



Prevalence and Predictors of Elevated Pulmonary Artery Pressure in Nigerian Children with Sickle Cell Anaemia

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Authors' contributions

This work was carried out in collaboration among all authors. Authors UMS and UMW conceptualized and designed the study, wrote the protocol and the first draft of the manuscript. Author UMW managed the analyses of the study and literature search. Authors HA, NMJ, KOI and BIG managed the literature searches and review of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Sickle Cell Anaemia (SCA) is the most common inherited disorder in Nigeria. Pulmonary Hypertension (PH) is a known complication of SCA that commences from childhood and progresses as they grow older.

Aim: To determine the prevalence and predictors of elevated pulmonary artery pressure (PAP) in children with SCA.

Study Design: This is an analytical cross-sectional study.

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Methods: Three hundred subjects with SCA in steady state and 300 HbAA controls, aged 6 months – 15 years, were enrolled into the study. Children with SCA were recruited by simple random sampling, from the Paediatric Sickle Cell Clinic, Usmanu Danfodiyo University Teaching Hospital, Sokoto. All the children had clinical evaluation, echocardiography, full blood count and reticulocyte count. Pulmonary artery systolic pressure (PASP) and mean pulmonary artery pressure (MPAP) were determined by measurement of tricuspid regurgitant velocity (TRV) and mean gradient (MG) respectively.

Results: Seventy-two children with SCA (24.0%) had elevated PAP (defined as TRV \geq 2.5 m/s) while only 9 (3.0%) had pulmonary hypertension (defined as MPAP \geq 25 mmHg). Older age (O.R = 1.03, $p < 0.001$), high systolic blood pressure (O.R = 1.2, $p = 0.01$), and high reticulocyte count (O.R = 1.33, $p = 0.04$) were weakly associated with increased likelihood of elevated PAP. Normal pulse oxygen saturation ($SPO_2 \geq 95\%$, O.R = 0.4, $p = 0.002$) and normal heart sounds on auscultation (O.R = 0.2, $p = 0.04$) were associated with a reduced likelihood of elevated PAP. Presence of left parasternal heave (O.R = 8.4, $p = 0.001$) significantly predicted elevated PAP in children with SCA.

Conclusion: PH occurs as a complication in children with SCA and certain clinical and laboratory parameters do predict this complication in children.

Keywords: Sickle cell anaemia; pulmonary pressure; prevalence; predictors.

1. INTRODUCTION

Sickle cell Disease (SCD) is one of the most common genetic disorder globally, and the homozygous form, manifesting as Sickle Cell Anaemia (SCA), is the commonest. The frequency of the heterozygous state in Africa has been estimated to be as high as 25.0-40.0% [1]. The greatest burden of SCA is in Sub-Saharan Africa, where 75.0% of the affected children live [2]. In Nigeria, about 25.0% of the population are carriers of sickle cell trait, while the homozygous state (HbSS) is found in about 3% of the population [1].

SCA (HbSS) occurs when a single base-pair mutation leads to replacement of glutamic acid with valine at position six of the β -globin subunit of adult haemoglobin (HbA). The major biochemical consequence of this disorder is the decreased solubility and deformability of the mutant haemoglobin S (HbS) [1], leading to frequent vaso-occlusion and haemolysis. With increasing age, SCA is associated with chronic end-organ complications such as chronic renal failure, stroke, avascular necrosis of bone and pulmonary hypertension [3,4]. Lung involvement in the form of acute chest syndrome and sickle cell chronic lung disease (SCCLD) accounts for a mortality rate of more than 20.0% in adults with SCA [5]. SCCLD is characterised by radiological and clinical features of ventilatory dysfunction and pulmonary hypertension (PH) [6]. About 20.0-40.0% of adult patients with sickle cell anaemia screened with echocardiography have evidence of PH [7]. In children, reported prevalence of PH varied from 8.3-33.0% [8-13].

There is paucity of published work on the prevalence of elevated pulmonary artery pressure and PH among children with SCA in Nigeria. Most of the available studies in Nigeria defined PH based on TRV of ≥ 2.5 m/s [9,14-16], which is more reflective of the systolic pulmonary artery pressure (SPAP) rather than the mean pulmonary artery pressure (MPAP) that defines PH. To the best of investigators' knowledge, there is no previous study in the study area or elsewhere in the country both in adults and children, which determines the prevalence of PH using mean pulmonary artery pressure (MPAP) cut off value of 25 mmHg, either by the mean gradient (derived from area under the curve) method or by right heart catheterization (RHC). This study was therefore conducted with the aim of identifying the prevalence and predictors of elevated PAP in Nigerian children with SCA using both TRV and MPAP (derived using mean gradient method).

2. MATERIALS AND METHODS

This was a cross-sectional analytical study carried out at the sickle cell clinic of the Department of Paediatrics, Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto, North-Western Nigeria.

2.1 Study Subjects

Study subjects comprised children with the diagnosis of SCA in steady state and an equal number of age and sex-matched Hb AA controls. Steady state in this study was defined as, absence of painful crisis, blood transfusion, acute

clinical symptoms or crisis, or febrile illness warranting hospitalisation in the preceding three months. Controls were apparently healthy children with haemoglobin electrophoretic pattern AA, who presented at the children section of the General Outpatient Clinic of the Department of Family Medicine with minor illnesses, or who were on follow up for minor illnesses at the Paediatrics Out-Patient Clinic.

Subjects that fulfilled the following inclusion criteria were recruited in to the study: 1) Age 6 months to 15 years, 2) Hb Electrophoretic pattern SS and 3) absence of crisis, inter current illness such as bronchopneumonia, asthma or any illness that warranted hospitalisation or blood transfusion in the preceding three months. For the controls, inclusion criteria include 1) children aged 6 months to 15 years with minor ailments that are not known to affect pulmonary pressure or tricuspid regurgitant velocity (TRV), 2) Haemoglobin electrophoretic pattern AA and 3) Packed cell volume (PCV) of at least 30%.

Subjects with the following conditions were excluded from the study: 1) Presence of chest wall deformities, 2) patients on therapies known to have effect on pulmonary artery pressure such as anorectic agents, hydroxyurea or chronic transfusion therapy, 3) presence of functional or structural abnormality of the heart or great vessels, like systolic dysfunction, congenital abnormalities of the heart and the great vessels including branch pulmonary stenosis, 4) presence of obvious clinical symptoms of cardiac involvement by infectious, neuromuscular or metabolic disorder; or clinical symptoms of lung disease, asthma, adenoidal hypertrophy, kidney or connective tissue disease and fever and 5) absence of measurable tricuspid regurgitation jet.

2.2 Sampling Technique

Subjects were selected by simple random sampling, using a table of random digits, according to the way they were numbered in the outpatient register for the day.

2.3 Sample Size

A total of 600 eligible children (300 with Sickle Cell Anaemia and 300 apparently healthy controls) were recruited for the study.

2.4 Clinical Assessment

All the children were subjected to clinical evaluation. Relevant clinical history including age, age at diagnosis of SCA, medications,

history of blood transfusion in the past, and presence or history of chronic complications were recorded. Each patient had general physical examination including measurement of anthropometric indices, body mass index (BMI), body surface area (BSA) and clinical assessment for pallor, jaundice and central cyanosis. Length/height were taken to the nearest 0.01 cm. BMI and BSA were calculated manually using Quetelet index $\{BMI = \text{Weight (Kg)}/\text{Height}^2 \text{ (M)}\}$ [17] and Mosteller formula $\{\sqrt{\text{weight(kg)} \times \text{height(cm)}/3600}\}$ [18] respectively. Pulse oxygen saturation was assessed by pulse oximetry using Alpha pulse oximeter (Lifeline Medical Devices. 155-156, Udyog Bihar, Phase-VI, Gurgaon-122001, Haryana, India). Oxygen saturation of 95-100% in room air was regarded as normal [19].

Cardiovascular examination to assess pulse rate, blood pressure, location of the apex beat, parasternal heave and heart sounds were carried out. Blood pressures were taken with the children less than 2 years of age sitting on their mother's/caregiver's laps while those greater than 2 years in sitting position, using mercury in glass sphygmomanometer and appropriate cuff bladder size with cuff width of approximately 50% the circumference of the arm [19]. Two readings were taken and the average of these used. Korotkoff sound 1 was taken as the systolic blood pressure while Korotkoff sound 5 was taken as the diastolic blood pressure in accordance with the Working group of the National High Blood Pressure Education program (NHBPEP, 2004) [19]. Heart sounds were regarded as normal when the first heart sound is single and louder at the apex with normally split second heart sound in inspiration appreciable at the second left intercostal space. Abdominal examination was done to check for the presence or absence of splenomegaly by manual deep palpation, defined in this study as palpable spleen of any size below the left costal margin.

2.5 Laboratory Investigations

About four millilitre of venous blood samples were collected in the EDTA bottles from all subjects. Haemoglobin electrophoresis was done for all the controls. Full blood count including total leucocyte count and thrombocyte count were done using Coulter counter haematology analyser (Orphée, Mythic model 22CT) and reticulocyte counting was carried out manually by reticulocyte staining in accordance with the criteria established by Lewis et al. [20].

2.6 Echocardiography

Standard two-dimensional and Doppler echocardiography was performed in the supine and left lateral decubitus positions using SSI-5000 Sonoscape echocardiography machine (SonoscapeYizhe Building, Yuquan Road, Shenzhen China) with a 3.5–7 MHz transducer. Standard parasternal long and short axes, apical, subcostal and suprasternal views were used. Screening echocardiography was done first to rule out structural heart abnormalities including right ventricular out flow and branch pulmonary artery obstruction. Left ventricular systolic function was assessed by calculating left ventricular ejection fraction using Simpson's rule. Subjects with ejection fraction of 55% - 75% were regarded to have normal left ventricular systolic function [21].

Colour Doppler interrogation was used to detect tricuspid regurgitation from the apical 4-chamber, RV inflow, parasternal short axis and subcostal views. Tricuspid valve morphology was assessed to ensure normal tricuspid valve morphology. Tricuspid regurgitant jet velocity (TRV) was recorded and the maximum value obtained was taken as the peak velocity. Mean gradient (MG))

was measured by continuous wave Doppler using area under the curve method as shown in Figs. 1 and 2.

Pressure gradient (ΔP) between the right ventricle and the right atrium was calculated using the Bernoulli equation:

$$P_1 - P_2 (\Delta P) = 4V^2$$

Where,

P_1 is the right ventricular pressure, P_2 is the right atrial pressure and V the peak TR velocity. Ten per cent of ΔP was taken as estimated right atrial pressure (RAP) [22]. This was added to the mean gradient (MG) derived from the area under the curve (see Figs. 1 and 2) to get the mean pulmonary artery pressure (MPAP) as shown below:

$$MPAP = MG + RAP (10\% \text{ of } 4TRV^2)$$

Pulmonary artery systolic pressure (PASP) was estimated using modified Bernoulli equation as follows:

$$PASP = (4 \times TRV^2) + \text{estimated RAP (10\% of } \Delta P) [22].$$

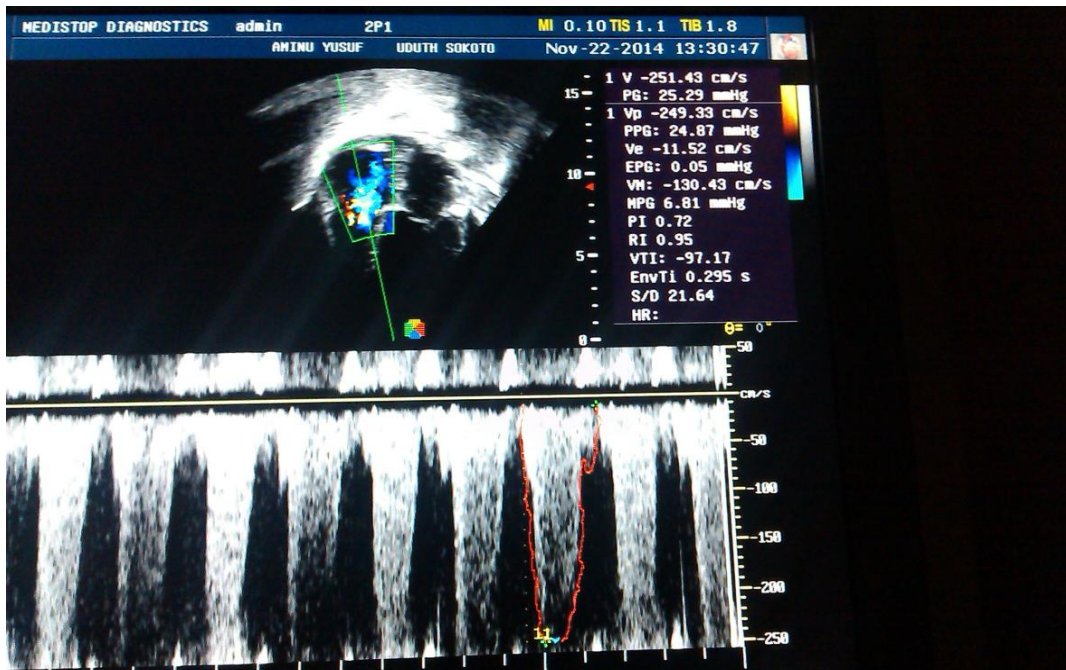


Fig. 1. Colour flow Doppler with area under the curve mapping in an 8-year old boy with SCA. The patient had elevated PAP with peak TRV of 2.51 m/s and the MG of 6.8 mmHg



Fig. 2. Colour flow Doppler with area under the curve mapping in a 5-year old girl with SCA and pulmonary hypertension. The peak TRV was 3.6 m/s while the mean gradient (MG) was 23.3 mmHg. Estimated RPA was 5 mmHg (10% of $4TRV^2$). The MPAP was 28 mmHg (MG + RPA)

2.7 Categorization/ Definition

To evaluate factors associated with elevated pulmonary artery pressures (PAP), children with SCA were categorized in to two groups: Those with tricuspid regurgitant jet velocity (TRV) ≥ 2.5 m/s were classified as having elevated PAP while those with TRV less than < 2.5 m/s were classified as having normal PAP (TRV < 2.5 m/s). Only patients with estimated MPAP ≥ 25 mmHg, calculated using mean gradient method and estimated RAP from the equation $MPAP = MG + RAP$ [23], were considered to have PH [19,21]. Demographic, clinical, haematological and echocardiographic findings in those SCA patients with elevated PAP were compared with those of SCA patients with normal PAP, with the aim of assessing the possible predictors of elevated PAP in SCA patients.

2.8 Quality Assurance

All echocardiographic measurements were done according to the recommendations of the American Society of Echocardiography [24]. The arithmetic mean of three consecutive measurements were used. The TR jet was interrogated from multiple different views (RV inflow, apical four chamber, parasternal short axis and subcostal views) to ensure that the ultrasound beam is parallel to the regurgitant signal, thus allowing optimal Doppler envelope quality and an accurate peak trans tricuspid flow velocity (TTFV) [24].

2.9 Data Analysis

Obtained data were analysed using the Statistical Program for Social Science (SPSS) version 20.0 for windows. Demographic and clinical characteristics, haematological values and echocardiographic measurements were compared between patients with SCA(HbSS) and HbAA controls, and between the two groups of SCA patients based on findings of normal or elevated PAP. Continuous variables were summarised as means and standard deviations and categorical variables as frequencies and percentages. Mean values were compared between two groups by independent sample t-test while frequencies and percentages between two groups were compared using Chi-square or Fisher's exact test where figures are small. Clinical events, haematological and echocardiographic variables with p-value < 0.05 were included in a logistic regression model with PAP dichotomized (elevated or normal) as the dependent variable for multivariate analysis of independent risk factors for the development of elevated PAP in children with SCA. Results of the regression analysis were presented as Odds Ratios (OR) with 95% confidence intervals (CI) and p-values. P-values < 0.05 were considered statistically significant.

2.10 Ethical Approval

The study was approved by research and ethics Committee of Usmanu Danfodiyo University

Teaching Hospital, Sokoto. Informed written consent was obtained from parents and/or guardians. Assent was also sought from subjects aged ≥ 7 years.

3. RESULTS

Six hundred subjects were recruited into the study, comprising 300 SCA patients and 300 Hb AA controls. The age range of all the subjects was 0.5- 15 years, with mean age of 6.5 ± 4.1 years for children with SCA and 5.9 ± 5.2 years for the controls ($p = 0.13$) as shown in Table 1. One hundred and fifty-six of the 300 SCA patients (52.0%) were males and 144 were females, giving a M: F ratio of 1.1:1. In the control group, 138 were males and 168 were females with M: F ratio of 0.9:1. With the exception of PCV, SPO₂ and BMI, the clinical, echocardiographic as well as haematological variables measured were significantly higher in patients with SCA than the controls (Table 1). The mean TRV, mean gradient (MG) and mean pulmonary artery pressure (PAP) were also significantly higher in children with SCA than the controls as shown in Table 1.

3.1 Prevalence of Elevated PAP in Subjects and Controls

Seventy two out of the 300 (24.0%) patients with SCA had elevated PAP (TRV of ≥ 2.5 m/s); but only 14 out of the 300 Hb AA controls (4.7%) had elevated PAP ($X^2(1) = 45.7$, $p = 0.001$). The age specific prevalence of elevated PAP in the subjects and control is shown in Table 2. There was significant difference in the prevalence of elevated PAP between the various age categories of children with SCA. Elevated PAP was found mostly among the older patients, with

the highest prevalence (44.6%) observed in children aged 10-15years. None of the subjects either from the SCA group or the controls aged less than 1 year had elevated PAP, as depicted in Table 2.

3.2 Predictors of Elevated Pap in Patients with Sca

3.2.1 Demographic factors

The mean age of patients with elevated PAP was 8.7 ± 3.9 years (range 2.3-15.0 years), which was significantly higher than that of patients with normal PAP 6.8 ± 3.9 (range 0.5-15.0) ($p < 0.001$). However, there was no statistically significant difference in gender and in mean age at diagnosis between children with elevated PAP and those with normal PAP (Table 3).

3.2.2 Clinical factors

The mean BMI of patients with elevated PAP was 14.6 ± 2.9 Kg/M² (range =8.2-27.9 Kg/M²) while the mean BMI of patients with normal PAP was 8.8-19.5 Kg/M² (range = 14.4 ± 1.9 Kg/M²). The difference was not statistically significant ($p = 0.14$). However, the mean systolic blood pressure and pulse oxygen saturation showed statistically significant difference between the two groups, with the elevated PAP group having higher mean SBP (113.4 ± 11.3 mmHg, range = 90.0-130.0 mmHg Vs 100.1 ± 8.9 mmHg, range=80.0-120.0 mmHg) and lower mean SPO₂ ($95.8 \pm 1.7\%$, range= 91.0-99.0%, Vs $98.3 \pm 1.1\%$, range = 96.0-100.0%) than the group with normal PAP (Table 3). A total of eleven patients (3.7%), all from the group with elevated PAP, had abnormal pulse oxygen saturation (SPO₂ < 95%).

Table 1. Characteristics of the study subjects and controls (N=600)

Variables	SCA patients n = 300	Normal n = 300	P Value
Age, years	6.5 ± 4.1	5.9 ± 5.2	0.13
M: F	1.1:1	0.9:1	0.14
BMI	14.7 ± 2.9	15.3 ± 1.9	0.002
BSA, M ²	0.8 ± 0.3	0.7 ± 0.4	0.09
SPO ₂ , %	97.8 ± 1.7	99.2 ± 0.8	<0.001
SBP, mmHg	103.3 ± 11.4	87.0 ± 11.5	<0.001
PCV, %	22.9 ± 3.5	37.4 ± 2.4	<0.001
WBC, x10 ⁹ /L	19.6 ± 7.0	6.6 ± 1.6	<0.001
Platelet count, x10 ⁹ /L	398.5 ± 109.6	138.5 ± 29.8	<0.001
Retic Count, %	10.3 ± 3.4	4.1 ± 1.1	<0.001
TRV, m/s	2.0 ± 0.7	1.6 ± 0.4	<0.001
MG, mmHg	8.4 ± 4.7	5.9 ± 3.9	<0.001
MPAP, mmHg	10.2 ± 5.8	7.8 ± 4.4	<0.001

Table 2. Age specific prevalence of elevated PAP in patients with SCA and controls (N=600)

Age category (years)	SCA patients n = 300		AA controls n=300		Total N (%)
	Normal PAP n (%)	Elevated PAP n (%)	Normal PAP n (%)	Elevated PAP n (%)	
0.5 -< 1	10 (100.0)	0 (0.0)	58 (100.0)	0 (0.0)	68 (100.0)
1 - <5	104 (86.0)	17 (14.0)	112 (99.1)	1 (0.9)	234 (100.0)
5 - <10	68 (79.1)	18 (20.9)	43 (91.5)	4 (8.5)	133 (100.0)
10 – 15	46 (55.4)	37 (44.6)	73 (89.1)	9 (10.9)	165 (100.0)
Total N (%)	228 (76.0)	72 (24.0)	286 (95.3)	14 (4.7)	600 (100.0)

$\chi^2 (3) = 29.44, p < 0.001$, χ^2 value is only for the SCA patient group

Table 3. Comparison of demographic, clinical and haematological parameters of children with SCA according to PAP (N=300)

Parameter	Normal PAP TRV< 2.5 m/s, n = 228	Elevated PAP TRV \geq 2.5 m/s n = 72	P-value
Demographic			
Age(mean \pm SD) years	6.8 \pm 3.9	8.7 \pm 3.9	< 0.001
Gender (M:F ratio)	1:0.9	1:1.1	0.35
Clinical			
BMI (kg/M ²) mean \pm SD	14.4 \pm 1.9	14.6 \pm 2.9	0.14
SPO ₂ (%), mean \pm SD	98.3 \pm 1.1	95.8 \pm 1.7	< 0.001
SBP (mmHg), mean \pm SD	100.1 \pm 8.9	113.4 \pm 11.3	< 0.001
Haematological			
PCV (%), mean \pm SD	23.5 \pm 3.5	20.4 \pm 3.8	< 0.001
WBC (x10 ⁹ /L), mean \pm SD	20.4 \pm 8.4	17.5 \pm 7.7	0.01
Platelets (x10 ⁹ /L), mean \pm SD	386.7 \pm 120.7	454.8 \pm 118.1	< 0.001
Reticcount (%), mean \pm SD	9.9 \pm 3.8	11.1 \pm 3.6	< 0.001

3.2.3 Haematological predictors

SCA patients with elevated PAP had lower mean steady state PCV (20.4 \pm 3.8%, range = 18.0 - 26.0%) and lower mean leucocyte count (17.5 \pm 7.7 x 10⁹/L, range= 7.4 - 23.6 x 10⁹/L) than those with normal PAP (mean PCV= 23.5 \pm 3.5%, range = 16-31%; mean leucocyte count = 20.4 \pm 8.4 x 10⁹/L, range= 9.7- 44.8x10⁹/L) respectively. However, the mean platelet count in patients with elevated PAP (454.8 \pm 118.1 x 10⁹/L, range = 251 - 613 x 10⁹/L) was significantly higher than that in patients with normal PAP (386.7 \pm 120.7 x 10⁹/L, range = 162-744 x 10⁹/L) as shown in Table 3. Similarly, the mean reticulocyte count was higher in patients with elevated PAP (11.1 \pm 3.6%, range=4.3-17.0%) than in those with normal PAP (9.9 \pm 3.8%, range = 1.8-18.4%). The difference was statistically significant (p <0.001) (Table 3).

3.2.4 Other clinical factors

Other categorical clinical parameters evaluated in relation to elevated PAP in children with SCA

are shown in Table 4. Splenomegaly was found in 74 (24.7%) of the 300 patients with SCA. Splenomegaly was found in 23.6% of the patients with elevated PAP compared with 25.0% of the patients with normal PAP. The difference was not statistically significant ($\chi^2 = 0.07, df = 1, P = 0.81$).

A total of 181 out of 300 (60%) patients gave history of blood transfusion in the past. The proportion of children with history of previous blood transfusion was higher among SCA children with elevated PAP (76.4%) that in those with normal PAP (55.3%). The difference was statistically significant ($\chi^2 = 10.20, df = 1, p < 0.001$).

Similarly, apex beat was displaced in 69 (95.8%) patients with elevated PAP, compared with 73 (32.0%) patients with normal PAP ($\chi^2 = 89.39, df = 1, p < 0.001$). Forty-eight (66.7%) patients with elevated PAP had parasternal heave while only 14 (6.1%) patients with normal PAP had parasternal heave. The difference was statistically significant ($\chi^2 = 122.27, df = 1, p < 0.001$). Sixty-six (92%) patients with elevated

PAP had abnormal heart sounds in form of single second heart sound with loud pulmonary component, with or without additional ejection systolic murmur. Whereas, seventy (30.7%) patients with normal PAP had abnormal heart sounds and the difference was statistically significant ($X^2 = 82.07$, $df = 1$, $p < 0.001$).

3.3 Multivariate Analysis of Factors Significantly Associated with Elevated PAP

Factors found to be significantly associated with elevated PAP in children with SCA from univariate analysis were subjected to logistic regression analysis.

As shown in Table 5, older age, high SBP, presence of left parasternal heave and high reticulocyte count were associated with increased likelihood of having elevated PAP as indicated by an odd ratio value greater than 1. Hb AA electrophoretic pattern, normal pulse oxygen saturation ($SPO_2 \geq 95\%$) and normal heart sounds on auscultation were associated with a reduction in the likelihood of having elevated PAP, as indicated by an odd ratio value of less than 1. Nagelkerke's R^2 of 0.781 indicated a moderately strong relationship between elevated PAP and the covariates. Prediction success overall was 95.0% (93.1% for elevated PAP and 95.6% for normal PAP).

Table 4: Comparison of categorical clinical parameters of patients with SCA according to pulmonary artery pressure

Clinical parameters	Normal PAP n (%)	Elevated PAP n (%)	Total N (%)	X^2	p-value
Splenomegaly					
Present	57 (25.0)	17 (23.6)	74 (24.7)	0.007	0.81
Absent	171 (75.0)	55 (76.4)	226 (75.3)		
History of past blood transfusion					
Yes	126 (55.3)	55 (76.4)	181 (60.3)	10.20	<0.001
No	102 (44.7)	17 (23.6)	119 (39.7)		
Location of the apex					
Normal	155 (68.0)	3 (4.2)	158 (52.7)	89.39	<0.001
Displaced	73 (32.0)	69 (95.8)	142 (47.3)		
Left parasternal Heave					
Present	14 (6.1)	48 (66.7)	62 (20.7)	122.27	<0.001
Absent	214 (93.9)	24 (33.3)	238 (79.3)		
Heart sound					
Normal	158 (69.3)	6 (8.3)	164 (54.7)	82.07	<0.001
Abnormal	70 (30.7)	66 (91.7)	136 (45.3)		

Table 5. Logistic regression result of the predictors of elevated PAP in children with SCA

Variables	Odds ratio	(95% CI)	p value
Age	1.03	(1.01- 1.02)	<0.001
Age category	0.98	(0.95 -1.01)	0.24
HbAA	0.16	(0.09 – 0.28)	0.001
History of transfusion	0.35	(0.05 – 2.27)	0.27
Normal oxygen saturation	0.40	(0.23 – 0.69)	0.001
SBP	1.18	(1.05 – 1.32)	0.01
Displaced apex	0.21	(0.03 – 1.71)	0.15
Parasternal heave	8.43	(2.34 –30.38)	0.001
Normal heart sounds	0.15	(0.02 – 0.89)	0.04
PCV	1.14	(0.88 – 1.49)	0.32
WBC count	1.02	(0.87 – 1.18)	0.83
Platelet count	1.00	(0.99 – 1.00)	0.95
Reticulocyte count	1.33	(1.01 – 1.75)	0.04

CI, confidence interval

4. DISCUSSION

In this study, the prevalence of elevated pulmonary artery pressure (TRV \geq 2.5 m/s) was 24.0% in children with SCA, which was significantly higher than 4.7% in Hb AA controls. Like other studies, our result shows that presence of normal haemoglobin (HbAA) is associated with decrease risk of elevated pulmonary artery pressure (PAP), whereas abnormal haemoglobin (HbSS) is independently associated with pulmonary hypertension. The pathogenesis of pulmonary hypertension in children with SCA has been well described in literature [25]. Chronic hypoxia, intravascular haemolysis, pulmonary thromboembolism and left ventricular dysfunction are some of the factors thought to play an important role in its development [25].

The prevalence of elevated PAP obtained in our study is within the range of 11.1 – 46.2% reported by other prospective studies involving children with SCA in steady state [8,10-13]. It was also comparable to an earlier study in Zaria, North-western Nigeria, which found a prevalence of 25.0% among adults and children older than 10 years [9]. Though subjects in the index study were relatively younger (6.5 ± 4.1 years Vs 22 ± 8 years), both studies share similar clinical and geographic characteristics. Our prevalence (24.0%) is also comparable to the prevalence of 21.6% reported by Colombatti et al. [26], from Padova, among children with sickle cell disease (SCD). This could be due to the similarity in the characteristics of their study cohorts: The Padova study had comparatively the same age range (3- 15 years) as the index study (2.3 - 15 years); and majority of their study patients were also Africans having SCA (HbSS). But unlike Padova study, the index study has a much higher sample size and the patients were not on any treatment known to affect PAP at the time of the study. This may contribute to the slightly higher value obtained in our study.

Our prevalence was however lower than what was reported by Dahoui et al. in Lebanon (31.8%) in 2010 [27] and Onyekwere et al. [11] (46.2%) in 2008. Unlike our study in which all the subjects had HbSS, the Lebanon study comprises patients with both SCA (HbSS) and other forms of SCDs especially HbSC. Patients with HbSC have been shown to have higher prevalence of elevated PAP compared to those with HbSS, probably due to other non-haemolytic processes [9,28]. Though patients in the

Lebanon study were said to be in steady state, majority presented with moderate to severe disease at the time of the study; this could have effect on the result since tricuspid regurgitant velocity (TRV) is known to increase during acute illness in patients with SCD [29]. In the same vein, the higher prevalence of elevated PAP obtained by Onyekwere et al. [11], could be due to the fact that their patients were relatively older, with up to 37.0% (14 of 38) not in steady state and were enrolled in to the study shortly after recovery from vaso-occlusive event, obstructive sleep apnoea, asthma or reactive airway disease, which are all known to increase TRV.s.

Elevated TRV, though a marker of elevated PAP, is not always diagnostic of PH. This was evident in the present study where significant difference was observed between the prevalence of elevated PAP (24.0%) defined by TRV \geq 2.5 m/s; and the prevalence of PH (3.0%) defined by MPAP \geq 25 mmHg. A similar observation was also made by a previous study among adults with SCA [30], where the prevalence of elevated PAP using TRV was 40.0% but only 10.0% were found to have PH after right heart catheterization (RHC). Another study [31] also observed a prevalence of elevated PAP (using TRV) of 27.0%, but only 6% of the subjects actually had PH following RHC. As highlighted by Caughey et al. [32], the limited positive predictive value of TRV could be due to inaccuracy in doppler measurement compared to invasive measurement technique; the unreliability of using a fixed TRV cut-off value (>2.5) for all patients, and the fact that TRV only estimate PASP rather than mean pulmonary arterial pressure [32].

The PH prevalence of 3.0% in children with SCA reported in this study is lower than what was reported by other studies [30,31,33]. Parent et al. [31] reported 6% while Fonseca et al. [30] and Castro et al. [33], reported prevalence rates of 10% and up to 58.8% respectively. The higher prevalence obtained from these studies may be due to the fact that they were carried out in adult subjects and the mean pulmonary artery pressure (MPAP) was estimated from right heart catheterization (RHC). This is in contrast to our study that was conducted in children, and in which the MPAP was estimated by echocardiography using mean gradient (MG) method, which is less sensitive than RHC. In addition, some of the subjects in the aforementioned studies were not in steady state, as they had symptomatic anaemia and had undergone blood transfusion [33], which may

overestimate the prevalence of PH). There may also be selection bias as the indication for cardiac catheterisation in most cases was the suspicion of pulmonary hypertension [33].

Like other studies (ref), our study has shown that older age, high systolic blood pressure (SBP), left parasternal heave, abnormal heart sounds (loud P2), abnormal pulse oxygen saturation ($SPO_2 \geq 95\%$) and high reticulocyte count were independent predictors of PH in children with SCA. This finding underscores the need for high index of suspicion of PH whenever any of these factors is detected. The positive association between age and elevated PAP is due to the age associated increase in pulmonary artery pressure, as reported by Carolyn et al. [34]. It is of note that none of our patients less than 1 year of age had elevated PAP, and the youngest child with elevated PAP was 2.3 years old. Further multi centre studies are needed to establish and possibly recommend the ideal cut-off age to start screening for PH in children with SCA.

The finding that high SBP was associated with elevated PAP in this study is consistent with similar findings from previous studies [14,16,22]. This could be explained by the fact that, part of the pathogenesis of PH in SCA is the progressive vasculopathy with increased vascular resistance [29], perhaps this process is not restricted to pulmonary vessels alone leading to increased systemic vascular resistance. Another clinical parameter that was found to be associated with elevated PAP in this study was left parasternal heave. The association between left parasternal heave and elevated PAP is not surprising as left parasternal heave is a marker of right ventricular hypertrophy [19] which could be as a result of high pulmonary artery pressure. Similarly, abnormal heart sounds on auscultation in form of loud pulmonary component of the second sound, single second sound and presence of an ejection systolic murmur are known to be associated with pulmonary hypertension irrespective of the cause [19]. Previous studies have demonstrated the relationship between hypoxia and pulmonary hypertension [13,35]. This was further buttressed by this study where all the eleven patients with $SPO_2 < 95\%$ were found to have elevated PAP. The mechanism of hypoxia in SCA may result from the degree of anaemia, or vaso-occlusive process in the lungs. Hypoxia is known to precipitate sickling process and haemolysis, leading to increased release of free haemoglobin and reduced NO bioavailability in patients with

SCA [35,36], which is a known pathogenic process in the development of PH. In addition, hypoxia is a potent stimulator of pulmonary vasoconstriction [37] and is therefore an important predictor of elevated PAP in children with SCA.

High reticulocyte count is a marker of haemolysis, during which free haemoglobin and intra-erythrocyte enzyme arginase are released. Free haemoglobin consumes NO which is an intrinsic vasodilator leading to state of reduced NO bioavailability. Arginase also through the conversion of arginine, a substrate for NO synthesis to ornithine further worsens the deficiency of NO. These two processes cause abnormal regulation of vascular smooth muscle relaxation and vasomotor tone, leading to PH [38,39,6]. Unlike reticulocyte count, other haematological parameters such as PCV, WBC count and platelets count were not significantly associated with elevated PAP. This is in contrast to the finding in a study by Pashankar et al. [40], where it was reported that high platelet count was significantly associated with elevated PAP.

5. CONCLUSION

Elevated PAP and pulmonary hypertension are relatively common findings in children with SCA. Older age, high systolic blood pressure (SBP), left parasternal heave, abnormal heart sounds (loud P2), abnormal pulse oxygen saturation ($SPO_2 < 95\%$) and high reticulocyte count are independent predictors of PH. It is therefore recommended that SCA children presenting with any of these findings should be further evaluated for PH, to enable early diagnosis and timely management.

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CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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