Original Article

Disease Severity of Children Attending the Pediatric Sickle Cell Clinic of a Tertiary Health Institution in Southwest Nigeria

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Abstract

Context: Sickle cell disease is the most common hemoglobinopathy worldwide. Its effects are pan-systemic, affecting every organ in the body; hence, the manifestations are variable and diverse. A scoring parameter is needed to group patients into similar severity brackets for prognostic purposes. **Aim:** This study aimed to determine the severity score of children attending the Pediatric sickle cell clinic of a tertiary institution using an existing set of scoring parameters. **Materials and Methods:** This was a cross-sectional study that involved 100 children attending the sickle cell clinic of a tertiary institution in Nigeria. We used semi-structured questionnaires to obtain relevant sociodemographic data. We determined the clinical severity of the population using a set of clinical-laboratory parameters. Data were analyzed using IBM Statistical Package for Social Sciences version 25.0 for Windows. The level of significance was set at $P < 0.05$. **Results:** Most of the children (80; 80%) had a mild index of disease severity. Age, gender, and social class did not significantly affect disease severity. However, a low white blood cell (WBC) count predicted mild disease severity. **Conclusion:** Our study showed that most of the children had a mild index of disease severity, and this was predicted by a low WBC count.

Keywords: Severity index, sickle cell disease, Southwest Nigeria

Introduction

Sickle cell disease (SCD) is the most common hemoglobinopathy worldwide, affecting every body organ.[1,2] The manifestations are due to two main pathophysiologic mechanisms: vaso-occlusion and hemolysis. The disease has a variable phenotypic expression with varying levels of severity.[2] Patients with severe disease tend to present with more complications, target-organ dysfunction, and early death, while others have albeit milder disease and longer lifespans.[2] Consequently, disease severity is one of the factors reported to determine the pattern of disease presentation, prognosis, and survival of affected persons.

Classifying the severity of the disease is paramount in counseling patients on follow-up, making accurate prognostication, and predicting important aspects of the clinical course to achieve the desired reduction in mortality in this group of patients. Accurate prognostication at an early stage of SCD will help to guide individualized treatments, especially for those predicted to follow a severe course.

Many methods have been previously used in Nigeria to classify the clinical severity of patients with SCD,[3-5] with only a few studies in children.[6,7]

This study, therefore, aimed to determine the disease severity of children with SCD attending the pediatric sickle cell clinic of a tertiary health facility in Southwest Nigeria

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to prognosticate and possibly recommend them for further care.

Materials and Methods

Ethical considerations

This study was approved by the Hospital Ethics/Research Committee, with reference number BUTH/REC-829, dated July 2020. In line with the Helsinki Declaration, consent was obtained from each parent/caregiver, and assent from children 7 years old and above, after a clear explanation of the study was given to them. Confidentiality was maintained throughout the period of the study.

Study design

This cross-sectional observational study involved children aged 6 months to 18 years attending the Pediatric sickle cell clinic of Bowen University Teaching Hospital (BUTH), Ogbomoso, Nigeria, from January 2021 to June 2022.

Study setting

The BUTH is a Christian missionary tertiary health facility located in Ogbomoso, Southwestern Nigeria. The hospital serves as a referral center to primary and secondary healthcare facilities in and around Ogbomoso, including the neighboring states of Osun and Kwara. Ogbomoso is the second-largest city in Oyo State, Nigeria, and the people are predominantly of Yoruba ethnicity.[8,9]

The BUTH Paediatrics Department cares for children and adolescents up to 18 years and has a Pediatric sickle cell clinic that runs once weekly. The average clinic attendance is eight, with 120 registered children. Patients receive preventive and routine care including health education during clinic visits.

Selection and description of participants

Children with SCD between the ages of 1 and 18 years who were in a steady state (no crisis, infection, or fever for at least 4 weeks and no blood transfusion in the preceding three months)[10] were consecutively enrolled in the study. Children with other hematologic disorders, such as glucose-6-phosphate dehydrogenase deficiency, and those with chronic liver, kidney, and heart diseases were excluded. Children who did not give assent and those whose parents refused consent were omitted.

Sample size calculation

The minimum sample size required for the study was estimated using the online sample size calculator (http://www.raosoft.com/samplesize.html). We obtained the minimum sample size from a prevalence of 33.9% for a mild index of severity earlier reported in southwestern Nigeria,[7] at a 95% level of confidence and 5% margin of error. We subsequently adjusted for the total number of registered patients (120) in the clinic and obtained a final minimum sample size of 90, which was rounded to 100 for the study.

Data collection

A semi-structured questionnaire was used to obtain relevant sociodemographic data. The clinical severity of the population was determined by a set of 15 clinical and laboratory parameters (frequency of painful episodes, blood transfusion, and hospitalization in the preceding 12 months; incidence of SCD-related complications; splenic and hepatic size, packed cell volume and leucocyte count) as documented by Adegoke and Kuti.[7] The parameters were scored thus: patients with a score of less than 8 were classified as having mild disease, 8 to 17 as moderate disease, and greater than 17 as severe disease from a maximum obtainable score of 34. Each parameter was scored according to the frequency of occurrence and severity; acute life-threatening events and neurological complications were assigned higher scores (e.g., Cardiovascular disease (CVD) was assigned a score of 5, and pneumococcal meningitis and Acute chest syndrome (ACS) were assigned scores of 3 points).

Five milliliters of blood samples were collected from all the selected children through aseptic means into Ethylene diamine tetraacetate (EDTA) vacutainer bottles.

Technical information

White blood cell (WBC) count and hematocrit levels were determined using an automated blood analyzer model/Sysmax KX-21N®.

Statistics

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) version 25.0 for Windows. Based on Oyedeji's social classification,[11] children in the socioeconomic classes I and II were classified as high socioeconomic class, those in class III were classified as a middle socioeconomic class, and those in classes IV and V were classified as low socioeconomic class. The age was not normally distributed; hence, it was summarized as a median with an interquartile range (not normally distributed) and compared with the Mann–Whitney U test. The discrete variables were summarized as proportions and percentages. Chi-square was used to determine the relationship between the index of clinical severity, and clinical-laboratory parameters and sociodemographic variables (age, sex, and educational status); Fisher's exact test was used when more than 20% of expected cell counts were less than 5. A binary logistic regression was used to determine factors that were associated with mild disease. The level of significance for all tests was set at $P < 0.05$.

Results

Of the 100 children with SCD enrolled in the study, the under-5 age group constituted about a fifth of the study population, while the adolescents were the majority [47 (47%)]. There were more males, 59 (59%), than females, 41 (41%), giving a male-to-female ratio of 1.4:1. Most, 48 (48%), of the children belonged to the middle social class according to the Oyedeji classification. Other sociodemographic details are presented in Table 1a and b.

Only 13 (13%) of the children were registered on the National Health Insurance Scheme (NHIS). Most 90 (90%) of the children were homozygous for SCD (hemoglobin genotype SS). Most of the children 80 (80%) in this cohort had the mild form of disease severity.

Table 1a: Demographic, clinical, and laboratory factors that are associated with disease severity

Variables	Total *n*=100 (%)	Mild (80)	Moderate (20)	test	*P*
Age (years)					
Median (IQR)	9.0 (6.0-13.0)	9.0 (5.0-13.0)	8.5 (6.5-12.5)	785.50[u]	0.9004
0 to 5	19 (19.0)	16	3	0.251[f]	0.947
6-<10	34 (34.0)	27	7		
10-18	47 (47.0)	37	10		
Sex					
Male	59 (59.0)	46	13	0.127[y]	0.722
Female	41 (41.0)	34	7		
Maternal educ.					
No formal educ.	4 (4.0)	4	0	4.017[f]	0.221
Primary	17 (17.0)	16	1		
Secondary	40 (40.0)	32	8		
Tertiary	39 (39.0)	28	11		
SEC					
Upper	26 (26.0)	19	7	3.625[f]	0.171
Middle	48 (48.0)	37	11		
Lower	26 (26.0)	24	2		
NHIS access					
Yes	13 (13.0)	11	2	0.006[y]	0.941
No	87 (87.0)	69	18		
Hb genotype					
SS	90 (90.0)	70	20	1.563[f]	0.211
SC	10 (10.0)	10	0		
Age (in years) at diagnosis					
Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-6.0)	2 (0.88-3.00)	1.723[U]	0.085
< 1	29 (29.0)	21	8	3.077[f]	0.381
1-<5	47 (47.0)	38	9		
5-<10	15 (15.0)	12	3		
≥ 10	9 (9.0)	9	0		
Medications					
Hydroxyurea					
Yes	2 (2.0)	0	2	0.385[y]	0.049
No	98 (98.0)	80	18		
Faradine					
Yes	30 (30.0)	23	7	0.074*	0.785
No	70 (70.0)	57	13		
Episodes of VOCs[#]					
0	32 (32.0)	29	3	9.889[f]	0.017
1	25 (25.0)	22	3		
2-3	26 (26.0)	20	6		
>4	17 (17.0)	9	8		

IQR-Interquartile range; educ.-education; SEC-Socioeconomic class; NHIS-National health insurance scheme; Hb-hemoglobin; VOC-Vaso-occlusive crisis; [#]number of episodes in the past one year; U-Mann-whitney *U* test, f-Fischer exact test, *Chi-square; *y*-yates corrected Chi-square; Faradine: polyherbal drug containing three herbs

There was no significant difference in severity score between the sociodemographic parameters. Use of hydroxyurea, the number of episodes of Vaso-occlusive crises (VOCs), hemolytic crises, blood transfusions, hospital admissions, WBC count, and liver size were factors associated with disease severity in this study [Table 1].

After adjusting for potential confounders, only a low WBC count predicted mild disease [Table 2].

Discussion

The majority of the children in our study had a mild clinical course of the disease, which is in keeping with a previous study in the same region (Southwest Nigeria).[6] In contrast, Adegoke and Kuti[7] and Okocha *et al*.[5] reported that most patients in their cohort had a moderate disease course. The reason for the difference between these studies may be a reflection of variability in phenotypic expression of SCD within the same population and even in the same individual as has been

Table 1b: Clinical and laboratory factors that are associated with disease severity

Variables	Total *n*=100 (%)	Mild (80)	Moderate (20)	test	*P*
Blood transfusions#					
0	70 (70.0)	63	7	15.804[f]	<0.001
1	25 (25.0)	15	10		
2	4 (4.0)	2	2		
3	1 (1.0)	0	1		
Hosp. admissions#					
0	58 (58.0)	54	4	22.717[f]	<0.001
1	34 (34.0)	23	11		
2-3	5 (5.0)	3	2		
>3	3 (32.0)	0	3		
Clinic visits#					
0	15 (15.0)	12	3	3.802[f]	0.283
1	12 (12.0)	12	0		
2-3	44 (44.0)	33	11		
>3	29 (29.0)	23	6		
Malaria episodes#					
0	18 (18.0)	13	5	5.151[f]	0.142
1	33 (33.0)	30	3		
2-3	41 (41.0)	32	9		
>3	8 (8.0)	5	3		
Hemolytic crisis#					
0	76 (76.0)	66	10	9.875[f]	0.011
1	13 (13.0)	7	6		
2-3	7 (7.0)	4	3		
>3	4 (4.0)	3	1		
Complications**					
0	65 (65.0)	59	6	15.631[f]	<0.001
1	28 (28.0)	18	10		
2	6 (6.0)	2	4		
WBC (per mm^3)					
<11,000	59 (59.0)	57	2	27.708[f]	<0.001
11,000 to 15,000	14 (14.0)	10	4		
>15,000	27 (27.0)	13	14		
PCV (%)					
≥24	60 (60.0)	51	9	2.985[f]	0.309
18-23	39 (39.0)	28	11		
<18	1 (1.0)	1	0		
Splenic size (cm)					
< 5.0	94 (94.0)	75	19	1.985[f]	0.484
5.0 to 10.0	2 (2.0)	1	1		
>10.0	4 (4.0)	4	0		
Liver size (cm)					
<2.0	28 (28.0)	27	1	9.405[f]	0.007
2.0 to 5.0	44 (44.0)	35	9		
> 5.0 cm	28 (28.0)	18	10		

Hosp.-hospital. #-number in the past year; ** lifetime complications (stroke, acute chest syndrome, osteomyelitis, avascular necrosis); PCV-Packed cell volume; WBC-white blood cells count; U-Mann–Whitney *U* test, f-Fischer exact test, *Chi-square

observed in previous studies in Nigeria and elsewhere.[12,13] Furthermore, previous studies in Nigeria have reported a mixed haplotype of the disease in the country, with the Benin β-haplotype being the most prevalent among the Nigerian population, especially among the people of Yoruba ethnicity, who predominate the study site.[14,15] Phenotypic expression and clinical course of SCD are partly dictated by the β-globin haplotype of the disease; the Benin haplotype is reported to be of intermediate severity.[14]

Age, gender, and social class did not significantly affect disease severity in our study. Although the number of children with moderate disease increased with age, this was not statistically significant. Similar to our observation, Adeodu *et al*.[6] and Adegoke and Kuti[7] reported that social class and

Table 2: Factors associated with mild disease

Variable	Subgroup	*n*	AOR	95% CI	*P*
Age (years)	≤5	17	1		
	>5	63	1.090	0.778, 1.527	0.616
Sex	Female	34	1		
	Male	46	0.955	0.727, 1.254	0.739
Hydroxyurea	No	80	1		
	Yes	0	0.905	0.703, 1.167	0.443
No of VOCs in the past year.	0	29	0.755	0.543, 1.052	0.097
	1	22	0.737	0.501, 1.083	0.121
	2-3	20	0.803	0.540, 1.196	0.803
	> 3	9	1		
No of blood transfusions in the past year.	0	63	1.063	0.781, 1.448	0.697
	1	15	1.060	0.698, 1.612	0.784
	2	2	0.885	0.618, 1.267	0.504
	3	0	1		
No of Hospital admissions in the past year	0	57	1.067	0.764, 1.491	0.702
	1	20	1.061	0.730, 1.544	0.755
	2-3	3	0.981	0.686, 1.347	0.818
	>3	0	1		
Hemolytic crisis in the past year	0	76	1.174	0.858, 1.606	0.316
	1	13	0.839	0.418, 1.687	0.623
	2-3	7	1.032	0.756, 1.407	0.844
	>3	4	1		
Lifetime complications (stroke, acute chest syndrome, osteomyelitis, avascular necrosis)	0	60	1.309	0.989, 1.732	0.060
	1	18	1.143	0.780, 1.674	0.494
	2	2	1		
White blood cell count (per mm^3)	<11,000	57	1		
	11,000 to 15,000	10	0.516	0.306, 0.870	0.013
	>15,000	13	0.879	0.665, 1.161	0.363
Liver size (cm)	<2.0	27	0.997	0.704, 1.412	0.988
	2.0 to 5.0	35	1.015	0.750, 1.373	0.924
	> 5.0	18	1		

AOR: adjusted odds ratio

gender did not correlate with clinical severity. Environmental factors such as socioeconomic class are known determining factors of the disease severity and presence of complications in our setting,[16] with poor people having inadequate access to healthcare and those belonging to the high social class having access to better healthcare with affordable out-of-pocket payments for health services. The reason there was no difference with respect to the social class and disease severity in our study might be because all patients recruited into this study had equal access to the individualized comprehensive supportive health care in our pediatric sickle cell clinic, irrespective of their social class.

This study further consolidates the already reported low coverage of the NHIS in Nigeria,[17-19] as only one-tenth of the children in this study were registered on the scheme. The NHIS is an effective tool in improving the health outcomes of children, as it reduces the financial burden of health shocks.[20] This observation further suggests the urgent need to scale up access to the NHIS, especially for special populations like children with SCD. This will improve access to healthcare and protection from catastrophic healthcare expenditures.

Factors associated with clinical severity in this study (number of episodes of VOCs, hemolytic crises, blood transfusions, complications, and hospitalizations) are in keeping with previous studies.[5,7,21]

After adjustment for potential confounders, a low WBC predicted a mild index of disease severity. Akinlosotu *et al*.[21] and Okocha *et al*.[5] also reported a correlation between WBC and disease severity. Meier *et al*.,[22] in a systematic literature review of the predictors of severity in pediatric SCD patients, had also reported that baseline leukocytosis, among other factors, was a predictor of disease severity.

Strength

We obtained the minimum sample with adequate power and precision. Furthermore, we used scientific means to recruit eligible respondents to the study.

Study limitation

Some indicators of severity (such as complications) used in this study relied on historical recall and so may be affected by

recall bias. This was, however, minimized by corroborating information from the patients' case notes.

Conclusion

Our study showed that most of the children had a mild disease severity index, which was associated with a low WBC count.

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Conflicts of interest

There are no conflicts of interest.

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