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Prevalence and risk factors for pulmonary artery systolic hypertension among sickle cell disease patients in Nigeria

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Abstract

Pulmonary artery systolic hypertension is common and associated with increased mortality among adult sickle cell disease (SCD) patients in the United States. While the prevalence of SCD is highest in sub-Saharan Africa, the frequency of pulmonary artery systolic hypertension and the risk factors for the development of pulmonary hypertension have not been reported from Africa. We studied 208 hydroxyurea naïve Nigerian SCD patients at steady state and 94 healthy controls. Pulmonary artery systolic hypertension was defined prospectively as tricuspid regurgitant jet velocity ≥ 2.5 meters per second. Results were compared with a previously published US prospective SCD cohort. Only 7% of Nigerians compared to 46% of US adults with SCD were ≥ 35 years. Tricuspid regurgitant jet velocity was ≥ 2.5 m/second in 25% of Nigerian SCD patients. Higher jet velocity was associated with greater serum globulin ($P=0.002$), blood urea nitrogen ($P=0.019$) and lactate dehydrogenase concentrations ($P=0.026$) and with inability to walk ≥ 300 meters in six minutes ($P=0.042$). Compared to the US cohort, Nigerian patients had more hemolysis as indicated by lower hemoglobin and higher lactate dehydrogenase concentrations ($P=0.003$). Pulmonary hypertension is common among Nigerian SCD patients. The public health implication of this finding is significant considering the potential number of individuals at risk for this complication. Better understanding of the long term outcome of pulmonary hypertension and causes of death in SCD and the institution of preventive measures are major public health challenges for Africa. The inclusion of African sites in sickle cell pulmonary hypertension clinical trials should be encouraged.

Keywords

Pulmonary hypertension; sickle cell disease; Nigeria

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Authorship

Z.Y.A provided initial study concept and study design. Z.Y.A, A.B, A.M, P.A, E.A, Y.S, N.A, J.Y and L.M contributed to recruitment, clinical assessment of patients and laboratory analysis of specimens for the study. Z.Y.A, V.S performed the echocardiography component of the study. Z.Y.A, V.G, performed data analysis. Z.Y.A, V.G, V.S, A.B, A.M, GK, and MTG contributed to the study design, data analysis, and preparation of the manuscript.

Introduction

The burden of sickle cell disease is highest in sub Saharan Africa, especially in the West African country of Nigeria where more than 150,000 children are born with the disease annually and approximately 4 million people are afflicted with the condition [1–3]. Survival has increased in sickle cell disease patients in the United States and perhaps globally [4], leading to increasing identification of chronic end organ complications associated with advancing age, including pulmonary hypertension. Pulmonary hypertension occurs in about 30% of adult patients with sickle cell disease in the United States and is associated with increased mortality [5,6]. Chronic hemolysis, renal insufficiency, increasing age, relative systemic hypertension and iron overload have been implicated in the pathogenesis of sickle cell disease-associated pulmonary hypertension [5–8].

While the prevalence of SCD is highest in sub-Saharan Africa, the frequency of high tricuspid regurgitant jet velocity and the risk factors for the development of pulmonary hypertension have not been reported from Africa. The analysis of the risk of developing pulmonary hypertension is of particular interest in this population, because the use of hydroxyurea, a history of blood transfusion and the presence of iron overload is extremely limited, allowing for a unique assessment of the natural history of progression of vasculopathy in young adults with sickle cell disease. Infections endemic to Africa (HIV, hepatitis B and C, possibly malaria) are risk factors for pulmonary hypertension; these infections combined with sickle cell disease-related vasculopathy could influence the prevalence and outcome of this complication [2,7,9].

Results

Clinical characteristics of patients and controls

208 consecutive sickle cell disease patients at steady state and 94 healthy non-matched controls were studied in Nigeria (Table 1). The age range of the patients was 10–52 years. 198 patients were hemoglobin S homozygotes and 10 were compound heterozygotes for hemoglobins S and C. Ninety percent of patients reported less than five units of whole blood transfused lifetime. Technically adequate echocardiography results for 178 sickle cell disease patients and 85 controls were available for evaluation. The patients with sickle cell disease were younger and more commonly of the female gender than the controls. Echocardiography was conducted on healthy Nigerian controls to determine the background distribution of tricuspid jet velocity.

Prevalence of elevated tricuspid regurgitant jet velocities

Tricuspid regurgitant jet velocity determination is robust in sickle cell patients owing to their thin body habitus, lack of emphysematous lung disease and the hyperdynamic cardiac output, all of which result in an excellent Doppler image. The correlation between echo-Doppler assessments of estimated pulmonary artery systolic pressures and measurements at right heart catheterization at the NIH are currently extremely robust ($R=0.9$; $P<0.001$; unpublished update of catheterization data) [5]. Right heart catheterization validation was not done in the Nigerian cohort as this technique was not available or feasible in the Nigerian setting at the present time. Additionally, subjecting Nigerian patients to such an invasive procedure for purely screening purposes was not justifiable from an international ethics standard. Patients with sickle cell disease had significantly higher mean $\pm$ SD values for tricuspid regurgitant jet velocity than did the controls (2.1 ± 0.6 vs. 1.8 ± 0.5 ; $p<0.001$) (Fig. 1 and Table 1.) Twenty five percent of patients with sickle cell disease had elevated systolic pulmonary artery pressure as defined by jet velocity ≥ 2.5 m/second (estimated systolic pulmonary artery pressure ≥ 30 mm Hg) compared to 7% of controls ($P<0.001$).

Four percent had jet velocities ≥ 3.0 m/second (estimated systolic pulmonary artery pressure ≥ 41 mm Hg) compared to 0% of controls.

Correlates of elevated tricuspid regurgitant jet velocity among patients with sickle cell disease

There was no difference in the prevalence of jet velocity ≥ 2.5 m/second between the homozygous hemoglobin SS group (25.0%) and the compound heterozygote hemoglobin SC group (30.0%) ($P=0.72$). Results of clinical and echocardiogram variables were compared according to tricuspid regurgitant jet velocities of <2.5 m/sec, 2.5–2.9 m/sec and ≥ 3.0 m/sec (detailed data are available upon request). Blood urea nitrogen differed significantly according to progressively higher categories. By linear regression, bivariate associations with tricuspid regurgitant jet velocity were noted for hemoglobin ($R=-0.23$; $P=0.002$) and natural log transformed serum levels of lactate dehydrogenase ($R=0.19$; $P=0.014$), blood urea nitrogen ($R=0.15$; $P=0.057$) and serum globulin (measured total serum protein minus measured serum albumin; this include alpha, beta and gamma globulins) ($R=0.22$; $P=0.004$). Gender, fetal hemoglobin level, white-cell count, and platelet count, reticulocyte count, total bilirubin, and N-terminal pro-brain natriuretic protein were not significantly associated with tricuspid regurgitant jet velocity at the 0.05 level. In a multiple linear regression model, age had a negative association with tricuspid regurgitant jet velocity ($P=0.062$) while log transformed serum concentrations of globulin ($P=0.002$), blood urea nitrogen ($P=0.019$) and lactate dehydrogenase ($P=0.026$) had positive associations. In contrast to the US cohort [5], N-terminal pro-brain natriuretic peptide was not significantly associated with jet velocity, suggesting that in the younger Nigerian cohort the high estimated pulmonary artery systolic pressures had not compromised resting biventricular function.

In a logistic regression analysis of tricuspid regurgitant jet velocity dichotomized as values <2.5 m/sec versus ≥ 2.5 m/sec, blood urea nitrogen had significant positive association with jet velocity while age had a negative association. A natural log increase in blood urea nitrogen concentration was associated with a 3.2-fold increase in the odds of jet velocity ≥ 2.5 m/sec (95% confidence interval: 1.2–8.4; $P=0.022$) and an increase in age of 10 years was associated with a 1.5-fold decrease in the odds (0.9–2.5; $P=0.13$).

Ventricular size and function

Compared to controls, sickle cell disease patients had significantly higher values of left ventricular cardiac-chamber size (Table 1); there was no qualitative evidence of left ventricular systolic dysfunction (ejection fraction ≥ 0.5). In fact, the patients had significant higher values of ejection fraction and E/A ratio. Within the sickle cell group, there was no clear pattern of worsening diastolic function with increased TRV. Furthermore, the E to A ratio had a significant positive relationship with jet velocity in bivariate analysis ($R=0.20$; $P=0.013$). Over all, this would indicate that the prevalence of pulmonary hypertension in Nigerian patients is independent of concomitant left ventricular systolic or diastolic dysfunction.

Infections and tricuspid regurgitant jet velocity

The prevalence of HIV, hepatitis B or hepatitis C seropositivity among both patients with sickle cell disease and controls (Table 1) was lower than expected based on the national HIV seropositivity rate and the Ahmadu Bello University Teaching Hospital hepatitis and HIV surveillance data among blood donors. The prevalence of malarial parasitemia was 4% among patients and 3% among controls ($P=0.8$); that the study was conducted during the dry season and that most patients were on malarial prophylaxis may help explain this low prevalence. There were no trends for increasing seroprevalence of HIV, hepatitis B or hepatitis C according to increasing jet velocity categories but malarial parasitemia increased

progressively from 3% in the patients with jet velocity <2.5 m/sec to 14% in those with jet velocity ≥ 3.0 m/sec ($P=0.15$). The significant positive association of serum globulin concentration with jet velocity in both bivariate and multivariate analyses ($P=0.004$) is consistent with the possibility that infections are a risk factor for pulmonary hypertension in Nigeria.

Tricuspid regurgitant jet velocity and six minute walk test

The average distance walked in six minutes did not differ significantly according to the increasing jet velocity categories (<2.5 m/sec, $2.5\text{--}2.9$ m/sec and ≥ 3.0 m/sec; mean $\pm$ SE values of 387 ± 7 , 380 ± 13 , 370 ± 29 ; $P=0.79$). However, proportions of patients who walked <300 meters increased significantly according to these categories, from 9% to 29% ($P=0.042$ for trend; Figure 2), suggesting a functional effect of rising tricuspid regurgitant jet velocity.

Comparison of Nigerian and US cohorts

The present Nigerian study included consecutive sickle cell disease patients ≥ 10 years whereas our previous US study [5] included consecutive patients ≥ 18 years. Even considering only those patients ≥ 18 years, there is a marked difference in the age distributions between the two cohorts. The peak age range was 18–24 years in the Nigerian cohort compared to >35 years in the US cohort. Only 7% of the adults in the Nigerian cohort were >35 years of age compared to 46% in the US cohort. Jet velocity declined with increasing age in the Nigerian cohort ($R=-0.15$; $P=0.053$) but increased with increasing age in the US cohort ($R=0.18$; $P=0.012$) (Figure 3). Comparison of Nigerian and US sickle cell patients of similar age groups in both studies is provided in Table 2. Sickle cell disease patients from Nigeria had markedly lower body mass index. They displayed a constellation of lower hemoglobin concentrations and higher lactate dehydrogenase concentrations suggesting a more hemolytic phenotype. They had lower blood urea nitrogen and alanine aminotransferase concentrations suggesting better renal and liver function, and lower transferrin saturations in the face of equivalent serum ferritin concentrations suggesting a greater degree of inflammation. Tricuspid regurgitant jet velocities did not differ significantly, but the left ventricular ejection fraction was significantly greater in the Nigerian cohort. Seven percent (6 out of 85) controls in Nigeria and 4.8% (2 out of 41) controls had tricuspid regurgitant jet velocity ≥ 2.5 m/sec. The difference in this proportion was not statistically significant ($p=0.7$).

Discussion

We found the prevalence of elevated systolic pulmonary artery pressure, as estimated by tricuspid regurgitant jet velocity ≥ 2.5 m/sec, to be 25% among hydroxyurea-naïve and minimally transfused adolescents and adults with sickle cell disease in an exclusively Nigerian population. The prevalence of jet velocity ≥ 3.0 was 4%. This high prevalence of pulmonary hypertension observed among sickle cell disease patients in Nigeria is similar to our previous report and that of others that suggest pulmonary hypertension is common among adults with sickle cell disease [5,6,10]. Pulmonary hypertension has also been reported in non sickle cell hemolytic disorders [11–13]. Adult sickle cell disease patients with elevated systolic pulmonary artery pressure have high mortality rates despite having much lower values for jet velocity and mean pulmonary artery pressure than patients with idiopathic and primary pulmonary hypertension [5,6]. The present report suggests that pulmonary hypertension may be of major importance among patients with sickle cell disease in Africa.

Data from this Nigerian cohort reveal significant bivariate associations of markers of red cell destruction (higher serum level of lactate dehydrogenase and lower hemoglobin

concentration) as well as higher blood urea nitrogen concentration with higher tricuspid regurgitant jet velocity. Additionally, by multivariate linear regression, lactate dehydrogenase and blood urea nitrogen had independent positive associations with jet velocity. These results support the recent hypothesis that the development of pulmonary, and likely systemic, vasculopathy in sickle cell disease is related to the extent of hemolytic anemia and not vaso-occlusive events or the acute chest syndrome [5,7,14–16].

Our Nigerian cohort included patients <10 years whereas our United States cohort included patients ≥18 years. The prevalence of elevated jet velocity was the same or higher in patients <18 years of age as those 18 years and older (Figure 3), suggesting that pulmonary hypertension occurs in both children and adults with sickle cell disease. Comparison of participants of the same age ranges indicates a markedly more hemolytic phenotype in the Nigerians (lower hemoglobin concentration and higher lactate dehydrogenase). Furthermore, jet velocities tended to decrease with age in the Nigerian patients and increase with age in the US patients (Figure 3). A striking finding of this study is that only 7% of adult sickle cell disease patients in Nigeria were over 35 years of age compared to 46% in our US cohort [5]. The few number of Nigerian sickle cell disease subjects above thirty-five years of age may be an important indirect measure of markedly reduced life expectancy compared to US patients. The possible contribution of pulmonary hypertension to mortality in the African setting is yet to be elucidated.

The Nigerian cohort in our study had low prevalences of HIV, hepatitis B, hepatitis C and malaria. Whether these infections do not play an important role in accentuating the risk of pulmonary hypertension versus whether they might result in increased mortality of pulmonary hypertension in sickle cell disease and thus lead to a decreased prevalence is not clear [2, 17–20]. The observed positive association of serum globulin concentration with jet velocity is consistent with a chronic infectious/inflammatory component to the elevated estimated systolic pulmonary artery pressures. Furthermore, the lower transferrin saturations in the Nigerian patients compared to American patients in the setting of equivalent ferritin concentrations is consistent with a more inflammatory phenotype. The relatively low observed incidence of infectious diseases in the Nigerian cohort may also reflect that i) patients with sickle cell disease are less likely to have multiple sexual partners, ii) the Nigerian cohort has relatively sparse transfusion history, iii) the patients are on routine malarial prophylaxis and iv) they have been receiving care mostly at a University hospital that adheres to proper blood transfusion practices. An interesting but not statistically significant observation in our study is the fact that malarial parasitemia increased progressively from 3% in the patients with jet velocity <2.5 m/sec to 14% in those with jet velocity ≥3.0 m/sec ($P=0.15$). Hemolysis associated with malaria produces a similar state of endothelial dysfunction secondary to NO scavenging by cell free hemoglobin and plasma arginase as that seen in sickle cell disease [7,9]. The interaction of malarial and SCD hemolysis in pulmonary hypertension is of potential interest.

Nigerian patients appear to have a high prevalence of pulmonary hypertension independent of left ventricular systolic or diastolic dysfunction in the setting of a striking hemolytic phenotype. Our study is limited by the indirect assessment of pulmonary artery systolic pressure rather than the “gold standard” right heart catheterization. Our sample size relative to the large sickle cell population in Nigeria is small. Additionally, accurate data on the causes of death among sickle cell disease patients in Zaria, Nigeria was not available and thus not included in our analysis to determine the possible contributions of cardiopulmonary diseases to mortality among sickle cell disease patients in Nigeria. Our study did not prospectively follow patients to determine the mortality effects of elevated pulmonary artery systolic pressures. However, our study represents the first and largest study of pulmonary hypertension among sickle cell disease patients in Africa. The public health implication of

our finding is significant considering the potential number of individuals at risk for this complication. More studies are needed to characterize the prevalence and long term outcome of sickle cell disease related increased pulmonary systolic artery pressure and interaction with other potential endemic causes of pulmonary hypertension in Africa. Additionally, the inclusion of African sites in sickle cell pulmonary hypertension clinical trials should be encouraged.

Methods

The study was approved by the National Heart Lung Blood Institute Institutional Review Board and the Ethical and Scientific Committee of Ahmadu Bello University, Zaria, Nigeria, and was designed to comply with the Fair Benefit Framework for international research [21]. The research subjects were Nigerians 10 years of both genders who volunteered and provided written informed consent. For children <18 years, a legally authorized representative provided written informed consent and assent of the child was also required. Additionally, based on local norms, individuals <18 years were included in the study without a legally authorized guardian if they were married, had children and/or established that they were living independently. Patients were recruited from the community but regional referrals were also accepted. Patients with sickle cell disease were required to have electrophoretic and or high-pressure liquid chromatography documentation of SS, SC, S β 0 or S β + thalassemia or other genotype. The control group was required to have electrophoretic documentation of hemoglobin A or AS genotype. Exclusion criteria included subjects unable to understand the investigational nature of the study or to give informed consent. Subjects underwent complete history and physical examination, six minute walk test to determine functional capacity, Doppler echocardiogram and laboratory testing.

Echocardiography

Cardiac measurements were performed with 2D transthoracic echocardiogram according to the guidelines of the American Society of Echocardiography [22]. Tricuspid regurgitation was assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical four-chamber views to determine the highest velocity. Continuous-wave Doppler sampling of the peak tricuspid regurgitant jet velocity is used to estimate the right-ventricular-to-right-atrial systolic pressure gradient with the modified Bernoulli equation ($\text{gradient} = 4 \times \text{jet velocity squared}$). The systolic pulmonary artery pressure is calculated as the sum of the pressure gradient and the estimated right atrial pressure [23]. Peak velocities of the E wave and A wave, the ratio of the E wave to the A wave, and the deceleration time were measured in a standard manner [22, 23]. Special emphasis was placed on these measurements to determine coexisting left ventricular diastolic dysfunction, a potential cause of pulmonary hypertension and an independent risk factor for death in patients with sickle cell disease [24]. Elevated systolic pulmonary artery pressure was defined prospectively as tricuspid regurgitant jet velocity ≥ 2.5 m/second [5]. Echocardiography studies were performed in Nigeria by a single investigator (ZYA) using the GE *Vivid i* Echo Color Ultrasound System® and read in a blinded manner at the Clinical Center, National Institutes of Health, Bethesda, MD by a single investigator (VS).

Laboratory tests

Analyses performed in Nigeria were complete blood count, reticulocyte count; hemoglobin electrophoresis and thick malaria smear. Analyses performed at the NIH, USA included assays for ferritin, complete metabolic profile, N-terminal-brain natriuretic peptide, fetal hemoglobin level and serology testing for hepatitis B, hepatitis C and HIV.

Comparison with the United States National Institutes of Health-Howard University Sickle Cell Disease Cohort

Results from the present cohort of Nigerian patients with sickle cell disease studied in 2006 were compared to results from the US NIH-Howard University cohort of patients with sickle cell disease studied in 2001–2003 and previously published [5]. Echocardiography data was obtained in both cohorts utilizing a uniform protocol. Interpretation of echocardiography results was conducted by the same cardiologist (VS). Clinical chemistry laboratory tests for both cohorts were performed at the laboratory of the Clinical Center, NIH.

Statistical methods

Sickle cell disease patients and controls were compared using the Kruskal-Wallis test for continuous variables and the chi square test or Fisher exact test for categorical variables. In sickle cell patients, associations of demographic, physical examination and laboratory variables with tricuspid regurgitant jet velocity as a continuous variable were assessed using Pearson correlation. Linear regression models were used to assess associations of sets of covariates with tricuspid regurgitant jet velocity. Stepwise logistic regression models were used to assess the associations of sets of variable with jet velocity dichotomized a priori as <2.5 m/sec or ≥ 2.5 m/sec. When echocardiography was done but tricuspid regurgitant jet velocity could not be determined or was non detectable, tricuspid regurgitant jet velocity was set at 1.0 m/s (5). Our prevalence estimates therefore assumed that non-detectable tricuspid regurgitant jet velocity was normal. The lowest tricuspid regurgitant jet velocity actually recorded was 1.5 m/s. Results for the Nigerian and US cohorts were compared with analysis of variance with adjustment for age category. An arbitrary level of 5% statistical significance is assumed to be significant. Statistical analysis was done using Systat software version 11 (San Jose, CA).

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Figure 1.
Box plots depicting median and interquartile ranges of tricuspid regurgitant jet velocity (TRV) values in controls and patients with sickle cell disease.

Figure 2. Functional consequence of elevated tricuspid regurgitant velocity in patients with sickle cell disease. Increasing proportions of patients are unable to walk more than 300 minutes in six minutes according to three categories of increasing jet velocity.

Figure 3.

Comparison of age distributions and tricuspid regurgitant jet velocities between the present Nigerian cohort and the previously published (5) NIH-Howard University US cohort of sickle cell disease patients. Proportions with jet velocities ≥ 2.5 m/sec according to age categories shown in a. Jet velocity declined with increasing age in the Nigerian cohort ($R = -0.15$; $P = 0.053$) but increased with increasing age in the US cohort ($R = 0.18$; $P = 0.012$) (Figure 3b).

Table 1

Baseline clinical and laboratory features of sickle cell patients and controls*

Variable	Sickle Cell		Control		p**
	n		n		
Age in years	208	22 ± 8	94	33 ± 12	<0.001
Female sex	208	106 (51.0%)	93	29 (31.2%)	0.001
TRV in m/sec	178	2.1 ± 0.6	85	1.8 ± 0.5	<0.001
Right atrial area in cm ²	82	15.7 ± 3.4	37	13.9 ± 2.8	0.003
RV outflow track peak velocity (m/sec)	114	1.0 ± 0.2	59	0.9 ± 0.2	0.001
LV ejection fraction	176	65 ± 2	85	64 ± 3	0.040
LV diastolic diameter in cm	176	4.9 ± 0.5	83	4.6 ± 0.4	<0.001
LV systolic diameter in cm	164	3.0 ± 0.5	74	2.7 ± 0.4	<0.001
Left atrial area in cm ²	80	18.3 ± 4.3	35	15.6 ± 4.4	<0.0001
E wave to A wave ratio	156	1.7 ± 0.4	78	1.6 ± 0.4	0.010
Deceleration time in millisecond	161	149 ± 27	78	148 ± 29	0.92
Hemoglobin in g/dL	204	8.5 ± 1.5	94	13.8 ± 1.7	<0.001
Reticulocyte count in %	128	11.1 ± 6.3	93	1.7 ± 1.1	<0.001
White blood cells in no × 10 ⁻³ /ul	204	13.2 ± 9.3	94	7.5 ± 9.5	<0.001
Serum globulin in g/dL	192	3.5 ± 0.7	78	3.1 ± 0.4	<0.001
Lactate dehydrogenase in U/L	196	441 ± 171	78	185 ± 57	<0.001
Aspartate aminotransferase	196	43 ± 18	78	30 ± 31	0.002
Alanine aminotransferase in U/L	196	19.1 ± 9.8	78	21.6 ± 20.5	0.31
Alkaline phosphatase in U/L	196	114 ± 68	78	87 ± 80	0.009
Creatinine in mg/dL	196	0.6 ± 0.2	78	0.9 ± 0.2	<0.001
Blood urea nitrogen in mg/dL	196	5.7 ± 2.4	78	8.4 ± 2.8	<0.001
Total bilirubin in mg/dL	196	2.6 ± 1.6	78	1.1 ± 2.6	<0.001
Direct bilirubin in mg/dL	196	0.4 ± 0.2	78	0.3 ± 1.0	0.20
Indirect bilirubin in mg/dL	196	2.2 ± 1.5	78	0.8 ± 1.6	<0.001
Ferritin	193	372 ± 373	77	139 ± 162	<0.001
NT-proBNP	196	132 ± 152	68	50 ± 76	<0.001
HIV positive	204	8 (3.9%)	94	0 (0.0%)	0.060

Variable	Sickle Cell		Control		p**
	n		n		
Hepatitis B surface antigen positive	204	4 (2.0%)	94	2 (2.1%)	1.00
Hepatitis C positive	204	8 (3.9%)	94	4 (4.3%)	1.00
Malaria smear positive	204	9 (4.4%)	94	3 (3.2%)	0.76

* Results given as mean $\pm$ standard deviation or number and percentage.

Table 2
Comparison of Nigerian and US sickle cell cohorts of similar age. Results in mean $\pm$ SD unless otherwise indicated.

	10–17 years		18–24 years		25–35 years		P*
	Nigeria (N = 63)	USA (N = 60)	Nigeria (N = 86)	USA (N = 25)	Nigeria (n = 46)	USA (N = 81)	
Female sex	44%	---	48%	56%	46%	57%	0.2
BMI	17.1 $\pm$ 4.2	---	18.3 $\pm$ 2.5	24.5 $\pm$ 7.8	19.6 $\pm$ 2.3	24.6 $\pm$ 7.8	<0.001
Systolic blood pressure	109 $\pm$ 13	---	116 $\pm$ 12	122 $\pm$ 10	119 $\pm$ 17	119 $\pm$ 16	0.4
Hemoglobin SS	94%	---	98%	84%	93%	79%	0.001
Hemoglobin	8.3 $\pm$ 1.1	---	8.5 $\pm$ 1.6	9.8 $\pm$ 1.8	8.8 $\pm$ 1.9	9.6 $\pm$ 1.7	<0.001
WBC	12.7 $\pm$ 3.9	---	12.3 $\pm$ 4.1	11.8 $\pm$ 4.7	11.5 $\pm$ 4.0	10.8 $\pm$ 3.5	0.2
Platelets	452 $\pm$ 123	---	474 $\pm$ 172	385 $\pm$ 125	428 $\pm$ 152	373 $\pm$ 141	0.002
Lactate dehydrogenase (U/L)	468 $\pm$ 147	---	459 $\pm$ 191	342 $\pm$ 105	391 $\pm$ 149	343 $\pm$ 148	0.003
Bilirubin	2.2 $\pm$ 1.2	---	3.0 $\pm$ 1.7	2.6 $\pm$ 1.0	2.6 $\pm$ 1.7	2.9 $\pm$ 1.9	0.9
ALT	19 $\pm$ 7	---	21 $\pm$ 13	28 $\pm$ 18	17 $\pm$ 6	28 $\pm$ 17	<0.001
Alkaline phosphatase	156 $\pm$ 56	---	104 $\pm$ 79	110 $\pm$ 61	85 $\pm$ 38	101 $\pm$ 54	0.2
BUN	5 $\pm$ 2	---	6 $\pm$ 3	7 $\pm$ 3	6 $\pm$ 2	8 $\pm$ 5	0.002
Creatinine	0.5 $\pm$ 0.1	---	0.6 $\pm$ 0.2	0.6 $\pm$ 0.1	0.6 $\pm$ 0.2	0.7 $\pm$ 0.9	0.7
Globulin	3.3 $\pm$ 0.5	---	3.5 $\pm$ 0.8	3.4 $\pm$ 0.6	3.6 $\pm$ 0.6	3.4 $\pm$ 0.5	0.1
Ferritin	193 (74–507)	---	228 (80–652)	303 (65–1408)	268 (89–808)	249 (57–1080)	0.7
Transferrin saturation (%)	26 $\pm$ 11	---	33 $\pm$ 18	40 $\pm$ 16	31 $\pm$ 16	38 $\pm$ 26	0.020
TRV (m/sec)	2.3 $\pm$ 0.3	---	2.1 $\pm$ 0.6	2.2 $\pm$ 0.5	2.0 $\pm$ 0.7	2.0 $\pm$ 0.6	0.5
Right atrial area	13.2 $\pm$ 2.4	---	16.6 $\pm$ 3.7	16.8 $\pm$ 2.9	16.8 $\pm$ 2.6	18.2 $\pm$ 4.5	0.2
LV diastolic diameter	4.6 $\pm$ 0.4	---	5.1 $\pm$ 0.5	5.1 $\pm$ 0.4	5.2 $\pm$ 0.5	5.1 $\pm$ 0.5	0.9
LV systolic diameter	2.8 $\pm$ 0.5	---	3.1 $\pm$ 0.5	3.2 $\pm$ 0.4	3.1 $\pm$ 0.5	3.3 $\pm$ 0.6	0.1
Deceleration time	144 $\pm$ 28	---	149 $\pm$ 25	201 $\pm$ 29	155 $\pm$ 29	209 $\pm$ 35	<0.001
Ejection fraction	64 $\pm$ 2	---	64 $\pm$ 3	64 $\pm$ 6	65 $\pm$ 1	62 $\pm$ 6	0.001

* Comparison of patients from Nigeria and patients from US as stratified by age.