - 0.57) year and the difference between defaults and compliants was statistically significant in each year (Log Rank Chi-square 75.34; $p<0.001$). All the 104 subjects who first visited in 2019 defaulted and none of them were visiting the hospital for treatment after 2.5 years. Similar event occurred in 2020. However, over the 2 years of those who first presented in 2022, 28% of those who defaulted were remaining after 6 months of visits [0.5-year Overall Default (OD) of 28%] while after 1 year of visits, no other default was observed. Table III and Figure 3.

Number of diagnoses observed across the age groups

The diagnosis, steady-state, was made most frequently in the 10- to 17-year-olds who accounted for 1,380 (42.3%) of all the diagnoses followed by the 5- to 9-year-olds [1,091 (33.4%)] and the 0.5- to 4-year-olds [792 (24.3%)]. Similarly, the non-steady-state diagnoses were observed in the 10- to 17-year-olds [922 (44.1%)], the 5- to 9-year-olds [658 (31.5%)] and the 0.5- to 4-year-olds [510 (24.4%)]. The VOCs (bone pain crises, abdominal crises, acute chest syndrome, stroke, avascular necrosis, leg ulcer, hyposthenuria, priapism, gross haematuria, seizures, retinopathy, and nephrotic syndrome) constituted 985 (89.1%) of the 2,090 non-steady state diagnoses. The relationship between diagnoses, age-group and sex was statistically significant (Chi-square 281.48; $p<$**0.001**). The occurrence of bone pain crises ($p=$**0.046)** and upper respiratory tract infection ($p<$**0.001**) in the male 0.5- to 4-year-olds was statistically significant. The top three most frequent diagnoses were steady-state, bone pain crises and malaria. Table IV.

Regression analysis of the significant diagnoses associated with age-group and sex

The multinomial logistic regression model was statistically significant ($\chi^2=109.378$; $p<0.001$) with non-statistically significant goodness of fit (Pearson and Deviance χ^2), explained 5.6% (Nagelkerke R^2) of the variance in the age groups and sex; and correctly predicted 53.1% of the diagnoses. In comparison with steady state and other parameters kept constant, age-group 0.5 to 4 years was 61.9% less likely to have bone pain crises than age-group 10 to 17 years and it was statistically significant. Hence, age-group 10 to 17 years was more likely to have bone pain crises than age-groups 0.5 to 4 years (OR 0.381; 95% CI: 0.487 - 0.787) and 5 to 9 years (OR 0.298; 95% CI: 0.573 - 0.861). However, age-group 0.5 to 4 years was 142.5% (2.425 minus 1) more likely to have URTI than age-group 11 to 17 years and it was statistically significant. Only the male 10- to 17-year-olds had gross haematuria. There was no significant relationship between sex and the diagnoses. Table V.

[DOI: 10.18502/ijpho.v15i2.18174]

Table I: Biodata, annual number of visits and hospitalisations of all children

Variables	Year					
	2018	2019	2020	2021	2022	2023
Median (IQR) Age (years) on first visit of CSCA	8 (4 - 12)	8 (5 - 13)	8 (4 - 11)	10 (6 - 13)	10 (5 - 14)	9 (5 - 13)
Age group (years) of CSCA						
0 – 4	44	54	42	29	42	30
5 – 9	59	73	57	51	68	63
10 – 17	55	90	61	82	113	82
Sex of CSCA						
Male	85	121	92	97	133	101
Female	73	96	68	65	90	74
Number of first visits of CSCA	158	217	160	162	223	175
Number of first visits of CSCA and other children	5,589	5,860	3,230	4,433	5,147	3,901
Frequency (%) of CSCA	2.83	3.70	4.95	3.65	4.33	4.49
Number of all visits of CSCA	232	628	294	346	653	543
Number of SCA steady-state visits	95	352	148	117	257	204
Number (%) of sick visits of CSCA	127 (54.7)	276 (43.9)	147 (50)	229 (66.2)	396 (60.6)	339 (62.4)
Number of non-steady-state SCA diagnoses	194	375	190	309	541	481
Number of hospitalisations of CSCA	114	133	72	149	235	176

CSCA=Children with SCA; IQR=Interquartile range; SCA=Sickle Cell Anaemia.

[DOI: 10.18502/ijpho.v15i2.18174]

Table II: Pattern of diagnoses in the clinics and emergency room

Diagnoses	Yearly number of diagnoses in clinic (C) and emergency room (E)												Total (%)	
	2018		2019		2020		2021		2022		2023			
	C	E	C	E	C	E	C	E	C	E	C	E	C	E
Steady-state	95	-	352	-	148	-	117	-	257	-	204	-	1173(48.45)	-
Bone pain crises	15	63	94	32	43	32	55	58	105	93	107	111	419(17.30)	389(46.20)
Malaria	9	27	67	18	29	10	54	15	107	43	80	22	346(14.29)	135(16.03)
URTI	7	-	41	-	26	-	22	-	47	-	39	-	182(7.52)	-
Sepsis	2	17	15	11	10	6	9	15	10	18	16	11	62(2.56)	78(9.26)
Severe anaemia	3	9	3	6	-	5	5	8	2	9	5	4	18(0.74)	41(4.87)
Pneumonia	2	6	8	3	1	1	2	3	6	18	9	6	28(1.16)	37(4.40)
ACS	-	9	6	8	-	1	-	6	-	4	-	4	6(0.25)	32(3.80)
Abdominal crises	-	1	11	4	6	-	5	6	8	4	5	7	35(1.45)	22(2.61)
HHC	-	1	-	1	3	1	2	2	1	7	1	7	7(0.29)	19(2.26)
Stroke	-	2	3	4	-	-	2	-	1	5	-	5	6(0.25)	16(1.90)
Septic Arthritis	-	2	2	2	2	1	3	3	2	2	1	2	10(0.41)	12(1.43)
Osteomyelitis	-	4	4	-	2	-	2	7	7	-	3	-	18(0.74)	11(1.30)
SSC	-	1	-	1	-	1	-	2	4	3	1	2	5(0.21)	10(1.19)
UTI	-	1	6	1	2	-	3	3	3	4	5	-	19(0.78)	9(1.07)
Pharyngitis/Tonsilitis	1	2	11	2	-	-	1	1	6	-	6	-	25(1.03)	5(0.60)
Hyposthenuria	-	2	1	-	-	1	2	-	-	-	2	1	5(0.21)	4(0.48)
Leg ulcer	-	-	3	1	1	-	-	1	3	-	3	2	10(0.41)	4(0.48)
Priapism	-	1	-	-	-	-	4	1	1	1	-	-	5(0.21)	3(0.36)
Asthma	1	1	1	2	1	-	-	-	4	-	1	-	8(0.33)	3(0.36)
Meningitis	-	-		-		-		-		2		1	-	3(0.36)
Seizures	-	1		1		-		-		-		-	-	2(0.24)
Gross haematuria	-	-	-	-	-	-	-	-	-	-	1	2	1(0.04)	2(0.24)
AVN	-	1	1	-	3	-	3	-	6	-	5	-	18(0.74)	1(0.12)
Gall stones	-	-	-	-	2	-	-	1	2	-	-	-	4(0.17)	1(0.12)
Pott's disease	-	1	-	-	-	-	1	-	-	-	-	-	1(0.04)	1(0.12)
TBL	-	-	-	-	-	-	1	-	1	-	-	-	2(0.08)	-
Otitis media	-	-	-	-	-	-	1	-	-	-	1	-	2(0.08)	-
Vertebral collapse	-	-	-	-	-	-	-	-	1	-	1	-	2(0.08)	-
Retinopathy	-	-	-	-	-	-	-	-	1	-	1	-	2(0.08)	-
Nephrotic syndrome	-	-	-	-	-	-	-	-	-	-	1	-	1(0.04)	-
Aplastic crises	-	1	-	-	-	-	-	-	-	-	-	-	1(0.04)	-
Total	135	154	630	97	279	59	294	132	585	213	498	187	2421(100)	842(100)

ACS=Acute Chest Syndrome; AVN=Avascular Necrosis; HHC= Hyperhaemolytic crises; SSC=Splenic sequestration crises; TBL=Tuberculous lymphadenitis; URTI=Upper Respiratory Tract Infection; UTI=Urinary Tract Infection.

Table III: Default time over the 6-year period of the children with SCA. n=482

Year	Number of subjects	Number of defaults	Median(IQR) DT_ year	0.5-year OD_%	1-year OD_%	1.5-year OD_%	2-year OD_%	2.5-year OD_%	3-year OD_%
2018	139	139	0.75(0.6-0.9)	58	39	23	13	5	1
2019	104	104	0.5(0.37-0.63)	42	18	9	3	NV	NV
2020	49	49	0.25(NA)	20	10	6	2	NV	NV
2021	60	57	0.25(NA)	30	10	5	ND	ND	ND
2022	83	60	0.5(NA)	28	ND	ND	ND	NA	NA
2023	47	1	NA	94	ND	NA	NA	NA	NA

DT=Default time; NA=Not applicable; ND=No default observed; NV=No visit; OD=Overall default.

[DOI: 10.18502/ijpho.v15i2.18174]

Table IV: Diagnoses made in both sexes across the age groups during the 6-year period

Diagnoses	Age group and sex [n (*p*-value_adj)]						Total [n (%)]
	0.5 to 4 years		5 to 9 years		10 to 17 years		
	Male	Female	Male	Female	Male	Female	
Steady-state	174(5.233)	108(4.286)	246(0.846)	187(2.520)	255(6.219)	203(1.040)	1173(35.95)
Bone pain crises	101(**0.046***)	50(0.430)	147(16.233)	116(27.855)	214(0.254)	182(0.252)	810(24.82)
Malaria	99(0.102)	36(16.379)	88(22.274)	69(29.407)	104(13.808)	85(10.680)	481(14.74)
URTI	51(<**0.001***)	25(0.178)	26(3.172)	28(23.231)	22(**0.01***)	30(10.418)	182(5.58)
Sepsis	32(0.780)	17(2.765)	24(18.533)	16(9.344)	25(4.425)	26(26.521)	140(4.29)
Pneumonia	9(20.099)	9(3.108)	19(1.038)	8(19.607)	9(2.433)	11(20.065)	65(1.99)
Severe anaemia	7(12.127)	3(11.944)	13(17.294)	10(18.850)	14(28.656)	12(26.709)	59(1.81)
Abdominal crises	12(9.500)	6(16.874)	11(30.221)	7(20.216)	14(24.950)	7(5.656)	57(1.75)
ACS	-	2(16.050)	9(14.488)	5(26.038)	13(3.172)	9(15.629)	38(1.16)
Pharyngitis/Tonsilitis	11(0.062)	2(24.074)	6(28.211)	6(12.468)	3(2.843)	2(2.514)	30(0.92)
Osteomyelitis	2(5.701)	1(11.058)	6(25.890)	3(16.755)	7(28.330)	10(1.185)	29(0.89)
UTI	5(25.313)	5(2.023)	1(1.187)	4(31.190)	6(26.918)	7(14.101)	28(0.86)
HHC	2(27.831)	1(13.216)	4(20.553)	6(6.787)	8(11.061)	5(31.847)	26(0.80)
Septic arthritis	1(4.503)	1(16.858)	4(29.679)	-	8(4.339)	8(1.327)	22(0.67)
Stroke	3(24.287)	1(16.858)	4(29.679)	2(15.039)	4(18.844)	8(1.327)	22(0.67)
Avascular necrosis	2(16.386)	-	2(11.132)	1(8.051)	11(**0.009***)	3(22.372)	19(0.58)
SSC	1(10.300)	-	1(7.168)	4(5.747)	4(23.562)	5(5.330)	15(0.46)
Leg ulcer	-	-	1(8.285)	-	5(8.255)	8(**0.01***)	14(0.43)
Asthma	4(2.097)	1(29.392)	-	1(19.520)	2(22.490)	3(16.021)	11(0.34)
Hyposthenuria	-	-	1(17.547)	-	7(**0.003***)	1(17.089)	9(0.28)
Priapism	2(15.635)	-	2(21.164)	-	4(2.222)	-	8(0.25)
Gall stones	-	-	1(30.454)	-	2(11.73)	2(7.672)	5(0.15)
Meningitis	1(13.238)	1(3.645)	1(16.781)	-	-	-	3(0.09)
Gross haematuria	-	-	-	-	3(**0.048***)	-	3(0.09)
Seizures	1(6.086)	-	-	-	1(11.663)	-	2(0.06)
Retinopathy	1(6.086)	-	-	-	-	1(8.657)	2(0.06)
Pott's disease	-	-	-	-	1(11.663)	1(8.657)	2(0.06)
TBL	-	-	-	-	2(0.309)	-	2(0.06)
Otitis media	1(6.086)	-	1(8.387)	-	-	-	2(0.06)
Vertebral collapse	-	-	-	-	2(0.309)	-	2(0.06)
Aplastic crises	1(0.706)	-	-	-	-	-	1(0.03)
Nephrotic syndrome	-	-	-	-	1(2.155)	-	1(0.03)

ACS= Acute chest syndrome; HHC= Hyperhaemolytic crises; n=number of diagnoses; *p*-value_adj=Bonferroni adjusted *p*-value; SSC=Splenic sequestration crises; TBL= Tuberculous lymphadenitis; URTI=Upper Respiratory Tract Infection; UTI= Urinary tract infection; *and bold figures=statistical significance.

Table V: Multinomial regression analysis of the significant diagnoses associated with age-group and sex

Diagnoses[a]	Age-group_years[b]	OR (95% CI)	Sex[c]	OR (95% CI)
Bone pain crises	0.5 to 4	0.619 (**0.487-0.787**)	Male	1.006 (0.838-1.207)
	5 to 9	0.702 (**0.573-0.861**)		
URTI	0.5 to 4	2.425 (**1.651-3.561**)	Male	0.819 (0.596-1.125)
	5 to 9	1.103 (0.737-1.650)		
Avascular Necrosis	0.5 to 4	0.211 (**0.047-0.938**)	Male	2.988 (0.983-9.085)
	5 to 9	0.223 (**0.064-0.781**)		
Leg ulcer	0.5 to 4	0.001 (0.000-19.883)	Male	0.626 (0.215-1.824)
	5 to 9	0.082 (**0.011-0.630**)		
Hyposthenuria	0.5 to 4	0.001 (0.000-19.854)	Male	6.664 (0.829-53.55)
	5 to 9	0.129 (0.016-1.036)		
Gross haematuria	0.5 to 4	0.001 (0.000-0.000)	Male	941.6 (941.6-941.6)
	5 to 9	0.001 (0.000-0.000)		

a=reference is steady state; b=reference is 10 to 17 years; c=reference is female; CI=Confidence interval; OR=Odds ratio; URTI=Upper respiratory tract infection.

[DOI: 10.18502/ijpho.v15i2.18174]

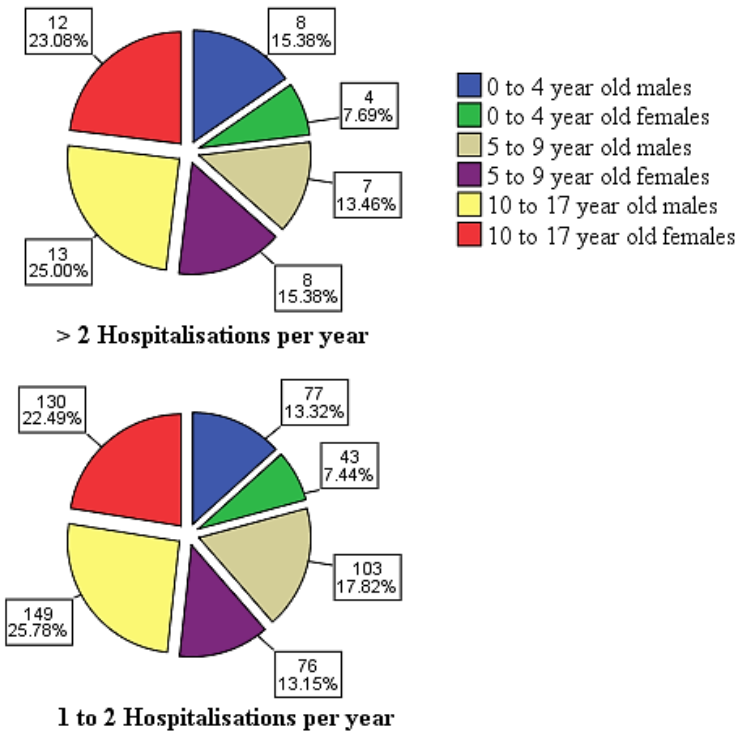

Figure 1. Age groups, sex and hospitalisations of the children with SCA over the 6-year period

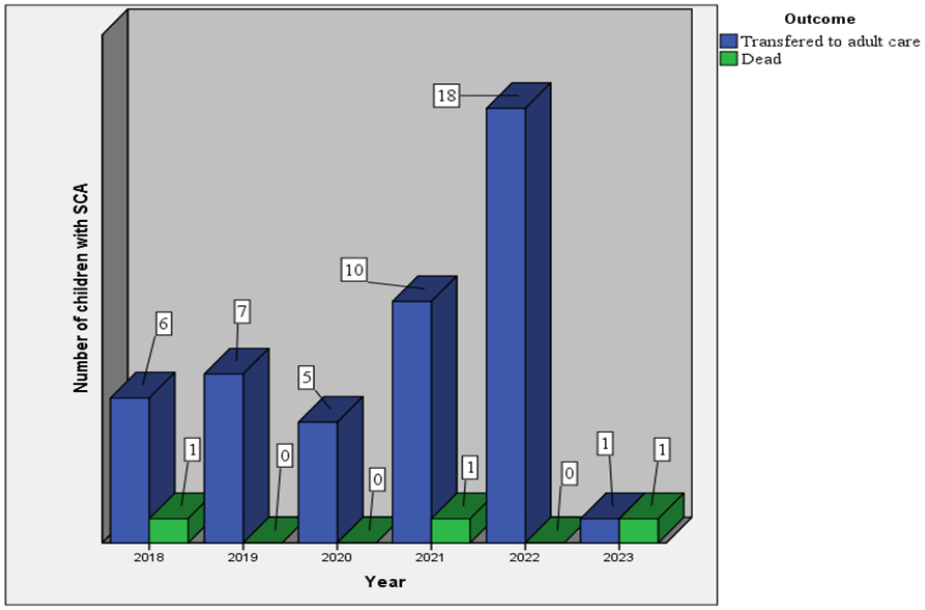

Figure 2. Children with SCA who were transferred to adult care and those that died over the 6-year period

[DOI: 10.18502/ijpho.v15i2.18174]

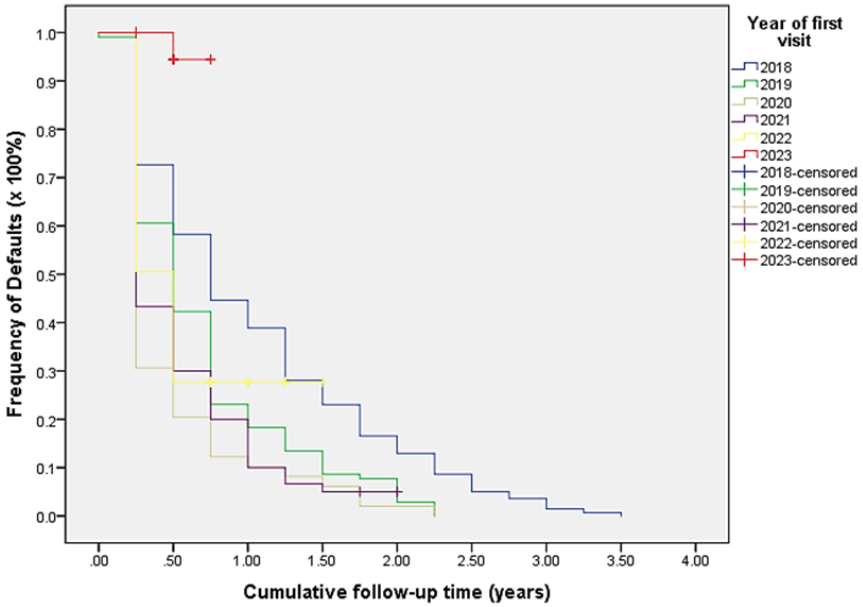

Figure 3. Kaplan-Meier analysis of time from visit compliance to default (Overall Default) in each of the years

Discussion

The prevalence of paediatric SCA in Calabar, Nigeria is 3.99%. They were predominantly males and in their high school ages with more than half of their hospital visits being sick visits. There were more clinic visits than emergency room visits. Thirty-one types of diagnoses that are not steady-state diagnoses were made 2,090 times, especially in the clinics. Majority had non-frequent (< 3) hospital admissions particularly among the male adolescents. The VOC constituted more than three quarters of the non-steady-state diagnoses with bone pain crises as the most common. The adolescents were more likely to have bone pain crises, avascular necrosis, leg ulcer, hyposthenuria and gross haematuria than others. Malaria was the most common infection. Majority of the patients substantially did not come for routine clinic visits for more than 3 months (i.e., defaulted) which worsened throughout the years. Few patients were referred to the adult haematologists for continued care while very few died.

This study found that childhood SCA prevalence in the region is higher than the 2.14% obtained from genotypes of all children and adults performed from 2008 through 2019 in the same region (6). This may be due to their increased survival in childhood when most of their care, including hydroxyurea, are strictly administered by their parents or guardians unlike in adulthood when there may be faulty transition of care to the patients and adult physicians (15). Other reasons may be due to regular counselling during childhood and increase in population growth (23). The Cross River State projected growth increase for persons 0 to 19 years of age as at 2018 and 2022 were 2,034,440 and 2,135,446 respectively with average annual increase of 1.2% (21). This finding on childhood SCA prevalence is similar to that obtained in other parts of Nigeria (7-11). The annual prevalence of childhood SCA was highest in year 2020. This is due to the low number of children that attended hospital that year when there was citywide lockdown due to the global severe acute respiratory syndrome

[DOI: 10.18502/ijpho.v15i2.18174]

coronavirus-2 (SARS-CoV-2) pandemic. Majority of these patients were adolescents who were seen most of the times in the clinics when they were not in their steady-state of health. This may be due to the non-emergency protracted crises and complications of the disease which has been shown to be associated with poor growth and delayed puberty in late childhood (24). The less frequent emergency room visits can be attributed to the disease severity of the patients which is predominantly mild (78.6%) (25). Most patients with SCA in Nigeria have the Benin/Senegal haplotype which is associated with few hospitalisations and VOC because of their high blood level of fetal haemoglobin (26, 27). Fetal haemoglobin prevents sickling of the red blood cells and it may explain why steady-state constituted more than a third of all the diagnoses. Most of the diagnoses, when the patients were not in their usual steady state of health, were VOC particularly bone pain crises. This is due to the sickled erythrocytes induced microvascular ischaemia-reperfusion injury and activation of peripheral nociceptors (12). These pain receptors are activated by inflammatory mediators that are generated by tissues dying as a result of the ischaemia (28). This implies that bone pain crises is the most common morbidity in these patients. This finding is akin to that observed in similar patient cohorts in other regions over the years (7, 9-11, 29-32). The consequential occurrence of bone pain crises, avascular necrosis, leg ulcer and nephropathy (hyposthenuria and gross haematuria) among the adolescents than other age-groups is noteworthy. This finding implies that increasing age is a predictor of the aforementioned diagnoses. These complications may be a result of the chronicity of tissue ischaemia in SCA as the children grow. This is in consonance with findings which showed predominance of kidney injury, leg ulcer and avascular necrosis in older children (30, 33, 34). The finding in this study of majority of the hospitalisations occurring among the adolescents may be due to the additional changes and energy requirements that occur during puberty which may worsen any crisis or complication (35). In addition, poor nutrition has been shown to affect puberty in SCA (24). Majority of the parents of the patients are of the low socioeconomic class which is associated with poor nutrition (36). The higher number of infrequent compared with frequent hospitalization in this study may be due to the mild nature of childhood SCA in the locality (25). The most common complication was infections, particularly malaria and upper respiratory tract infections, and their sequelae especially severe anaemia. Sickle cell anaemia is associated with abnormalities in the immune system. Specifically, there is impaired antibody production, aberrant activation of alternate complement pathway, impaired leucocyte phagocytic and oxidative burst activities (37, 38). This leads to pneumonia, bone infections, hyperhaemolysis, among others. Low level malaria infection in childhood SCA can trigger severe anaemia unlike in those with genotype AA (39). Furthermore, malaria is hyperendemic in the region (40). Upper respiratory tract infections were found to be more common than pneumonia in this study. This is in contrast to the findings in other regions of the country where lower respiratory tract infections were the most common respiratory tract infections (41). Malaria and upper respiratory tract infections have been shown to be associated with severe anaemia (42). Follow-up clinic visit is essential in the management of SCA. This study found that very few of the patients were compliant to hospital visits. The total time of no hospital visit for many of the patients was six months. The non-compliance to

[DOI: 10.18502/ijpho.v15i2.18174]

hospital visits may be due to caregiver fatigue, financial constraints and some parents' idea of no need of coming to the hospital when their children are not sick. It may also be as a result of the mild disease severity (25). The few patients who were transited to adult care may be a consequence of the non-compliance to visit by the majority. Only three children with SCA died during the period in review. These patients were adolescents who complied poorly to routine hospital care. Their death was largely due to infective complications. The 0.56% mortality rate found in this study is closer to the 1.7% reported in Ibadan compared to the higher rate of 4.6% found in Zaria (10, 43). No death occurred in the pre-school age in this study; in contrast to a model-estimate, which has been critiqued, that showed 4.2% Nigeria under-5 mortality rate attributable to sickle cell disease (44, 45). The finding in this study is also incongruous with a malaria study in Garki, Kano state, Nigeria (1970 – 1974) which assumed that 98% of children with SCA die by the age of 5 years and a review that speculated early death rate of 50% to 90% among children with SCA in Africa (17, 46). There is dearth of data on childhood SCA mortality in resource-poor countries: available studies describe mainly under-5 mortality (23). This information gap on comprehensive childhood burden of SCA in Nigeria as well as other low- and middle income country, can be closed by creating awareness and strengthening already existing database for tracking SCA survival (47). In contrast, the mortality rate reported in adult SCA patients is high and it may be a consequence of improper transition to adult care, predominant inadequate care in adulthood and low life expectancy at birth especially in resource-poor nations like Nigeria where it is 53.6 years as at 2022 (48, 49). This implies that there is need to integrate SCA into universal health coverage and ensure all levels of care, especially the primary health centers, are involved in their appropriate management (50). Nevertheless, information on intake of hydroxyurea, blood levels of fetal haemoglobin, frequency of blood transfusion, socioeconomic status including monthly income, and amount of money parents spend per hospital visit were incomplete, inconsistent or lacking in the medical records. These limitations may have hindered further elaboration of the burden of SCA in the children. Moreover, acknowledgement of the status (morbidity and mortality) of the patients that were lost to follow-up and; the parental psychological and physical wellbeing via community survey could have significantly elucidated the childhood SCA burden.

Conclusion

In conclusion, the childhood SCA prevalence in Calabar, Nigeria is approximately 4%. The SCA morbidity was largely influenced by age. The disease morbidity includes more than one diagnoses per hospital visit, predominance of VOC, one hospitalisation per sick visit, more hospitalisations among the adolescents per sick visit and preponderance of non-compliance to hospital visits. However, the mortality rate was 0.56% which probably underscores the effective clinical care they receive during childhood. Continuing paediatric SCA treatment strategies into adulthood may aid in reducing the morbidity and mortality of SCA globally. This will entail the institution of properly constituted and collaborative transition teams made up of paediatricians, paediatric haematologists, adult haematologists/physicians, social workers, among others; in each tertiary center that care for persons with SCA.

[DOI: 10.18502/ijpho.v15i2.18174]

Ethical Considerations

Ethically required registration and clearance to conduct the study were obtained from the Health Research and Ethics Committee of the tertiary health institution (UCTH/HREC/33/Vol.III/355).

Acknowledgments

The Authors never used artificial intelligence (AI) in the study.

Authors' Contributions

Anthony Nlemadim: conceptualized the study and designed it; acquired data, sample analysis and interpretation; statistical analysis; drafted and revised the manuscript, agreed on the journal to which it will be published, reviewed and agreed all manuscript versions before submission, agreed to take responsibility and accountable for its contents and gave final approval for publication. Elizabeth Nkanga: contributed to the study conceptualization and design, sample interpretation, critically reviewed the manuscript, agreed on the journal to which it will be published, reviewed and agreed all manuscript versions before submission, agreed to take responsibility and accountable for its contents and gave final approval for publication. Jacinta Okoi-obuli, Chimaeze Torty, Kingsley Akaba, Juliet Venn, Kelechi Uhegbu, Sunday Okonkwo, Grace Nwankwo, Ofonime Essien, Glory Bassey, Friday Odey and Martin Meremikwu contributed to the study design, data interpretation, review of manuscript, agreed on the journal to which it will be published, reviewed and agreed all manuscript versions before submission, agreed to take responsibility and accountable for its contents and gave final approval for publication.

Funding

None

Conflict of Interest

The authors report there are no competing interests to declare.

References

1. Weil PA. Molecular Genetics, Recombinant DNA & Genomic Technology. In: Rodwell VW, Bender DA, Botham KM, Kennelly PJ, Weil PA, editors. Harpers's Illustrated Medical Biochemistry. 31st ed. New York: Mc Graw Hill; 2018. 442-443.
2. World Health Organization. Sickle-cell anaemia: report by the secretariat. Fifty-ninth World Health Assembly A59/9; Provisional agenda item 11.4 24. 2006. Available from https://apps.who.int/gb/archive/pdf_files/WHA59/A59_9-en.pdf [Accessed 30-May-2024].
3. World Health Organization. Fifty-Ninth World Health Assembly. Resolutions and decisions annexes. Resolution WHA59.20. Sickle-cell anaemia. Geneva. WHO; 2006 Available fromhttp://apps.who.int/iris/bitstream/handle/10665/21447/A59_R20-en.pdf;jsessionid=1143FD4ECA6BF1366DCBE3387165C0FD?sequence=1. [Accessed 30-May-2024].
4. Thomson AM, McHugh TA, Oron AP, Teply C, Lonberg N, Tella VV, et al. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: a systematic analysis from the Global Burden of Disease study 2021. Lancet Haematol 2023; 10:e585–599.
5. WHO. Sickle-cell anaemia: report by the Secretariat. World Health Organization; 2006. Available from https://apps.who.int/iris/bitstream/handle/10665/20890/A59_9-en.pdf?sequence=1&isAllowed=y [Accessed 19-July-2024].
6. Kingsley A, Enang O, Essien O, Legogie A, Cletus O, Oshatuyi O.

[DOI: 10.18502/ijpho.v15i2.18174]

Prevalence of sickle cell disease and other haemoglobin variants in Calabar, Cross River state, Nigeria. Annu Res Rev Bio 2019:1-6.
7. Diwe K, Iwu AC, Uwakwe K, Duru C, Merenu I, Ogunniyan T, et al. Prevalence and patterns of sickle cell disease among children attending tertiary and non-tertiary health care institutions in a South eastern state, Nigeria: A 10 year survey. J Res Med Dent Sci 2016; 4(3):75-81.
8. Stephen N, Nden N, Gusen NJ, Kumzhi PR, Gaknung B, Auta DA, et al. Prevalence of sickle cell disease among children attending plateau specialist hospital, Jos, Nigeria. Acta Med Int 2018; 5(1):20-23.
9. West BA, Aitafo JE. Prevalence, Pattern of disease and outcome of children with sickle cell disease admitted in a private health facility in southern Nigeria. Asian J Pediatr Res 2023; 12(1):17-27.
10. Faruk JA, Adebiyi MN, Ahmad HR. Clinico-demographic characteristics, morbidity and mortality patterns of sickle cell disease in a tertiary institution. Sahel Med J. 2022; 25(2):52-56.
11. Abhulimhen-Iyoha BI, Israel-Aina YT, Joel-Utomakili K. Sickle cell anaemia: morbidity profile and outcome in a paediatric emergency setting in Nigeria. Afri J Med Health 2015; 14(2):79-82.
12. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet 2017; 390(10091):311-323.
13. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers 2018; 4(1):1-22.
14. Kayle M, Docherty SL, Sloane R, Tanabe P, Maslow G, Pan W, et al. Transition to adult care in sickle cell disease: a longitudinal study of clinical characteristics and disease severity. Pediatr Blood Cancer 2019; 66(1): e27463-274669.
15. Alashkar F, Aramayo-Singelmann C, Böll J, Hoferer A, Jarisch A, Kamal H, et al. Transition in sickle cell disease (SCD): a German consensus recommendation. J Pers Med 2022; 12(7):1-9.
16. Barbara S, Margulies S, Moffitt B, Holloway P, Campbell A, Martin B. Transitioning from Pediatric to adult care in sickle cell disease: patient and caregiver feedback. J Clin Ped Res 2022; 1(2):1-12.
17. Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med 2011; 41(6): S398-S405.
18. Hamideh D, Alvarez O. Sickle cell disease related mortality in the United States (1999-2009). Pediatr Blood Cancer 2013; 60(9):1482-1486.
19. Federal Ministry of Health Nigeria. National guideline for the control and management of sickle cell disease Abuja, Nigeria 2014; 2-7.
20. Adegoke S, Adeola S, Ambe J, Dawodu O, Ibrahim U, Israel-Aina Y, et al. Paediatric Association of Nigeria guidelines on the management of acute chest syndrome in children with sickle cell disease (2023). Niger J Paediatr 2024; 51(1):37-54.
21. National Population Commission. Nigeria population projections and demographic indicators-national and states. Abuja, Nigeria: National Population Commission; 2020.
22. Ballas SK. More definitions in sickle cell disease: steady state v base line data. Am J Hematol 2012; 87(3):338-339.
23. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and

[DOI: 10.18502/ijpho.v15i2.18174]

interventions. PLoS Med 2013; 10(7): e1001484-1001490.
24. Zemel BS, Kawchak DA, Ohene-Frempong K, Schall JI, Stallings VA. Effects of delayed pubertal development, nutritional status, and disease severity on longitudinal patterns of growth failure in children with sickle cell disease. Pediatr Res 2007; 61(5):607-613.
25. Nlemadim AC, Ikpeme OE, Meremikwu MM, Anah MU, Ineji EO. Steady-state electrocardiograms and disease severity of childhood sickle cell anemia in Calabar, Nigeria. Dysona Life Sci 2023; 4(1):1-9.
26. Adabale A, Makanjuola SBL, Akinbami A, Dosunmu A, Akanmu A, Javid FA, et al. Frequency of beta S globin gene haplotypes among sickle cell patients in Nigeria. J Int Med Res 2021; 49(6):1-11.
27. Steinberg MH. Genetic etiologies for phenotypic diversity in sickle cell anemia. Sci World J 2009; 9:46-67.
28. Fields HL, Rathmell JP. Pain: pathophysiology and management. In: Jameson JL, Kasper DL, Fauci AS, Longo DL, Loscalzo J, Hauser SL, editors. Harrison's Principles of Internal Medicine. 20th ed. New York: Mc Graw Hill; 2018. 65-72.
29. Adegoke S, Adeodu O, Adekile A. Sickle cell disease clinical phenotypes in children from South. Western, Nigeria. Niger J Clin Pract 2015; 18(1):95-101.
30. Utuk E, Akpan MU. The pattern of morbidity in children with sickle cell anaemia at the University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria. Inter J Health Sci Res 2015; 5(5):91-97.
31. Nri-Ezedi C, Ulasi TO, Ogamba MI, Obi DC, Echendu ST. Beyond emergencies: a five-year clinical profile on the pattern of presentation and seasonal trend of out-patient visits among children with sickle cell anaemia. Trop J Med Res 2022; 21(1):35-43.
32. Ambe J, Mava Y, Chama R, Farouq G, Machoko Y. Clinical features of sickle cell anaemia in northern Nigerian children. West Afr J Med 2012; 31(2):81-85.
33. Stallworth JR, Tripathi A, Jerrell JM. Prevalence, treatment, and outcomes of renal conditions in pediatric sickle cell disease. South Med J 2011; 104(11):752-756.
34. Olatunya O, Albuquerque D, Adekile A, Costa F. Evaluation of sociodemographic, clinical, and laboratory markers of sickle leg ulcers among young Nigerians at a tertiary health institution. Niger J Clin Pract 2018; 21(7):882-887.
35. Rhodes M, Akohoue SA, Shankar SM, Fleming I, An A, Yu C, et al. Growth patterns in children with sickle cell anemia during puberty. Pediatr Blood Cancer 2009; 53(4):635-641.
36. Jesus ACdSd, Konstantyner T, Lôbo IKV, Braga JAP. Socioeconomic and nutritional characteristics of children and adolescents with sickle cell anemia: a systematic review. Rev Paul Pediatr 2018; 36(4):491-499.
37. Aboderin FI, Oduola T, Davison GM, Oguntibeju OO. A review of the relationship between the immune response, inflammation, oxidative stress, and the pathogenesis of sickle cell anaemia. Biomedicines. 2023; 11(9):2413-2419.
38. Akinbo DB, Ajayi OI, Eluji OM, Olatunji I, Okoroloko TM. Impaired phagocytosis and oxidative respiratory burst activity in sickle cell anemia leukocytes. J Taibah Univ Med Sci 2024; 19(4):867-876.
39. Uyoga S, Olupot-Olupot P, Connon R, Kiguli S, Opoka RO, Alaroker F, et al. Sickle cell anaemia and severe plasmodium falciparum malaria: a secondary analysis of the Transfusion and Treatment of African Children Trial (TRACT). Lancet Child Adolesc Health 2022; 6(9):606-613.

[DOI: 10.18502/ijpho.v15i2.18174]

40. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Williams TN, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. Nat Commun 2010; 1(1):1-7.
41. Ibraheem RM, Abdulkadir MB, Aliu R, Issa A, Ibrahim OR, Bello AO, et al. Burden and outcome of respiratory morbidities among children and adolescents with sickle cell disease-A retrospective review of emergency presentations in some Nigerian tertiary institutions. PLoS One 2024; 19(5): e0303323-0303329.
42. Juwah A, Nlemadim A, Kaine W. Clinical presentation of severe anemia in pediatric patients with sickle cell anemia seen in Enugu, Nigeria. Am J Hematol 2005; 72(3):185-191.
43. Brown B, Jacob N, Lagunju I, Jarrett O. Morbidity and mortality pattern in hospitalized children with sickle cell disorders at the University College Hospital, Ibadan, Nigeria. Niger J Paed 2013; 40(1):34-39.
44. Nnodu OE, Oron AP, Sopekan A, Akaba GO, Piel FB, Chao DL. Child mortality from sickle cell disease in Nigeria: a model-estimated, population-level analysis of data from the 2018 Demographic and Health Survey. Lancet Haematol 2021; 8(10): e723-e731.
45. Wonkam A, Kengne AP. Modelling the mortality of sickle cell disease in Africa. Lancet Haematol 2021; 8(10): e677-e678.
46. Fleming AF, Storey J, Molineaux L, Iroko EA, Attai EDE. Abnormal haemoglobins in the Sudan savanna of Nigeria. Ann Trop Med Parasitol 1979; 73(2):161-172.
47. Nnodu O, Madu A, Chianumba R, Isa HA, Olanrewaju I, Osagie S, et al. Establishing a database for sickle cell disease patient mapping and survival tracking: the sickle pan-african research consortium Nigeria example. Front Genet 2022; 13:1041462-1041469.
48. Kayle M, Docherty SL, Sloane R, Tanabe P, Maslow G, Pan W, et al. Transition to adult care in sickle cell disease: a longitudinal study of clinical characteristics and disease severity. Pediatr Blood Cancer 2019; 66(1): e27463-27469.
49. World Bank Group. DataBank: World Development Indicators: World Bank Group; 2024.
50. Moeti MR, Brango P, Nabyonga-Orem J, Impouma B. Ending the burden of sickle cell disease in Africa. Lancet Haematol 2023; 10(8): e567-e569.

[DOI: 10.18502/ijpho.v15i2.18174]