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Predictors of hypoxaemia during steady-state among children with Sickle Cell Anaemia in North-Western Nigeria

AE Orimadegun[1], AO Alohan[2] and S Onazi[3]

Institute of Child Health[1], Department of Paediatrics[2], College of Medicine, University of Ibadan, Ibadan and Department of Paediatrics[3], Federal Medical Centre, Gusau, Zamfara State, Nigeria

Abstract

Background: Haemoglobin desaturation, which presents as hypoxaemia, is a known phenomenon in the cycle of red blood cells sickling in sickle cell anaemia (SCA). Thus, early and accurate recognition of hypoxaemia is important in order to ameliorate its adverse effects on vital organs. This study was carried out to investigate clinical and laboratory features that predict hypoxaemia in children with SCA during steady-state.

Methods: We prospectively measured percutaneous haemoglobin saturation of 208 children with SCA in room air during steady-state at a secondary health facility in the north-west of Nigeria. Demographic, clinical and laboratory features and anthropometry were recorded. Hypoxaemia was defined as haemoglobin saturation <90%. Chi square test and logistic regression were used to assess the associations of selected factors with hypoxaemia.

Results: Participants comprised 132 males and 76 females and their age ranged from 9 to 168 months. Prevalence of hypoxaemia was 17.3%. Though hypoxaemia was significantly associated with age, time of first symptom to presentation, body mass index (BMI), weight-for-height z-score <2.0, tachycardia, chest retraction and palpable spleen, age (OR=0.78; 95% CI=0.62, 0.96), time of first symptom to presentation (OR = 1.28; 95% = 1.03, 1.59), BMI (OR = 0.87; 95% = 0.76, 0.92) and palpable spleen (OR = 2.87; 95% CI = 1.43, 16.65) remained independent predictors in the logistic regression model.

Conclusion: Careful consideration should be given to time of first symptom to presentation, body mass index and palpable spleen when evaluating children with sickle cell anaemia for hypoxaemia in resource limited settings.

Keywords: *Hypoxaemia, Sickle cell anaemia, Haemoglobin saturation, Early childhood*

Correspondence: Dr. Adebola E. Orimadegun, Institute of Child Health, College of Medicine, University of Ibadan, Nigeria. E-mail: beorimadegun@yahoo.com.

Résumé

Contexte: La dé-saturation de l'hémoglobine, qui présente comme l'hypoxémie, est un phénomène connu dans le cycle de globules rouges drépanocytaires à l'anémie falciforme (drépanocytose). Ainsi, l'identification précoce et précise de l'hypoxémie est importante afin d'améliorer ses effets néfastes sur les organes vitaux. Cette étude a été réalisée pour étudier les caractéristiques cliniques et laboratoires qui prédisent l'hypoxémie chez les enfants atteints de drépanocytose au cours de l'état d'équilibre.

Méthodes: Nous avons prospectivement mesurés la saturation percutanée de l'hémoglobine de 208 enfants atteints de drépanocytose dans l'air de pièce pendant l'état d'équilibre dans un établissement de santé secondaires dans le nord-ouest du Nigeria. Les caractéristiques démographiques, cliniques et laboratoires ainsi que l'anthropométrie ont été enregistrées. Hypoxémie a été définie comme la saturation en hémoglobine <90%. Test de chi carré et de régression logistique ont été utilisés pour évaluer les associations de facteurs sélectionnés avec hypoxémie.

Résultats: Les participants comprenaient 132 garçons et 76 filles et leur âge variait de 9 à 168 mois. La prévalence d'hypoxémie était de 17,3%. Bien que l'hypoxémie était significativement associée avec l'âge, le temps des premiers symptômes à la présentation, indice de masse corporelle (IMC), le poids-pour-taille z-score <2,0, tachycardie, rétraction de la poitrine et la rate palpable, l'âge (OR = 0,78; IC à 95% = 0,62, 0,96), le temps des premiers symptômes à la présentation (OR = 1,28; 95% = 1,03, 1,59), l'IMC (OR = 0,87; 95% = 0,76, 0,92) et la rate palpable (OR = 2,87; IC à 95% = 1.43, 16.65) sont restés des facteurs prédictifs indépendants dans le modèle de régression logistique.

Conclusion: Une attention particulière doit être accordée aux temps des premiers symptômes à la présentation, indice de masse corporelle et la rate palpable lors de l'évaluation des enfants atteints d'anémie falciforme pour l'hypoxémie en situation de ressources limitées.

Mots-clés: *hypoxémie, drépanocytose, saturation d'hémoglobine, petite enfance*

Introduction

Sickle cell anaemia (SCA) is a haematological genetic disorder which causes red blood cells of affected individuals to assume abnormal, rigid,

sickled shape [1]. Individuals with SCA inherit the two homozygous recessive genes (SS), responsible for the characteristic sickling of the red blood cells. The SCA is a major cause of childhood morbidity and mortality. It is among the three leading causes of hospital deaths among children beyond the age of 5 years in a typical tertiary hospital in Nigeria [2]. Children with SCA make frequent visits to the clinics and they often require frequent admissions into hospitals due to complications of entrapment of sickled red blood cells in the microcirculation, often manifest as acute painful crisis. Though malaria is the most commonly diagnosed precipitating factor for acute painful crisis in SCA, other causes include: excessive cold, dehydration, infection, and haemoglobin desaturation [3]. Majority of known causes of acute painful crisis in SCA are not only treatable, but are also preventable.

Among many preventable causes of painful crisis in SCA is haemoglobin desaturation from any of the risk factors. Haemoglobin desaturation, often defined on the basis of percutaneous assessment of arterial blood oxygenation in clinical settings, is a common problem in children with SCA even in steady-state (period of no painful crisis) [4]. Haemoglobin desaturation has been attributed to a rightward shift of the oxy-haemoglobin dissociation curve due to chronic anaemia and the sickled nature of the red cells which impairs oxygen release under stressful conditions [5]. Haemoglobin desaturation was initially thought to be relatively not life-threatening, but recent evidence has revealed its association with many serious complications including stroke and death [6]. Thus, monitoring of arterial blood oxygenation and early detection of haemoglobin desaturation (hypoxaemia) has now assumed serious importance in the day-to-day management of patients suffering from SCA and during scheduled follow-up clinics.

The main objective of scheduled follow-up of children with SCA is to prevent painful crisis and lessen frequency of hospital admissions. In a typical Nigerian clinic, preventive measures such as antimalarial prophylaxis, adequate fluid intake, folic acid supplementation and general personal hygiene are emphasised to patients and caregivers. Pulmonary complications and hypoxaemia are common in SCA and may exacerbate microvascular occlusive phenomena. Thus, detecting hypoxaemia is of particular importance in the care of SCA patients. Though hypoxaemia has been reported as one of the main factors that may precipitate painful crisis in the SCA patients, little attention is currently been paid to its contributions to morbidity and mortality in Nigeria. There is increasing evidence that simple pulse oximetry measurements in SCA patients can detect hypoxaemia needing immediate intervention [7]. Thus, pulse oximetry, with the use of finger-tipped pulse oximeters, are routinely done at home and during clinic visits in developed world, but less practiced in resource limited countries. The ease, affordability and availability of routine pulse oximetry suggest that it is possible to reduce the incidence of painful crisis and hospital admissions attributable to haemoglobin oxygen desaturation [8], if it is introduced as part of the scheduled clinic care practices for patients with SCA. However, this may be challenging for deficiency of knowledge of pulse oximetry and lack of appropriate device in many health facilities in Nigeria [9].

The need for routine pulse oximetry for monitoring SCA patients during outpatient follow-up clinics, even at home and how to identify those who would require such care remain an open question in Nigeria. A recent study in the South-eastern Nigeria showed that hypoxaemia could be as high as 13% among SCA patients in their steady-state [10]. The authors suggested the need for physicians to have high index of suspicion and take swift action in managing individuals with SCA who are prone to developing haemoglobin desaturation because it might worsen morbidity and hospital admission outcomes. To address these policies and practice gaps in the care of SCA patients relating to haemoglobin desaturation, the burden, severity and predictors of haemoglobin desaturation need to be well understood in the context of the Nigeria child health care system. This study was therefore carried out to describe the burden of hypoxaemia in SCA steady-state. It was also hypothesised that certain socio-demographic and clinical features are more frequent among children with SCA who have hypoxaemia in steady-state than those without.

Materials and methods

Study design and setting

In this cross sectional study, we prospectively recruited 208 children previously diagnosed with SCA during scheduled follow up clinic visits at the Federal Medical Centre (FMC), Gusau, Zamfara state, Nigeria over a 10-month period (May 2012 to February, 2013). The FMC Gusau provides secondary health care to the people of the Zamfara state, north-west of Nigeria. The "Children Sickle Cell Anaemia Clinic" runs weekly with attendance ranging from 15 to 25 per clinic session. The old cases of SCA are seen at scheduled interval of 2 to 4 weeks by the Consultant Paediatrician. The

population of Gusau, the capital city of Zamfara state is 226,857 (2006 Census). The city is located at latitude 12.1628 degrees, longitude 6.66135 degrees with average elevation (altitude) of 459 meters [11].

Study population, sampling and sample size

Children diagnosed with SCA were the target of this study. The exact prevalence of SCA in Gusau and the neighbouring communities was unknown but they constitute about 5.5% of over 200 children seen weekly in the children outpatient department of the FMC. These children are mainly Hausa-Fulani ethnic group of the Northern Nigeria. In the present study, during follow up clinic visits, every alternate child who had established diagnosis of SCA were systematically recruited after random selection of the first. In addition to being SCA patients, other inclusion criteria were being free from SCA painful no history of hospital admission and having consistently being given the routine daily oral folic acid and chlorproguanil tablets for at least a 2-month period. Given that 446 children with SCA were seen during the 10 months of the study, enrolling 208 children at an assumed prevalence of hypoxaemia of 10% gave an estimated exact error of ±3.0% at 95% level of confidence and power of 80%.

Data collection and variable measurements

Data were recorded by one of the medical officers and a trained nurse who routinely run the SCA follow up clinic while one of the investigators reviewed hospital records to establish patients' eligibility. Socio-demographic characteristics and history signs and symptoms in the six months preceding the clinic visit were recorded into a structured pre-tested case record form (CRF). At recruitment, each child was examined, and findings were entered into the same CRF. After this, arterial oxygen saturation was measured with an appropriately sized oxygen sensor placed on a toe or finger using the Nellcor N-395 pulse oximeter (Nellcor Puritan Bennett Inc., CA, USA), while the patients breathe room air. Oxygen saturation was categorised as normal (SpO_2 >95%), mild desaturation (SpO_2 90–94%) and hypoxaemia (SpO_2 <90%) as in previous reports [12-14]. The SpO_2 measurement was recorded after 3 minutes of stable observation. Though it was decided a priori that any child who had SpO_2 less than 85% would be given nasal or nasopharyngeal oxygen therapy immediately, no patient was found to have such degree of desaturation. To ensure quality control, two of the investigators independently measured SpO_2 of each child at 10 minutes interval and measurements were repeated whenever there was discrepancy (>2%).

Data analyses

The main outcome variable in this study was arterial oxygen saturations (SpO2). Independent variables measured included: demographic variables including age and gender, clinical features and anthropometry. Weight-for-height z-scores were calculated using the World Health Organization Anthro version 1.0.4 software and individuals whose z-scores were less than -2.0 were classified as malnourished. The data were entered into spreadsheet and analysed using SPSS 17.0 statistical software (SPSS Inc. USA). For bivariate analysis, Chi-square test was utilised for cross-tabulations between the dependent and independent categorical variables, associations between continuous independent variables and the dependent variables were done by Student t test. A multivariate logistic regression was used to determine independent predictors of hypoxaemia. Level of statistical significance was set at $p = 0.05$ for all the analyses.

Ethical considerations

Participation in the study was completely voluntary and based on written informed consent obtained from caregivers. Caregivers were made to understand that they are free to withdraw consent at any time, and that they will continue to receive the routine care for the disease according to standard protocol. Privacy of participants was ensured by using a serial number on the CRF, rather than a name or hospital number. The research was relatively risk-free as, there is no interference with the patients' treatments. Approval for the study was obtained from the Ethical Review Committee of FMC, Gusau.

Results

Characteristics of study participants

Of the 208 children with SCA who participated in the study, there were 132 males and 76 female children. The age of the patients ranged from 9 to 168 months (mean = 75.2±44.4 months). Children aged 9 months to 5 years constituted 40.4% (n = 84) and 59.6% were aged 6 to 15 years. The socio-demographic and anthropometric characteristics of the male and female SCA patents were compared as shown in table 1. Significantly more males (29.5%) than females (15.8%) had weight-for-height z-score less than -2.0, indicating undernutrition ($p = 0.030$).

Regarding clinical and laboratory features, tachycardia (92.3%), tachypnoea (69.2%), chest-in-drawing (12.0%), significant palpable liver (17.3%)

and spleen (7.7%), serum bicarbonate <15mmol/L (19.7%) and haemoglobin <5g (59.1%) were present at the time of recruitment. Majority (n = 197; 94.7%) had some degree of jaundice, but none had history of recent dark coloured urine at the time of recruitment.

Prevalence of hypoxaemia among SCA patients in steady-state

The SpO_2 recordings ranged from 71% to 99% (median = 98%). Overall, 36 (17.3%) out of the 208

Table 1: Characteristics of children with Sickle Cell Anaemia

	All SCA cases n = 208	Male n = 132	Female n = 76	P
Mean Age (months)	75.2±44.4	73.2±40.9	78.5±49.9	0.410
Mean Weight (kg)	19.0±7.2	18.4±6.5	20.1±8.4	0.125
Mean Body mass index (kg/m²)	14.3±2.2	13.2±0.7	15.3±2.8	0.069
Weight-for-height z-score < -2.0, n (%)	51 (24.5)	39 (29.5)	12 (15.8)	0.030
* Time of first symptom to presentation	56.4±42.0	53.7±39.3	61.2±46.2	0.220

*Approximate time from the first symptoms/diagnosis to date of recruitment

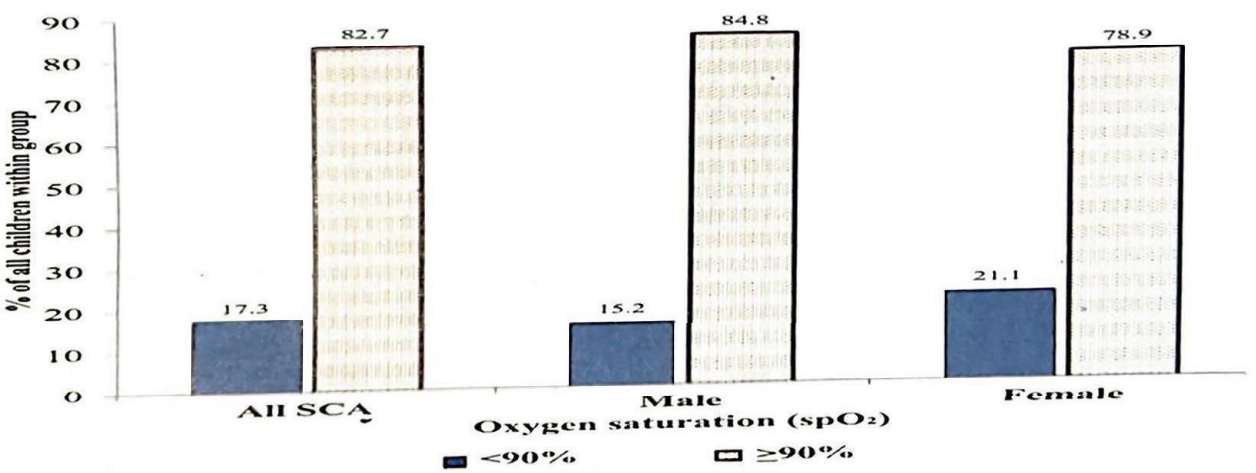

Fig.1: Distributions of SCA Patients according to Oxygen Saturation and Gender

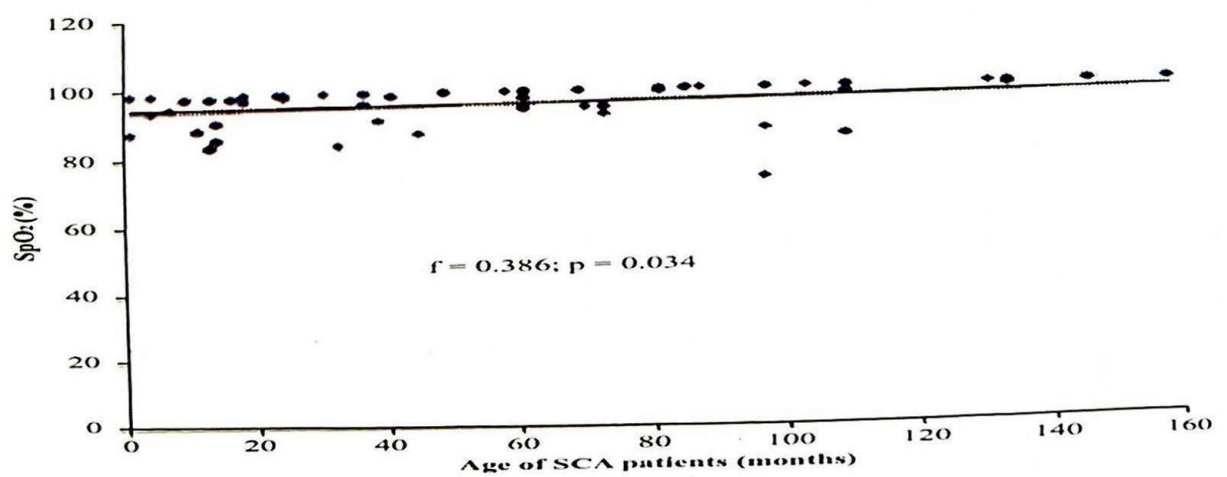

Fig. 2: Correlation of haemoglobin saturation with age in sickle cell anaemia patients
r – Spearman correlation coefficient

Table 2: Associations of demographic, selected clinical and laboratory characteristics with steady-state haemoglobin oxygenation status among children with sickle cell anaemia

	Hypoxaemia (n = 36)	No Hypoxaemia (n = 172)	P
Mean age of SCA patients	59.2±46.8	78.5±43.3	0.017
Maternal education <6years, n (%)	28 (77.8)	97 (56.4)	0.017
* Time of first symptom to presentation (months)	46.1±40.5	58.6±42.1	0.105
Mean BMI (kg/m²)	15.3 ±2.8	13.2 ±0.7	0.054
Weight-for-height z-score < -2.0, n (%)	4 (11.1)	47 (27.3)	0.053
**Tachycardia, n (%)	32 (88.9)	160 (93.0)	0.488
***Tachypnoea, n (%)	20 (55.6)	124 (72.1)	0.051
Chest retractions, n (%)	9 (25.0)	19 (11.0)	0.034
'Significant palpable liver, n (%)	8 (22.2)	28 (16.3)	0.391
''Significant palpable spleen, n (%)	12 (33.3)	4 (2.3)	<0.001
Hepatosplenomegaly, n (%)	8 (22.2)	4 (2.3)	<0.001
Serum Bicarbonate <15mmol/L	19 (52.8)	22 (12.8)	<0.001
Haemoglobin <5g/dL	22 (61.1)	101 (58.7)	0.395

**Approximate time from the first symptoms/diagnosis to date of recruitment*
***Heart rate per minute > expected for age*
****Respiratory rate per minute > expected for age*
'Liver size >2cm below costal margin at mid-clavicular line
''Spleen palpable below the left costal margin

Table 3: Predictors of hypoxaemia (SpO_2<90%) among children with sickle cell anaemia

Predictor variables	UOR (95% CI)	AOR (95% CI)
Male gender	0.67 (0.32, 1.39)	1.09 (0.18, 6.53)
Age of SCA patients	0.97 (0.96, 0.99)	0.78 (0.62, 0.96)
Maternal education <6years	2.71 (1.17, 6.28)	1.28 (0.98, 1.57)
*Duration of SCA symptoms (months)	0.98 (0.96, 0.99)	1.28 (1.03, 1.59)
BMI (kg/m²)	0.91 (0.90, 0.95)	0.87 (076, 0.92)
Weight-for-height z-score < -2.0	0.33 (0.11, 0.99)	1.31 (0.63, 2.77)
**Tachycardia	0.67 (0.18, 1.97)	0.55 (0.14, 2.19)
**Tachypnoea	0.48 (0.23, 1.01)	0.88 (0.56, 1.92)
Chest retractions	2.68 (1.10, 6.55)	2.15 (0.14, 7.34)
'Significant palpable liver	1.47 (0.61, 3.56)	1.65 (0.47, 3.66)
''Significant palpable spleen	21.0 (6.26, 70.41)	2.87 (1.43, 16.65)
Hepatosplenomegaly	12.0 (3.39, 42.52)	1.23 (0.91, 4.42)
Serum Bicarbonate <15mmol/L	7.62 (2.45, 16.84)	4.34 (0.97, 10.32)
Haemoglobin <5g	1.11 (0.53, 2.31)	1.02 (0.41, 2.14)

UOR – Unadjusted Odds Ratio *AOR - UOR – Adjusted Odds Ratio*
**Approximate time from the first symptoms/diagnosis to date of recruitment*
***Heart rate per minute > expected for age*
****Respiratory rate per minute > expected for age*
'Liver size >2cm below costal margin at mid-clavicular line
''Spleen palpable below the left costal margin

SCA patients had SpO_2 less than 90% (Figure 1). The distributions of SCA patients according to oxygen saturation and gender were as shown in fig.1. Though more females than males had SpO_2 less than 90%, there was no statistically significant difference between male and female groups ($\chi^2 = 1.174$, df = 1; p = 0.279). Figure 2, scatter plot with line of best-fit, shows that there was significant positive correlation between SpO_2 and age of SCA patients (r = 0.386; p = 0.034).

Comparisons of demographic, clinical and laboratory features between SCA patients who had hypoxaemia and those without hypoxaemia were as shown in table 2. The mean age of SCA patients with

hypoxaemia (59.2±46.8 months) was significantly lower than those without hypoxaemia (78.5±43.3 months); p = 0.017. Also, hypoxaemia was significantly more frequent in SCA patients whose mother had less than 6 years of formal education, those who presented with chest retractions, palpable spleen, hepatosplenomegaly and serum bicarbonate <15mmol/L than their respective counterparts without these features (Table 2).

Predictors of hypoxaemia among SCA patients in steady-state

The odds ratio for occurrence of hypoxaemia in steady-state among SCA patients obtained from bivariate multivariate analyses using demographic, selected clinical and laboratory characteristics as independent variables were as shown in table 3. The bivariate analyses revealed that hypoxaemia was significantly associated with age (OR = 0.97; 95% = 0.96, 0.99), duration of SCA symptoms (OR = 0.98; 95% = 0.96, 0.99), BMI (OR = 0.91; 95% = 0.90, 0.95), weight-for-height z-score category (95% = 0.33; 95% = 0.11, 0.99), tachycardia (OR = 0.67; 95% = 0.18, 1.97), chest retraction (OR = 2.68; 95% = 1.10, 6.55) and palpable spleen (OR = 21.0; 95% = 6.26, 70.41). However, age, duration of SCA symptoms, BMI and palpable spleen remained as independent predictors of hypoxaemia after adjusting for other variables in a logistic regression model (adjusted OR in Table 3).

Discussion

Children with SCA may have significant hypoxaemia during the steady-state and its recognition is usually challenging. In clinical practice, early identification of haemoglobin desaturation is important in order to limit associated complications and deaths [13]. However, haemoglobin desaturation is usually identified by pulse oximetry in research while in clinical practice some clinical features are used [13-16]. In this study, we investigated the haemoglobin desaturation and elucidated clinical and laboratory features that can predict hypoxaemia among children with SCA in their steady-state.

This study revealed that children with SCA in northern Nigeria have significant burden of haemoglobin desaturation. The prevalence of hypoxaemia (SpO_2 <90%) among the study participants was 17.3%. This finding corroborates earlier reports but with a relatively higher prevalence than reported among children in South-Eastern Nigeria by Chinawa *et al* [10] using the same cut-off value of saturation (SpO_2 less than 90%). Depending on the altitude of the study site, different cut-off values of saturation have been used to define severe hypoxaemia; at sea level 90% has been widely accepted [17]. One reason that may explain the difference in the prevalence of hypoxaemia between the two studies in the same country is the altitude. While Gusau, the setting of the present study is at altitude 459 metres [11], Enugu is located 152 m above sea level [18]. Hypoxaemia may be more frequent and more severe in children who live at higher altitude, because of reduced partial pressure of atmospheric oxygen. Largely, the desaturation observed in SCA during steady state has essentially been attributed to a rightward shift of the oxy-haemoglobin dissociation curve due to chronic anaemia [5] and the unstable properties of the sickle haemoglobin in the plasma [19].

Our data also revealed that, during steady-state, SpO_2 positively correlates with age and much of the age-related decline in SpO_2 occurs in the first 8 years of life (Figure 2). According to Serjeant and Serjeant [20], the decline of foetal haemoglobin F to its steady-state level may take up to 5 years. The effect of age on SpO_2 could be explained by the normal developmental decline in haemoglobin F concentration. The higher affinity of haemoglobin F oxygen affinity than haemoglobin S might have contributed to the correlation association between age and SpO_2. On the contrary, Rackoff and colleagues [21] found a negative correlation between SpO_2 and age, but this association was not significant when haemoglobin F was included in the multivariate regression model. Haemoglobin F was not measured in our study so it is impracticable to test this proposition. Similarly, in two studies [22, 23] no association was found between age and SpO_2, probably because these studies included SCA patients who were 9–18 and 3–19 years of age, respectively, and did not include sufficient under-5 children in whom we found correlation with age.

In the present study, we demonstrated that SCA patients who had weight for height z-score < -2.0 are less likely to have hypoxaemia compared with those who are well-nourished, a finding not reported in past studies [10]. However, the effect of weight for height z-score < -2.0 on SpO_2 was small and it was not statistically significant after adjusting for other factors. These suggest that the protective effect of weight for height z-score <-2.0 is probably being exerted through other factors. It is, however, likely that those children who had weight for height z-score < -2.0 among the study group had relatively lower quality haemoglobin oxygen carrying capacity and exhibited less rightward shift of the oxy-haemoglobin dissociation curve. Although the frequency of some

complications of SCA may differ between sexes and the two categories of nutritional status, we did not investigate any potential biological explanations for this interesting finding.

Of the 14 clinical and laboratory features investigated in the logistic regression model, only four independently predicted hypoxaemia among children with SCA. These findings provide remarkable support for age, duration of symptoms, BMI and palpable spleen as important factors associated with hypoxaemia among children with SCA during steady-state. Since age and duration of SCA symptoms are quantitative numerical variable, an increase in one-month in age has a 22% decrease in odds of having hypoxaemia and an increase in one-month duration of symptoms has 12% increase in odds of having hypoxaemia (Table 3). The increase in odds of having hypoxaemia appears to be the highest in the presence of significant palpable spleen (87%). Notably, the clinical features predictive of hypoxaemia are known consequences of sickle cell diseases pathology. The implication of these findings is that the presence of any one of these four features, irrespective of aetiology, would be sufficient evidence to consider careful administration of oxygen to children with SCA in clinical settings especially during.

One main issue that limits the generalisability of our findings is that less than half of the children who presented with SCA during the study period participated. Nevertheless, the regression model explains over half of the variation in SpO_2. This model provides mechanistic insights into steady-state desaturation and the ability to predict its occurrence in children who have SCA. Because of the association of hypoxaemia with vaso-occlusive complications, including clinically overt stroke in children with SCA [24], further study on the role of hypoxaemia as a cause or consequence of SCA-related morbidity is needed.

Conclusion

This study presents an update on the burden of hypoxaemia in SCA during steady-state, and revealed that young age, increasing duration of symptoms, decreasing BMI and/or palpable spleen are important factors associated with hypoxaemia. These findings imply that children with SCA having any of these features deserve objective assessment for hypoxaemia and they should be given oxygen therapy, as potential life-saving intervention. Specifically, physicians need to pay attention to occurrence of hypoxaemia among children with SCA in steady-state.

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