

Original Research Article

Prevalence, Pattern of Disease and outcome of Children with Sickle Cell Disease admitted in a Private Health Facility in Southern Nigeria

Abstract

Aim: To determine the prevalence, pattern of disease and outcome of children with sickle cell disease admitted at a private health facility in southern Nigeria.

Study design: A retrospective study

Place and duration of study: Study was carried out at a private paediatric hospital in Port Harcourt, Rivers State over a 1-year period.

Methodology: Data was retrieved from the hospitals' Health Management System. Information obtained were age, sex, diagnosis, indication for transfusion if any, number and types of transfusions, duration of admission, mode of payment of bills and outcome.

Results: Out of 1597 admissions, 59 were children with sickle cell disease giving a prevalence of 3.7%. Males predominated with a M:F ratio of 1.7:1, majority were ≤ 5 years (50.8%) and had insurance (86.4%). Most were admitted during the rainy season (61.0%) and had duration of stay of 1 – 5 days (74.6%). Commonest diseases among these children were sepsis (69.5%), vaso-occlusive crises (52.5%), malaria (52.5%) and severe anaemia/hyper-haemolytic crisis (30.5%). Of the 35.6% who received blood transfusion, majority received sedimented cells (81.0%), were transfused once (71.4%) with majorly blood group O Rhesus D Positive blood (44.8%). One child died with mortality rate of 1.7%. Vaso-occlusive crisis and tonsillitis were significantly observed more in older children ≥ 12 years whereas there was no statistically significant association between gender and duration of stay with the pattern of disease.

Conclusion: Sickle cell disease accounted for 3.7% of total admissions with a mortality rate of 1.7%. Sepsis, vaso-occlusive crisis, malaria and severe anaemia/hyper-haemolytic crisis were the commonest diagnosis. Neonatal screening, parental education, patient compliance, vaccinations, regular follow up, and comprehensive health insurance will significantly reduce morbidity and mortality in persons with Sickle cell disease.

Keywords: Sickle cell disease, Prevalence, Disease Pattern, Nigeria

Introduction

Sickle cell disease (SCD) is an autosomal recessive genetic disorder caused by a single point mutation in the gene encoding the β -globin chain of haemoglobin [1]. It is characterized by red blood cells becoming sickle shaped and viscous thus clogging the blood flow especially in the small vessels resulting in sluggish flow, ischaemia, pain and damage to the organs [1,2]. It is found worldwide occurring mostly in Africa, the Mediterranean, south and central America, Asia and the middle East [1,3]. It is characterized by chronic haemolytic anaemia which often lead to sudden life-threatening events triggered by acute sickling of red blood cells and microvascular occlusion resulting in severe pains and/or damage to organs especially with repeated attacks [1]. This leads to frequent hospitalization which results in a burden on the family and the health care system [1,3]. Sickle cell disease patients have a poorer quality of life in comparison to the general population and even other chronic non-communicable diseases [1,3,4,5].

Common reasons for admissions include painful or vaso-occlusive crisis, infection and severe anaemia [1-5]. Salako et al [6] reported vaso-occlusive crisis (VOC) as being the most common cause of admission among children with SCD. Abd El-Ghany et al [1] also reported VOC followed by infection as the most common cause of hospitalization whereas Jain et al [3] reported febrile illness followed closely by severe anaemia as the most common cause of hospitalization with both studies reporting peak occurrence from August to October. Jain et al [3] reported duration of stay more than 4 days in patients with infections, acute chest syndrome and those not compliant with hydroxyurea therapy. Several studies have shown that hydroxyurea reduces risk of complications such as VOC (by up to 50%), frequency of hospitalization as well as duration of hospital stay by improving the level of haemoglobin F and the haemoglobin level [1,7-9].

Brown et al [10] reported a mortality rate of 1.9% among 174 admissions of 161 children with sickle cell disease in Ibadan, western Nigeria, mostly attributed to cerebrovascular accidents, adverse reaction to blood transfusion and meningitis.

Nnodu et al [11] estimated the Nigerian national average under-5 mortality rate (2003-2013) for children with sickle cell disease as 490 per 1000 live births, 4 times higher than children with HB AA. About 4.2% of the national under-5 mortality rate was as a result of excess mortality from sickle cell disease [11]. Sickle cell disease therefore presents a significant burden of child mortality in Nigeria most of which can be prevented with adequate allocation of resources and speedy implementation of focused interventions [11]. Prevention and prompt management of crises and other complications of sickle cell disease would significantly reduce morbidity and mortality caused by this disease.

This study which is first of its' kind in a private hospital in the southern part of Nigeria, was carried out therefore to assess the burden attributable to sickle cell disease by determining the prevalence, pattern of disease and outcome of children admitted at our centre, a private health facility, in southern Nigeria.

Methods

This was a retrospective study involving all children admitted in a private paediatric hospital in Port Harcourt, Rivers State over a 1-year period (from 1st of January 2021 to 31st of December, 2022). The study centre was a 38-bedded private hospital with well-equipped neonatal unit, children's ward, fully functional radiology unit and medical laboratory with attached blood bank services. It also had a fully functional theatre, piped oxygen supply and a paediatric ventilator. Age group seen was 0-17 years with an average monthly admission rate of 80-90 children excluding the neonatal age. Its' staff strength included 7 paediatricians, a dermatologist, a paediatric surgeon, an ENT surgeon, a neurosurgeon, a burns and plastics surgeon, an orthopaedic surgeon, 2 anaesthetists, 2 radiologists, a radiographer as well as other support staff including nurses.

Data of all children admitted during the study period was retrieved from the hospitals' Health Management System. Information obtained included age, sex, diagnosis, indication for transfusion if any, number and type of transfusions, duration of admission, mode of payment of bills and outcome. Outcome measures included discharged, death, left against medical advice and referral.

Genotype was used for diagnosis of SCD in children above 6 months while for younger children, High performance liquid chromatography (HPLC) was done. Diagnosis of sepsis was based on the presence of leucocytosis ($WBC > 20 \times 10^9/L$) or leucopenia ($WBC < 4 \times 10^9/L$) or thrombocytopenia ($< 100 \times 10^9/L$) or neutrophilia or neutropenia (interpreted according

to the age of the child) [9], [12]. Vaso-occlusive crisis was defined as an acute onset of pain in a child with SCD localized to the extremities, chest, back or abdomen [9]. Severe anaemia was defined as packed cell volume < 15% [9]. Peripheral blood film was used for diagnosis of malaria while other diagnosis was based on the hospital's standard operating protocol as well as their management.

Blood transfusion was prescribed for severe anaemia or a sudden drop of PCV below the patients' steady state or otherwise higher PCV when patient showed features of heart failure. Transfusion for severe anaemia was with 15mls/kg of sedimented cells (partially packed cells) because of lack of facilities for packing red cells. For overwhelming sepsis, whole blood was used at 20mls/kg. In almost all cases, blood for transfusion was sourced from voluntary non-remunerated donors recruited by patient's relations. In other cases, blood used was obtained from the blood bank. Screening for HIV, HBV, HCV and VDRL were carried out routinely in our hospital blood bank on all potential donors and only those confirmed to be negative were allowed to donate. Blood deemed fit for transfusion was properly grouped, cross-matched and labelled.

Data was recorded in an Excel spreadsheet and analysed using SPSS version 23. Results were presented as frequency, percentages, pie and bar charts. Test of association was done using χ^2 test and Fishers' Exact test. Statistical significance was set at *P* value < .05 at 95% confidence intervals.

Result

Demographic characteristics of the study population

There were 1597 admissions, of which 59 were children with sickle cell disease giving a prevalence of 3.7%. Males predominated 37(62.7%) with a M:F ratio of 1.7:1. Majority of the children were \leq 5 years old 30 (50.8%) with age range from 3 months to 17 years and most had insurance 51 (86.4%). Most were admitted during the rainy season 36 (61.0%) and had duration of stay of 1 – 5 days 44 (74.6%), Table I.

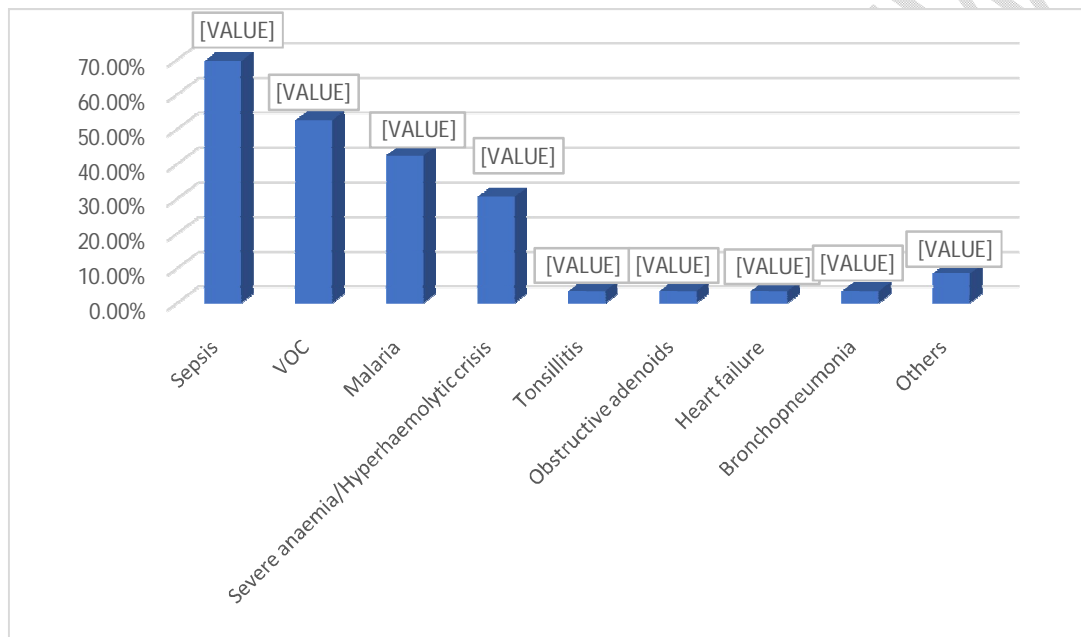
Table I: Demographic characteristics of the study population

Variables	Frequency, n=59 (%)
Sex	
Male	37 (62.7)
Female	22 (37.3)
Age (years)	
\leq 5	30 (50.9)
6 - 11	17 (28.8)
\geq 12	12 (20.3)
Mode of payment	
Insurance	51 (86.4)
Non-insurance	8 (13.6)
Season	

Rainy	36 (61.0)
Dry	23 (39.0)
Duration of stay (days)	
1 – 5	44 (74.6)
≥ 6	15 (25.4)

Pattern of disease among children admitted with SCD

Commonest disease among admitted children with SCD was sepsis 44 (69.5%), followed by VOC 31(52.5%), malaria 25 (52.5%) and severe anaemia 18 (30.5%), Figure 1.



VOC=Vaso-occlusive crisis; Others = Malnutrition, Acute osteomyelitis, Acute sequestration crisis, Priapism, Septic arthritis with frequency of 1 each

Figure 1: Pattern of disease among children admitted with SCD

Blood transfusion history

Of 59 children with SCD admitted, 21 (35.6%) received blood transfusion. Majority received sedimented cells 17 (81.0%), transfused once 15 (71.4%) and had blood group O Rhesus D Positive blood 26 (44.8%), Table II.

Table II: Blood transfusion history

Variables	Frequency, n (%)
Received blood transfusion	
Yes	21 (35.6)
No	38 (64.4)
Type of blood transfused	

Sedimented cells	17 (81.0)
Whole blood	4 (19.0)
Number of transfusions done	
One	15 (71.4)
Two	5 (23.8)
Three and above	1 (4.8)
Blood group of patients transfused	
O Rhesus D Positive	26 (44.8)
B Rhesus D Positive	18 (31.1)
A Rhesus D Positive	13 (22.4)
O Rhesus D Negative	1 (1.7)

Outcome of Patients with SCD

Out of 59 children with SCD admitted, 58 (98.3%) were discharged home while 1 (1.7%) died, Figure 2.

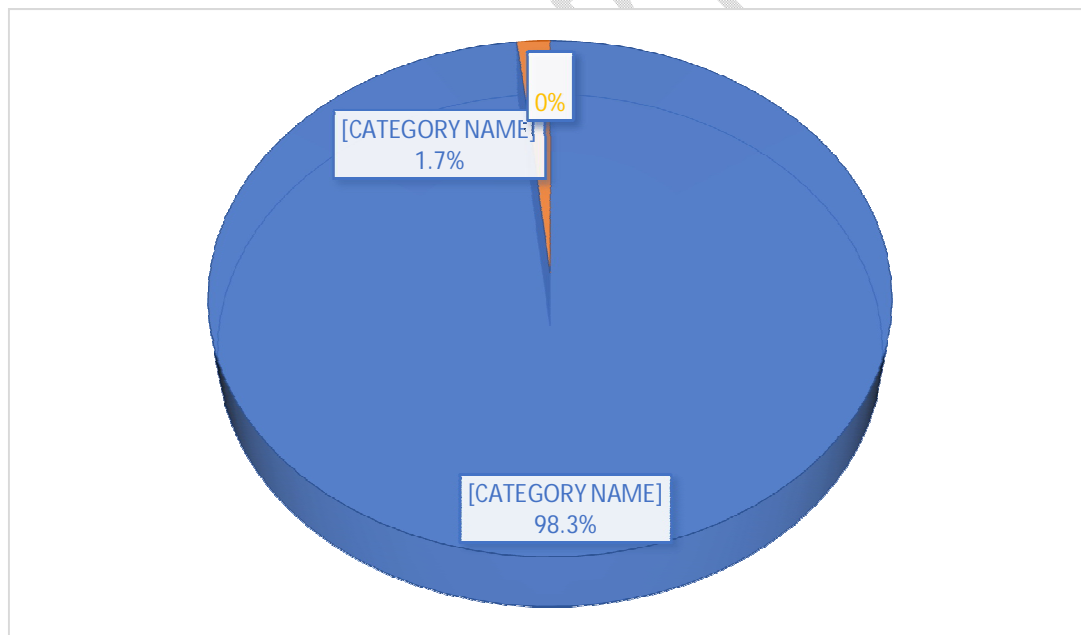


Figure 2: Outcome of Patients with SCA

Pattern of admission by month

Most admissions were in the month of March (8.8%) followed by May (7.9%), April (7.6%) and June (6.9%) while the least admission was in July (1.0%) and August (1.7%), Figure 3.

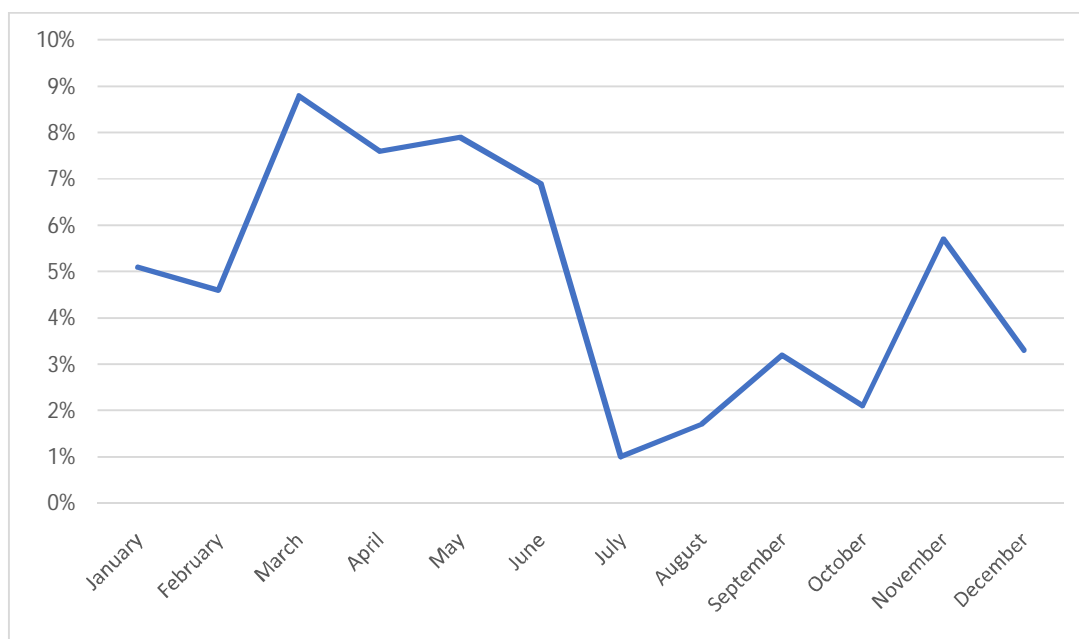


Figure 3: Pattern of admission by month of year

Association of pattern of disease among children with SCD and sex

There was no significant association between the pattern of disease among children with SCD and sex, P value > 0.05 (Table III).

Table III: Association of pattern of disease among children with SCD and sex

Variables	Sex		Fishers' Exact Test
	Male, n=37(%)	Female, n=22(%)	P value
Sepsis	26 (70.3)	15 (68.2)	1.000
VOC	16 (43.2)	15 (68.2)	0.105
Malaria	16 (43.2)	9 (40.9)	1.000
Severe anaemia/HHC	11 (29.7)	7 (31.8)	1.000
Tonsillitis	0	2 (9.1)	0.135
Obstructive adenoids	2 (5.4)	0	0.524
Heart failure	1 (2.7)	1 (4.5)	1.000
Bronchopneumonia	1 (2.7)	1 (4.5)	1.000

VOC=vaso-occlusive crisis; HHC=Hyper-haemolytic crisis

Association of pattern of disease among children with SCD and age group

VOC and tonsillitis were significantly seen more in children ≥ 12 years (P value =0.034 and 0.039 respectively), Table IV.

Table IV: Association of pattern of disease among children with SCD and age group

Variables Test	Age groups (years)			Fishers' Exact
	≤ 5,n=30(%)	6-11,n=17(%)	≥ 12,n=12(%)	P value
Sepsis	22 (73.3)	11 (64.7)	8 (66.7)	0.809
VOC	12 (40.0)	9 (52.9)	10 (83.3)	0.034*
Malaria	13 (43.3)	4 (23.5)	8 (66.7)	0.070
Severe anaemia/HHC	9 (30.0)	8 (47.1)	1 (8.3)	0.096
Tonsillitis	0	0	2 (16.7)	0.039*
Obstructive adenoids	2 (6.7)	0	0	0.702
Heart failure	1 (3.3)	1 (5.9)	0	1.000
Bronchopneumonia	2 (6.7)	0	0	0.702

voc=vaso-occlusive crisis; HHC=Hyper-haemolytic crisis ; * = Statistically significant

Association of the pattern of disease among children with SCD and duration of stay

There was no statistical significant association between the pattern of disease among children with SCD and duration of stay, *P* value > 0.05 (Table V).

Table V: Association of the pattern of disease among children with SCD and duration of stay

Variables Test	Duration of stay (days)		Fishers' Exact
	1-5, n = 44 (%)	≥ 6, n = 15 (%)	P value
Sepsis	30 (68.2)	11 (73.3)	1.000
VOC	26 (59.1)	5 (33.3)	0.134
Malaria	18 (40.9)	7 (46.7)	0.767
Severe anaemia	12 (27.3)	6 (40.0)	0.517
Tonsillitis	2 (4.5)	0	1.000
Obstructive adenoids	0	2 (13.3)	0.061
Heart failure	1 (2.3)	1 (6.7)	0.447
Bronchopneumonia	2 (4.5)	0	1.000

voc=vasoocclusive crisis; HHC=Hyperhaemolytic crisis

Discussion

Sickle cell disease in the present study accounted for 3.7% of the total admission. This is similar to the 3.9% reported in Enugu [13] eastern Nigeria but higher than the 3.1%, 2.9% and 2.2% reported in Malawi [14], Port Harcourt [15] southern and another study in Enugu [16], eastern Nigeria respectively. It was however lower than the 4.1%, 5.75% and 10.1%

documented in Uyo [17] southern Nigeria, Iraq [18] and Zaria [19] northern Nigeria respectively. The higher prevalence in the present study compared with the earlier study in the same locality in Port Harcourt [15] southern Nigeria could be attributable to the fact that the present study was carried out a decade later and thus the possibility of better diagnostic tools facilitating earlier diagnosis. In addition, over time improved parental education could lead to better health seeking habit. This thus highlights the fact that SCD is a significant cause of childhood morbidity and a major health issue especially in sub-Saharan Africa.

Males predominated in the present study as similarly documented in other studies in Nigeria [10,15-17,19,20], Malawi, [14] India [3], [21] Iraq [18] and Barbados [22]. Although SCD is an autosomal recessive disorder and as such not related to gender, Gladwin et al [23] and Ilesanmi [24] in their studies showed that nitric oxide was found more in females than males during both steady state and crisis which thus indicates that males could be more prone to crisis and attendant complications.

In the present study, about half (50.8%) of the children with SCD admitted were of age group ≤ 5 years which was consistent with reports by George & Opara [15] Faruk et al [19] and Nayak et al [21] in a previous study in Port Harcourt, Zaria in Nigeria and India respectively. Ikefuna and Emodi [16] in Enugu, Nigeria reported age group 1-5 years as the commonest age group admitted whereas Jain et al [3] in India reported 1- < 3 years as the commonest age group implicated. In contrast, older children above 5 years were reported as the commonest age groups documented by Abd El-Ghany et al [1], Chibatata et al [14], Salman and Hassan [18], Brown et al [10] and Etuk & Akpan [17] in Saudi Arabia, Malawi, Iraq, and Nigeria respectively. These variations could be due to differences in the pattern of diseases and their varying geographic locations.

Most children with SCD were admitted during the rainy season (61%) in the present study as similarly reported by Ikefuna & Emodi [16] in Enugu, eastern Nigeria (61.4%). Redwood et al [25] and Amjad et al [26] also corroborated the later. This trend could be because during the rainy season, children with SCD could be exposed to cold which could predispose them to crisis. There could also be challenges in sewage management systems as well as inadequate drainage as seen in developing countries which predispose them to infections including malaria. Contrary to the above findings, Slovis et al [27] and Seeler et al [28] in Chicago, USA did not substantiate any seasonal variation in patients admitted with SCD.

Most children with SCD were admitted in the month of March (8.8%) followed by May (7.9%) and April (7.6%) while the least was July (1.0%) and August (1.7%). This was at variance with a similar study by Abd El-Ghany [1] and Jain et al [3] in Saudi Arabia and India respectively who reported maximum number of admissions in the month of August followed by September and October. This difference could be due to variation in geographic locations and varying pattern of diseases.

The commonest diagnosis at hospitalization was sepsis (69.5%) followed by VOC (52.5%), malaria (42.4%) and severe anaemia/hyper-haemolytic crisis (30.5%) in the present study. Similarly, acute febrile illness/infections were also documented as the commonest diagnosis in India [3], Ibadan [10] and Enugu [16] Nigeria. This observation was not unexpected as children with SCD are at increased risk of bacterial infection or sepsis due to their immune deficit opsonin effect [29] as well as splenic dysfunction/asplenia common with these children [9]. Other factors that predispose them to infections include neutrophil dysfunction, impaired cell mediated immunity, impaired phagocytosis and the presence of ischaemia which form a suitable environment for the growth of bacteria [30]. It is worthy of

note that it is a regular practice to commence all children diagnosed with SCD in the present study centre on prophylactic penicillin. Acute painful crisis/VOC which was 2nd commonest in the present study was reported as the commonest morbidity in other parts of Nigeria [10,15,19,20], Saudi Arabia [1], Iraq [18] and Barbados [22] whereas severe anaemia was the commonest in Malawi [14] and India [21] while malaria was the commonest in Ibadan [17] and a previous study in Port Harcourt [15] Nigeria. Malaria being the 3rd commonest cause of hospitalization in the present study, a private health facility could be attributed to the possibility of less exposure to the mosquitoes, better housing and better compliance to malaria chemoprophylaxis. This could be deduced from the fact that private health facilities are more assessed by those in the middle and higher socioeconomic class being more expensive than the public hospitals which are readily funded by the Government. These variations in the pattern of disease could be attributable to the difference in geographic location, variation over time even within the same locality as well as different age groups implicated in the different studies. The slightly lower prevalence of VOC in the present study could also be because hydroxyurea is routinely commenced in all children diagnosed with SCD which has been shown to reduce the rate of hospitalization for painful crisis by up to 50% [9]. It is pertinent to note that priapism and acute sequestration crisis were one of the least observed morbidities in children admitted with SCD in the present study. This was consistent with other studies [14,17] which observed priapism as the least common morbidity. In contrast, priapism was not documented in some other studies [3, 10,15,18,21]. This is not surprising as priapism is an uncommon event, mainly seen in much older children above 15 years [9]. In addition, acute sequestration crisis is on the decline with newborn screening, earlier diagnosis of SCD and parental education [9]. It is pertinent to note that the youngest child in the present study was 3 months of age.

More than a quarter (35.6%) of the children admitted in the present study had blood transfusion. This corroborates studies in Ibadan [10] Nigeria and Barbados [22] accounting for 39.1% and 39.7% respectively. In Zaria [19] northern Nigeria however, close to half (48.9%) of the patients had blood transfusion whereas in Enugu [16] eastern Nigeria, close to 3/4th (73.2%) of the patients had blood transfusion. This much higher rate of blood transfusion in Zaria could be because only 15.9% were on hydroxyurea. In the present study however, all patients with SCD were routinely commenced on hydroxyurea. The varying rates of blood transfusion could also be attributed to the varying levels of cut-off value for severe anaemia as well as different guidelines for blood transfusion in the various centres. In addition, variations in the compliance of patients with routine haematinics and malaria prophylaxis could also account for the rate of blood transfusion.

The mortality of 1.7% reported in the present study was consistent with the 1.9% reported in a similar study in Ibadan [10], western Nigeria but higher than the 1.4% and 0.9% documented in Malawi [14] and Uyo [17] southern Nigeria respectively. Higher mortalities of 2.4%, 2.7%, 4.6% and 8.5% were however documented in India [3] and Nigeria [16,19,20]. Interestingly, there was no mortality reported in a private hospital in Saudi Arabia [1] and Iraq [18]. These differences could be because of the varying geographic locations, difference in the morbidity pattern as well as the availability of good health care services and the expertise of the health personnel in the management of SCD in children. It is important to note that early diagnosis with prompt and effective treatment of the morbidities seen in SCD is key to survival. The relatively low mortality in the present study could have been contributed by the ready availability of health insurance in more than three-quarters of these sick children as SCD has huge economic burden on the caregivers.

Septicaemia and severe anaemia were the causes of mortality in the present study. Severe sepsis and acute splenic sequestration were implicated in India [3] while severe anaemia was documented as the commonest cause of death in Zaria [19] Nigeria followed by pain crisis, stroke and acute chest syndrome. Cardiovascular accidents, adverse reaction to blood transfusion and meningitis were documented in Ibadan [10], western Nigeria. These differences could be attributable to the varying geographic locations and morbidity patterns as well as the availability of standardized health care and the expertise of the health staff. There was no significant association between the diagnosis at hospitalization and the sex of children with SCD as corroborated by Abd El-Ghany et al [1] and Abd Elmoneim et al [31]. This could be because SCD is an autosomal recessive disorder and as such not sex related. The present study showed that VOC and tonsillitis were observed significantly more in older children ≥ 12 years (P value = 0.034, 0.039 respectively). Abd El-Ghany [1] in Saudi Arabia similarly reported VOC as significantly more in older children ≥ 12 years. In addition, Nayak et al [21] in India documented VOC more in older children 11-15 years although the test of significance was not ascertained. This finding of tonsillitis and VOC being observed more in older children is not surprising as this age group are more likely to express themselves more than the younger children. Vaso-occlusive crisis being commoner in older children could also be attributed to their high prevalence of low adherence to treatment and instructions [32] such as the use of hydroxyurea which has been found to reduce the incidence of VOC as well as instructions that would help prevent its occurrence such as adequate hydration. There was also no significant association between the pattern of disease in children with SCA that were admitted and the duration of stay. This was also observed by Brown et al [10] in a similar retrospective study in Ibadan, western Nigeria.

Conclusion

Sickle cell disease accounted for 3.7% of total admissions in a private health facility in southern Nigeria thus an important public health problem. There was male preponderance with admissions involving mainly children of age group ≤ 5 years and during the rainy season. Sepsis, VOC, malaria and severe anaemia/hyper-haemolytic crisis were the commonest diagnosis at admission in descending order with mortality rate of 1.7%. Vaso-occlusive crisis and tonsillitis occurred significantly more in children ≥ 12 years whereas there was no significant association between the pattern of disease with sex and duration of hospitalization.

Neonatal screening, parental education on the disorder and patient compliance with the various supportive care (malaria chemoprophylaxis, penicillin, hydroxyurea therapy etc) and vaccinations will therefore reduce morbidity and mortality of SCD. Regular follow up of children with SCD must be encouraged as it reduces the frequency of crisis thereby would improve the quality of life of affected children. Comprehensive health insurance will also significantly reduce morbidity and mortality in persons with SCD.

Ethical approval

Ethical approval was given by the hospital's management board. Confidentiality was ensured by removing unique identifiers.

References

1. Abd El-Ghany SM, Tabbakh AT, Nur KI, Abdelrahman RY, Etarji SM, Almuzaini BY. Analysis of causes of hospitalization among children with sickle cell disease in a group of private hospitals in Jeddah, Saudi Arabia. *J Blood Med* 2021; 12: 733-40. Doi: 10.2147/JBM.S318824
2. Alhumaid AM, Aleidi AS, Alfakhri AS, Alosaimi NK, Ali YZ, Alzahrani MS. Clinical features and outcome of sickle cell anaemia in a tertiary center: A retrospective cohort study. *J Appl Hematol* 2018; 9: 22-28. Doi: 10.4103/joah.joah_48_17
3. Jain D, Bagul AS, Shah M, Sarathi V. Morbidity pattern in hospitalized under five children with sickle cell disease. *Indian J Med Res* 2013; 138(3): 317-21. PMID: 24135175; PMCID: PMC3818593
4. Mc Clish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL et al. Health related quality of life in sickle cell patients: The PISCES project. *Health Qual Life Outcomes* 2005; 3:50. Doi: 10.1186/1477-7525-3-50
5. Baghat VM, Baviskar SR, Mudey AB, Goyal RC. Poor health related quality of life among patients of sickle cell disease. *Indian J Palliat Care* 2014; 20(2): 107-11. Doi: 10.4103/0973-1075.132622
6. Salako A, Aworanti O, Opaneye B, Abimbola S. Pattern of childhood morbidity in a private paediatric centre in Lagos, Nigeria. *Saudi J Nurs Health Care* 2019; 2(8): 276-83. Doi: 10.21276/sjnhc.2019.2.8.4
7. Agrawal RK, Patel RK, Shah V, Nainiwal L, Trivedi B. *Indian J Hematol Blood Transfus* 2014; 30(2): 91-6. Doi: 10.1007/s12288-013-0261-4
8. Mulaku M, Opiyo N, Karumbi J, Kitonyi G, Thiothi G, English M. Evidence review of hydroxyurea for the prevention of sickle cell complications in low-income countries. *Arch Dis Child*. 2013; 98(11): 908-14. Doi: 10.1136/arch-dischild-2012-302387
9. Smith-Whitley K. Sickle cell disease. In: Kliegman RM, Blum NJ, Shah SS, St Geme III JW, Tasker RC, Wilson KM (ed). *Nelson Textbook of Pediatrics*. 21st ed. Inter ed, Elsevier 2020; 2541-51
10. Brown BJ, Jacob NE, Lagunju IA, Jarrett OO. Morbidity and mortality pattern in hospitalized children with sickle cell disorders at the University College Hospital, Ibadan, Nigeria. *Nig J Paed* 2013; 40(1): 34-9. Doi: 10.4314/njp.v40i1.6
11. 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. Doi: 10.1016/S2352-3026(21)00216-7
12. Savlov D, Beck CE, DeGroot J, Odame I, Friedman JN. Predictors of bacteraemia among children with sickle cell disease presenting with fever. *J Pediatr Hematol Oncol* 2014; 36(5): 384-8 doi:10.1097/MPH.0000000000000070
13. Edelu BO, Eze BN, Oguonu T, Ndu I. Morbidity and mortality pattern in the children emergency unit of the University of Nigeria Teaching Hospital, Enugu. *Orient J Med* 2014; 26(3-4): 73-5
14. Chimatata CS, Chisale MRO, Kayira AB, Sinyiza FW, Mbakaya BC, Kaseka PU, et al. Paediatric sickle cell disease at a tertiary hospital in Malawi: A retrospective cross-sectional study. *BMJ Paediatr Open* 2021; 5: e001097.doi: 10.1136/bmj.po-2021-001097
15. George IO, Opara PI. Sickle cell anaemia: A survey of associated morbidities in Nigerian children. *Afr J Haematol Oncol* 2011; 2(2): 187-90

16. Ikefuna AN, Emodi IJ. Hospital admission of patients with sickle cell anaemia pattern and outcome in Enugu area of Nigeria. *Niger J Clin Pract* 2007; 10(1): 24-9
17. Etuk EE, 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): 91-7
18. Salman ZA, Hassan MK. Hospitalization events among children and adolescents with sickle cell disease in Basra, Iraq. *Hindawi* 2015; <http://dx.doi.org/10.1155/2015/195469>
19. Faruk JA, Adebiji MN, Ahmad HR. Clinico-demographic characteristics, morbidity and mortality patterns of sickle cell disease in a tertiary institution. *Sahel Med J* 2022; 25(2): 52-6 DOI: 10.4103/smj.smj_78_20
20. Abhulimhen B, Isreal-Aina Y, Joel-Utomakili K. Sickle cell anaemia: Morbidity profile and outcome in a paediatric emergency setting in Nigeria. *Afr J Med Health Sci* 2015
21. Nayak S, Motwani NP, Dewangan M, Jain A. Clinical and haematological profile of children with sickle cell anaemia admitted to a rural medical college of Chhattisgarh, India. *Int J Contemp Pediatr* 2018; 5(1): 173-7. DOI:<http://dx.doi.org/10.18203/2349-3291.ijcp30175581>
22. Grannum D, Lashley PM. The morbidity pattern of children with sickle cell disorders admitted to the Queen Elizabeth Hospital, Barbados (2009 – 2013). *SAGE J* 2017; 48(1): <https://doi.org/10.1177/0049475517740309>
23. Gladwin MT, Schechter AN, Ognibene FP, Colen WA, Reiter CD, Schenke NH et al. Divergent nitric oxide bioavailability in men and women with sickle cell disease. *Circulation* 2003; 107: 271-8
24. Ilesanmi OO. Gender differences in sickle cell crisis: Implication for genetic counselling and psychol *Psychother* 2013; 3: 123
25. Redwood AM, Williams EN, Desai P, Sergeant GR. Climate and painful crisis in sickle cell diseases in Jamaica. *Br Med J* 1976; 1: 66-8
26. Amjad H, Bannerman RM, Judisch JM. Sickling, pain and season. *Br Med J* 1974; 1: 54-7
27. Slovis CM, Talley TD, Pitts RB. No relationship of climatic factors and painful sickle cell anaemia crisis. *J Chron Dis* 1986; 39: 121-6
28. Seeler RA. Non-seasonality of sickle cell crisis. *Lancet* 1973; ii: 734
29. Cetiner S, Akoglu TF, Killine Y, Akoglu E, Kumi M. Immunological studies of sickle cell disease. Comparison of homozygous mild and severe variants. *Clin Immunol Immunopathol* 1989; 53: 52
30. The spleen and lymph node in sickle cell disease. In: Konotey Ahulu FID (ED). *The Sickle cell disease patient*. England Teheh-A'domeno company 1996; 111: 77-291
31. Abd Elmoneum AA, Al Hawsawi ZM, Mahmoud BZ, Bukhari AA, Almulla AA, Sonbol AM, et al. Causes of hospitalization in sickle cell diseased children in western region of Saudi Arabia. A single center study *Saudi Med J* 2019; 40(4): 401-4. doi: 10.15537/smj.2019.4.24049
32. Taddeo D, Egedy M, Frappier J. Adherence to treatment in adolescents. *Paediatr Child Health* 2008; 13(1): 19-24. doi.10.1093/pch/13.1.19