Comparison of Patients from Nigeria and U.S.A. Highlights Modifiable Risk Factors for Sickle Cell Complications

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Abstract

To identify factors that affect manifestations of sickle cell anemia (SCA), we compared patients 11-30 years of age from University of Ibadan, Nigeria (n=214) and University of Illinois at Chicago, U.S.A. (n=209). Paralleling findings in the general populations of the two countries, Chicago patients were more often overweight or obese defined by CDC Guidelines (Age<18: 6% vs. 3%, P=0.02; Age≥18: 25% vs. 3%, P<0.0001) and more often had elevated blood pressure defined by NHLBI Guidelines (Age<18: 16% vs. 3%, P=0.02; Age≥18: 47% vs. 17%, P<0.0001). Ibadan patients less often had received pneumococcal vaccination (Age<18: 0% vs. 88%, P<0.0001; Age≥18: 1% vs. 91%, P<0.0001) or hydroxyurea therapy (Age<18: 7% vs. 44%, P<0.0001; Age≥18: 3% vs. 46%, P<0.0001). Consistent with lower rates of elevated blood pressure and increased body mass index (BMI), stroke history was less frequent in Ibadan patients ≥ 18 years old (2% vs. 24%, P<0.0001). Furthermore, in combined analyses, systolic and diastolic blood pressure directly correlated with BMI, and elevated weight status independently associated with history of stroke (OR 2.7, P=0.019). In conclusion, our findings are consistent with the possibility that higher values for BMI and blood pressure in Chicago SCA patients may contribute to an increased risk of stroke and highlights the need for measures to reduce these risk factors. On the other hand, in Ibadan patients, lower pneumococcal vaccination and hydroxyurea therapy rates highlight the need for more improved vaccination coverage and for studies to define the role of hydroxyurea therapy in Africa.
Introduction

Sickle cell anemia (SCA) is among the most common monogenetic diseases worldwide. It is caused by a single base pair mutation resulting in an amino acid substitution in the β-globin chain and results in a structurally abnormal hemoglobin molecule, hemoglobin S. Heterozygous carriers of hemoglobin S have protection from malaria mortality and carrier rates for hemoglobin S range from 5 to 40% in malaria endemic regions (1). Sickle cell anemia is a consequence of homozygosity for the hemoglobin S gene and results in polymerization of deoxygenated hemoglobin in red blood cells. Approximately 20-25 million people have SCA world-wide with 12-15 million living in sub-Saharan Africa (http://www.who.int/genomics/public/Maphaemoglobin.pdf). Migration patterns have led to the distribution of the sickle cell gene to non-endemic regions for malaria and the estimated prevalence of SCA in the United States of America (U.S.A.) is approximately 100,000 (2).

Polymerization of hemoglobin in the red blood cells (RBC) of patients with SCA leads to vaso-occlusion and hemolysis and causes both acute and chronic complications. The disease severity varies markedly among patients with SCA. Genetic factors, notably alpha thalassemia and loci that regulate hemoglobin F (Hb F) expression contribute to this variation, and the pharmacologic agent, hydroxyurea can have a substantial effect through increasing Hb F levels but much of the variation is still unexplained (3-7). Elevated blood pressure is another modifier of clinical severity in SCA, being associated with stroke, renal dysfunction, pulmonary hypertension and early mortality (8-10). Increased BMI, which may be a consequence of differences in life-style factors such as dietary habit or activity level as well as other genetic modifiers, is associated with higher blood pressure in patients with SCA (8, 11-13).
General population comparisons between Nigerians and African Americans have shown that Nigerians have shorter height, lower BMI, lower systolic blood pressure, and lower prevalence of hypertension (14). Furthermore, the rate of full childhood vaccination coverage is lower in the general population of Nigerians versus African Americans (15, 16). It is likely that these trends also occur among patients with SCA. In this study, we compared differences in anthropometric, clinical, and hematologic variables between two cohorts of patients with SCA from the University of Ibadan, Nigeria and University of Illinois at Chicago, U.S.A in light of background population differences. The objective of this study was to identify adverse outcome-influencing variables that may be amenable to public health interventions such as improving vaccination coverage, increasing appropriate hydroxyurea therapy, promoting normal BMI, and preventing elevated blood pressure.
Methods

We analyzed 214 individuals with a diagnosis of SCA (Hb SS) between the ages of 11 and 30 years old receiving routine medical care at the University of Ibadan, Nigeria and 209 individuals with SCA between the ages of 11 and 30 years old receiving routine medical care at the University of Illinois at Chicago, U.S.A. In both cohorts, all patients with a diagnosis of SCA and between the ages of 11 and 30 years old at the time of the analysis were included. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The protocol was approved by the Institutional Review Board of the respective institutions prior to initiating the study.

Laboratory and clinical data were obtained from a steady-state visit, which we defined as a visit without mention of the patient being in an acute vaso-occlusive pain episode and at least four weeks from a blood transfusion or acute vaso-occlusive pain episode requiring medical attention. Laboratory variables that were collected included the white blood cell count (WBC) and differential, hemoglobin concentration, mean corpuscular volume (MCV), platelet count, and Hb F%. Complete blood counts and WBC differentials were performed using the Sysmex KX-21 (Lincolnshire, USA) and Mindray 3000plus (Shenzhen, China) machines in the Ibadan cohort and the Siemens ADVIA 2120 (Erlangen, Germany) machine in the Chicago cohort. The Hb F% was measured using the Kleihauer-Betke method in the Ibadan cohort and high-performance liquid chromatography in the Chicago cohort. Clinical data was obtained by the medical health professionals and chart review from each institution. Clinical variables included age, sex, height, weight, systolic blood pressure, diastolic blood pressure, medication history (hydroxyurea, pneumococcal vaccination), and a history of SCA related complications (vaso-occlusive crisis
(VOC) episode frequency, acute chest syndrome, stroke, and red blood cell (RBC) transfusion requirements). In both cohorts, blood pressure measurements were made using automated blood pressure machines while the patients were in a seated position.

Weight status was defined as per the Center of Disease Control and Prevention Guidelines (17, 18). For individuals less than 18 years old, underweight was defined as a BMI < 5\textsuperscript{th} percentile, normal as a BMI in the 5\textsuperscript{th} - 84\textsuperscript{th} percentile, overweight as a BMI in the 85\textsuperscript{th} - 94\textsuperscript{th} percentile, and obesity for a BMI ≥ 95\textsuperscript{th} percentile for age and gender-specific values. For individuals 18 years or older, underweight was defined as a BMI < 18.5 kg/m\textsuperscript{2}, normal as a BMI between 18.5 - 24.9 kg/m\textsuperscript{2}, overweight as a BMI between 25 – 29.9 kg/m\textsuperscript{2}, and obesity as a BMI ≥ 30 kg/m\textsuperscript{2}.

Hypertension categories were defined as per the Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure guidelines (19). Pre-hypertension was defined in individuals less than 18 years old as a systolic or diastolic blood pressure in the 90 - 94\textsuperscript{th} percentile and hypertension as a systolic or diastolic blood pressure ≥ 95\textsuperscript{th} percentile based on age, height, and gender-specific values. For those individuals 18 years or older, pre-hypertension was defined as a systolic blood pressure 120 – 139 mm Hg or a diastolic blood pressure 80 – 89 mm Hg, and hypertension as a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. An elevated blood pressure was defined as any individual with pre-hypertension or hypertension.

Continuous variables were compared according to site or clinical outcomes with the Kruskall-Wallis test and categorical variables with Pearson’s chi square test. Comparisons between the two cohorts were stratified by age group (< 18 years old and ≥ 18 years old). The Bonferroni
correction was applied to adjust for multiple comparisons. Multivariate analysis was performed using logistic regression and linear regression analysis and adjustments for age, gender, hydroxyurea use, and cohort were applied to all final models. Variables with a $P \leq 0.1$ in univariate analysis were entered into the initial model and a stepwise approach was applied to select the final regression models adjusted for age, gender, hydroxyurea use and site. Systat 11 (Systat Software Corporation, Chicago, IL, USA) was used for statistical analyses.
Results

Patient Characteristics

Gender distribution was similar between the Ibadan and Chicago cohorts in both age groups (Table 1). Hydroxyurea therapy, pneumococcal vaccination, and influenza vaccination use were observed in lower proportions of SCA patients from the Ibadan cohort versus the Chicago cohort in both SCA patients < 18 years and ≥ 18 years of age while a difference in a lifetime history of > 5 units of RBC transfusions was significantly different in SCA patients ≥ 18 years of age.

Anthropometric Measures

In SCA patients ≥ 18 years old, weight, height, and BMI were lower in the Ibadan cohort versus the Chicago cohort (Table 1). In SCA patients < 18 years old, these differences persisted for weight (33 vs. 42 kg) and BMI (15.7 vs. 17.8 kg/m²) between the Ibadan and Chicago cohorts, respectively, although the differences were not significant after the Bonferonni correction. A higher proportion of patients from the Ibadan cohort were underweight (Figure 1A, 1B) while a higher proportion of patients from the Chicago cohort were overweight or obese in both age groups of SCA patients (Figure 1A, 1B).

Blood Pressure

The systolic blood pressures were higher in both age groups and the diastolic blood pressures were higher in the adult SCA patients from the Chicago cohort compared to the Ibadan cohort (Table 1). Correspondingly, the proportion of patients with an elevated blood pressure (defined as being pre-hypertensive or hypertensive) was higher in both age groups of SCA patients from the Chicago cohort than the Ibadan cohort (Figure 2A, 2B).
Clinical Complications

Lower proportions of adult SCA patients from the Ibadan cohort had histories of stroke or acute chest syndrome compared to the Chicago cohort while similar proportions of patients had ≥ 3 VOC per year requiring medical attention (Table 1). In the SCA patients < 18 years old, a history of stroke was present in similar proportions between the Ibadan and Chicago cohorts. Rates of acute chest syndrome were lower and the proportion of SCA patients with ≥ 3 VOC per year requiring medical attention were higher in the Ibadan cohort of SCA patients < 18 years old, although the differences were not significant after the Bonferroni correction.

Combined Analysis

Among both cohorts combined, the body mass index was associated with both systolic (Figure 3A) and diastolic blood pressures (Figure 3B) after adjusting for age, gender, hydroxyurea status, and cohort. On univariate analyses, an elevated blood pressure (defined as pre-hypertension or hypertension) was associated with greater age, higher hemoglobin concentration, higher BMI, male gender, and a history of stroke ($P < 0.006$). On multivariate analysis, an elevated blood pressure was associated with male gender (OR 4.9, 95% CI: 2.8 – 8.5; $P < 0.0001$), being from the Chicago cohort (OR 3.6, 95% CI: 2.0 – 6.5; $P < 0.0001$), higher BMI (natural log OR 7.0, 95% CI: 1.3 – 38.4; $P = 0.025$), and greater age (5-year OR 1.5, 95% CI: 1.1 – 2.1; $P = 0.004$).

Stroke history was associated with higher systolic blood pressure and BMI, lower Hb F%, and being from the Chicago cohort on univariate analyses ($P < 0.006$). On multivariate analysis, after adjusting for age, gender, and hydroxyurea status, stroke history was associated with the
natural log of Hb F% (OR 0.4, 95% CI: 0.3 – 0.6; \( P < 0.0001 \)), being from the Chicago cohort (OR 8.9, 95% CI: 3.4 - 23.4; \( P < 0.0001 \)), and being overweight or obese (OR 2.7, 95% CI: 1.2 – 6.0; \( P = 0.019 \)). Acute chest syndrome history was associated with a higher systolic blood pressure and weight status \( (P < 0.006) \) on univariate analyses. After adjusting for age, gender, hydroxyurea status, and cohort, neither variable remained significantly associated with a history of acute chest syndrome. A history of \( \geq 3 \) VOC per year requiring medical attention was associated with a higher absolute granulocyte count \( (4.1 \text{ vs. } 3.3 \times 10^3/\mu\text{L}, P = 0.045) \) and lower Hb F% \( (4.7\% \text{ vs. } 6.5\%, P = 0.017) \) although the associations were not significant after the Bonferroni correction. On multivariate analysis, a history of \( \geq 3 \) VOC per year requiring medical attention was associated with the natural log of Hb F% \( (\text{OR } 0.7, 95\% \text{ CI: } 0.5 – 0.9; P = 0.0067) \) after adjusting for age, gender, hydroxyurea status, and cohort.
Discussion

In this study, we compared the clinical and laboratory features between two cohorts of SCA patients from Ibadan, Oyo Nigeria and Chicago, IL U.S.A in light of known population differences to better understand the potential role for environmental and genetic influences on SCA phenotype. We observed higher rates of overweight or obesity, and elevated blood pressure in the Chicago cohort of SCA patients and lower rates of pneumococcal vaccination and hydroxyurea use in the Ibadan cohort. These differences may reflect environmental effects such as access to care, diet, and activity levels as well as potential differences in genetic modifiers of metabolic indicators affecting the clinical course of SCA.

Overweight and obesity are risk factors for elevated blood pressure and cardiovascular sequelae in the general population (20). Similarly, increased BMI in patients with SCA has been shown to be associated with elevated blood pressure and hypertension (8, 11-13). In turn, elevated blood pressure has been associated with complications in SCA including stroke, kidney disease, and early mortality (8-10, 21). We observed a significantly higher proportion of SCA patients that were overweight or obese in the Chicago versus Ibadan cohort (Age < 18: 6% vs. 3%, Age ≥ 18: 25% vs. 3%, respectively) and increasing BMI was independently associated with increasing systolic blood pressure, relative hypertension, and a history of stroke. Corresponding with a higher BMI in the Chicago cohort, SCA patients from Chicago also had higher systolic blood pressures and higher prevalence rates of pre-hypertension and hypertension than the Ibadan cohort. Public health measures such as dietary counseling to address weight status in Chicago may help mitigate hypertension and stroke risk in SCA patients. Other genetic factors that modulate weight status and blood pressure are suggested based on our findings of an independent
association of being from the Chicago cohort with relative hypertension. Future studies to identify these genetic modifiers may help guide the identification and therapeutic development for metabolic abnormalities in both SCA patients as well as the general population.

Patients with SCA are functionally asplenic and infections by encapsulated bacteria such as Streptococcus pneumoniae are an important cause of morbidity and mortality in children with SCA. Penicillin prophylaxis in early childhood and pneumococcal vaccination can reduce the rate of systemic pneumococcal infections (22-24). In our analysis, pneumococcal vaccination was underutilized in SCA patients from Ibadan and future strategies to increase pneumococcal vaccination are warranted.

Hydroxyurea therapy is currently the only therapy that has been shown in randomized studies to improve the clinical course of SCA (7). Hydroxyurea reduces the rate of VOC, acute chest syndrome, and RBC transfusion requirements and recent data suggests improved survival with long-term hydroxyurea therapy use (7, 25, 26). However, hydroxyurea can cause myelotoxicity and the cost of frequent CBC monitoring and purchasing the medication may be prohibitive in Nigeria (27). Correspondingly, we observed a significantly lower rate of hydroxyurea use in the cohort of SCA patients from Ibadan compared to Chicago. This highlights the importance for future investigations to overcome barriers to the use of hydroxyurea and evaluate potential risks for hydroxyurea therapy such as infections specific to Nigeria.

The prevalence of complication rates between the Ibadan and Chicago adult cohorts were similar for VOC ≥ 3 per year requiring medical attention while a higher frequency of adult patients from
the Chicago cohort had a history of stroke or acute chest syndrome. These differences may reflect actual differences in patterns for these complications between the two cohorts although differences in survival and detection rates will need to be elucidated in future prospective studies. Consistent with the literature in both Nigerians (28-30) and African Americans (4, 31) with SCA, the Hb F% was independently associated with a history of stroke or VOC ≥ 3 per year highlighting the importance of Hb F% in modulating the clinical phenotype of SCA in both cohorts. We observed a lower proportion of patients with a history of >5 units RBC in the Ibadan cohort and this may reflect inherent problems with availability of units as well as the inability of many patients to afford transfusions which can cost the patient upwards of $40 U.S.A. dollars per unit.

There are several limitations to our study. This comparison is a cross-sectional analysis which introduces the potential for survival bias contributing to the observed differences in complications between the Ibadan and Chicago cohort. However, the prevalence of stroke history in our Ibadan cohort was comparable with the pediatric and adult literature from Nigeria (28, 32, 33). Another limitation is that stroke history was determined by chart review and medical interview and does not include silent strokes by magnetic resonance imaging. Differences in rates of detection and recall bias may also be explaining differences between the two cohorts. The associations between clinical variables such as BMI and elevated blood pressure with clinical outcomes such as a history of stroke do not infer causality in a cross-sectional analysis and these biases will need to be addressed in future prospective studies. Different methodologies for measuring the CBC parameters and Hb F% between the two cohorts limited our ability to compare these variables between the two cohorts and comparisons with
standardized methods are warranted in future studies. Another potential limitation is that steady-state was defined as not being in a VOC and being at least four weeks from an RBC transfusion or VOC requiring medical attention. This definition does not include other illnesses such as a viral infection with fever and it is also unclear whether four weeks from a VOC or RBC transfusion is sufficient time for a patient to return to steady-state.

In conclusion, we observed higher rates of overweight or obesity and elevated blood pressure in SCA patients from Chicago and lower rates of hydroxyurea and pneumococcal vaccination use in SCA patients from Ibadan. Life style modifications such as a healthy diet and moderate exercise should be incorporated into treatment guidelines for SCA patients from Chicago to improve increased weight status and elevated blood pressure. Strategies to better implement pneumococcal vaccination to SCA patients from Ibadan are necessary to prevent infection in children with SCA. Future studies to assess the feasibility and safety of hydroxyurea in Nigeria and studies to understand potential genetic modifiers and environmental risk factors for the metabolic abnormalities in SCA patients from the U.S.A. are also warranted.
Acknowledgement:

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References

Figure Legends

Figure 1A: Weight status in sickle cell anemia (SCA) patients < 18 years old from the Ibadan and Chicago cohorts. A higher proportion of SCA patients from Ibadan were underweight (42% vs. 13%) while higher proportions of SCA patients from Chicago were overweight or obese (6% vs. 3%), respectively.

Figure 1B: Weight status in sickle cell anemia (SCA) patients ≥ 18 years old from the Ibadan and Chicago cohorts. A higher proportion of SCA patients from Ibadan were underweight (34% vs. 9%) while higher proportions of SCA patients from Chicago were overweight or obese (25% vs. 3%), respectively.

Figure 2A: Hypertension stage in sickle cell anemia (SCA) patients < 18 years old from the Ibadan and Chicago cohorts. Lower proportions of SCA patients from Chicago were normotensive (84% vs. 98%) and higher proportions were pre-hypertensive or hypertensive (16% vs. 3%) compared to SCA patients from Ibadan, respectively.

Figure 2B: Hypertension stage in sickle cell anemia (SCA) patients ≥ 18 years old from the Ibadan and Chicago cohorts. Lower proportions of SCA patients from Chicago were normotensive (53% vs. 83%) and higher proportions were pre-hypertensive or hypertensive (47% vs. 17%) compared to SCA patients from Ibadan, respectively.

Figure 3A: Body mass index and systolic blood pressure. On linear regression analysis, the body mass index (BMI) was independently associated with systolic blood pressure with
adjustment for age, gender, hydroxyurea therapy, and cohort (Systolic Blood Pressure =
12.2(natural log BMI, \( P = 0.0023 \)) + 0.4(Age, \( P = 0.00047 \)) + 8.1(Male Gender, \( P < 0.0001 \)) –
10.0(Nigeria Cohort, \( P < 0.0001 \)) + 1.3 (Hydroxyurea therapy, \( P = 0.4 \)).

**Figure 3B:** Body mass index and diastolic blood pressure. On linear regression analysis, the
body mass index (BMI) was independently associated with diastolic blood pressure with
adjustment for age, gender, hydroxyurea therapy, and cohort (Diastolic Blood Pressure =
7.7(natural log BMI, \( P = 0.01 \)) + 0.2(Age, \( P = 0.02 \)) – 0.7(Male Gender, \( P = 0.4 \)) - 0.4(Nigeria
Cohort, \( P = 0.7 \)) + 2.5(Hydroxyurea therapy, \( P = 0.051 \)).
Table 1: Comparison of clinical and laboratory factors between all patients from the University of Ibadan, Nigeria and the University of Illinois at Chicago (UIC), U.S.A.

<table>
<thead>
<tr>
<th>Variable</th>
<th>&lt; 18 Years Old</th>
<th>≥ 18 Years Old</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UIC</td>
<td>32</td>
<td>14 (11 – 17)</td>
<td>59</td>
</tr>
<tr>
<td>Gender (male:female)</td>
<td>32</td>
<td>47% : 53%</td>
<td>59</td>
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<tr>
<td>Hydroxyurea therapy</td>
<td>32</td>
<td>14 (44%)</td>
<td>58</td>
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<tr>
<td>Pneumovax</td>
<td>26</td>
<td>23 (88%)</td>
<td>59</td>
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<tr>
<td>Influenza vaccination</td>
<td>29</td>
<td>26 (90%)</td>
<td>57</td>
</tr>
<tr>
<td>Transfusion (&gt;5U/lifetime)</td>
<td>28</td>
<td>12 (43%)</td>
<td>59</td>
</tr>
<tr>
<td>History of stroke</td>
<td>32</td>
<td>2 (6%)</td>
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<td>History of 3 or more vaso-occlusive crises per year</td>
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<td>32</td>
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<tr>
<td>Weight (kg)</td>
<td>32</td>
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</tr>
<tr>
<td>Height (cm)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>32</td>
<td>17.8 (12.6 – 26.9)</td>
<td>59</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>32</td>
<td>112 (95 – 129)</td>
<td>59</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>32</td>
<td>61 (42 – 74)</td>
<td>59</td>
</tr>
</tbody>
</table>

Continuous variables are presented as median values (range).

* P values significant after the Bonferroni Correction

U = unit, BP = blood pressure, MCV = mean corpuscular volume
Figure 1A

- **Underweight**: n = 25
- **Healthy**: n = 32, n = 26
- **Overweight**: n = 1
- **Obese**: n = 1, n = 0

Proportion of Patients (%)

Ibadan
Chicago

$p = 0.02$
Figure 1B

![Bar chart showing the proportion of patients in different weight categories for Ibadan and Chicago.]

- **Ibadan**: n = 15, n = 52, n = 99, n = 117
- **Chicago**: n = 39, n = 4, n = 0

**Proportion of Patients (%)**

- **Underweight**: n = 15
- **Healthy**: n = 99, n = 117
- **Overweight**: n = 4
- **Obese**: n = 0

*P < 0.0001*
Figure 2A

Proportion of Patients (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ibadan</th>
<th>Chicago</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>n = 56</td>
<td>n = 27</td>
</tr>
<tr>
<td>Pre-Hypertension</td>
<td>n = 2</td>
<td>n = 1</td>
</tr>
<tr>
<td>Hypertension</td>
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$P = 0.02$
Figure 2B

Proportion of Patients (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Ibadan</th>
<th>Chicago</th>
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<tr>
<td>Normal</td>
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<td>92</td>
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<tr>
<td>Pre-Hypertension</td>
<td>22</td>
<td>69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>13</td>
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</tbody>
</table>

P < 0.0001
Figure 3A

Cohort:
- Ibadan
- Chicago

$r = 0.56$

$P < 0.0001$
Figure 3B

Diastolic Blood Pressure (mmHg) vs. Body Mass Index (kg/m²) for Ibadan and Chicago cohorts.

- Ibadan (open circles)
- Chicago (filled circles)

Correlation coefficient: $r = 0.29$

Statistical significance: $P < 0.0001$