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ORIGINAL ARTICLE

High Systolic Blood Pressure, Anterior Segment Changes and Visual Impairment Independently Predict Sickle Cell Retinopathy

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ABSTRACT

Sickle cell disease is often complicated by retinopathy, which can be proliferative or non proliferative. Proliferative sickle cell retinopathy potentially leads to blindness. There is a paucity of data on sickle cell disease-related retinopathy from Africa, where the disease is most prevalent. We aimed to determine the clinical, ophthalmic, and laboratory predictors of sickle cell retinopathy in an African population. We conducted a cross-sectional study of 262 participants, aged 13 years and above, with sickle cell disease. Demographic and clinical data were collected using a structured questionnaire and standard physical examinations. Vitreo-retinal specialists performed eye examinations on all the participants. Hematological and biochemical assessments were conducted using standard methods. A multivariate stepwise forward logistic regression was performed to determine the predictors of retinopathy. The median age of the participants was 20 years (interquartile range: 17–25 years). Most of the participants had a homozygous Hb S (*HBB*: c.20A>T) genotype (96.9%), with 3.1% who carried a Hb S/Hb C (*HBB*: c.19G>A) genotype. The prevalence of non proliferative sickle cell retinopathy was 24.4%. Only 1.9% had proliferative sickle cell retinopathy (PSCR). Elevated systolic blood pressure (BP) [odds ratio (OR): 6.85, 95% confidence interval (95% CI): 1.05–44.45, $p = 0.059$], moderate visual impairment (OR: 5.2, 95% CI: 1.39–19.63, $p = 0.015$), and anterior segment changes (OR: 2.21, 95% CI: 1.19–4.13, $p = 0.012$) were independently predictive of retinopathy. This study provides new insight into predictors of retinopathy in sickle cell disease, with implications on early screening and prevention.

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Ophthalmic changes; predictors; retinopathy; sickle cell anemia; sickle cell disease

Introduction

Sickle cell disease has variable clinical manifestations, which can be associated with either repeated vaso-occlusion or frequent hemolysis [1]. As a systemic disease, sickle cell disease often presents with complications involving several organs, including the eye [2]. Proliferative sickle cell retinopathy (PSCR) and non proliferative sickle cell retinopathy (NPSCR) are common eye complications of sickle cell disease. Retinopathy, particularly the proliferative type, is disabling when associated with the visual loss [3]. However, spontaneous regression of the retinopathy seen in several persons with sickle cell disease makes the incidence of blindness comparatively low, despite the relatively high prevalence of retinopathy [4]. Other eye complications reported in individuals with sickle cell disease include conjunctival vasculopathy, refractive errors, anterior uveitis, hyphema with raised intraocular pressure (IOP), and optic nerve damage resulting from a slight increase in IOP [2,5].

Despite the high prevalence of sickle cell disease in sub-Saharan Africa, where 75.0% of the global burden occurs, there is a paucity of data on sickle cell disease-related eye complications, including retinopathy. The risk factors for eye complications in the high-risk patient population with sickle cell disease have not been adequately investigated. Thus, some of the potential blindness complications of sickle cell disease go unrecognized by both the patients and their care providers. Additionally, the clinical and laboratory risk factors of sickle cell disease-related retinopathy need to be systematically explored in resource-limited settings such as Nigeria, with a high burden of sickle cell disease. As part of our efforts to address some of the literature gaps about sickle cell disease-related eye complications, we designed the Retinopathy in Sickle Cell Anemia (RETSCAN) study, which has both cross-sectional and longitudinal phases. In this phase of the study, we aimed to estimate the prevalence of sickle cell retinopathy and its potential predictors.

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Supplemental data for this article can be accessed here.

Methods

Study design and population

This was a cross-sectional study of sickle cell disease adolescents and adults aged 13 years and above, over a period of 5 months (April to August 2019). Participants were recruited from the sickle cell disease clinics of Aminu Kano Teaching Hospital (AKTH) and Murtala Mohammad Specialist Hospital (MMSH) in Kano, northwestern Nigeria. Participants were recruited during routine clinic visits.

Ethics considerations and basic demographic data

Ethics approvals to conduct the study were received from the Health Research Ethics Committees of AKTH and Kano State Ministry of Health. Informed consent was obtained from the adult participants and parents of children less than 18 years old. All children less than 18 years old included in the study provided assent after obtaining their parents' consent. Confidentiality was ensured by storing source documents in a secure place, and data in a password-protected computer accessed only by the researchers. We administered a structured questionnaire designed to collect baseline demographic data and clinical history relevant to the study objectives.

Physical examinations and laboratory analyses

We also conducted a physical examination of each participant. We measured each participant's blood pressure (BP) while sitting, using mercury in a glass sphygmomanometer following standard protocols [6]. Weight was measured using a calibrated standard bathroom weighing scale, while height was measured using a calibrated stadiometer scale. Body mass index (BMI) was calculated using the formula BMI = Weight in kilograms divided by the square of height measured in meters and expressed in Kg/m^2 unit. Venous blood samples were collected for complete blood count (CBC), high performance liquid chromatography (HPLC) [to assess hemoglobin (Hb) variants], and serum lactate dehydrogenase (LDH).

Eye examination

The eye examinations were conducted by ophthalmologists in an eye clinic at the AKTH, Kano, Nigeria. Visual acuity was tested monocularly at a distance of 6 m in a brightly illuminated area of the clinic using black-on-white illuminated Snellen and Illiterate E charts with standardized protocols. This was done unaided if a participant was not wearing spectacles or contact lenses. However, they were not asked to remove them if they presented with spectacle or contact lens correction. It was expected that these participants had been refracted earlier and this was recorded as presenting visual acuity. Visual impairment was determined for each eye according to standard WHO categorizations [7] and documented accordingly. Anterior segment examination was done using the slit lamp (Carl Zeiss Meditec AG, Jena, Germany) to assess for the presence or absence of conjunctival comma-shaped vessels, hyperemia, iris atrophy, neovascularization, posterior synechiae, abnormal pupil, lens and anterior vitreous abnormalities, and hyphema. Intraocular pressure measurements were conducted for each participant's eyes using Goldmann applanation tonometer (GAT) with the participant in a sitting position at the slit lamp and according to the standard procedure at our hospital. The tonometer was reset to 10.0 mmHg before each measurement. The applanation tonometer's tip was disinfected with 1.0% sodium hypochlorite and wiped with a clean, dry swab prior to testing each participant. A topical proparacaine (anesthetic agent) and 2.0% fluorescein were instilled into each eye per standard protocol for the procedure. Two sequential measurements with a difference of not more than 2.0 mmHg were obtained and recorded. A third measurement was required if the difference between the two eyes was more than 2.0 mmHg. Dilated stereoscopic examination of the fundus using slit-lamp biomicroscopy with +90 Diopter lens (Volks Opticals, Mentor, OH, USA) was used to assess the retina and optic nerve head, using tropicamide or phenylephrine. The vertical cup-disc ratio (VCDR), defined as the ratio of the longest vertical diameter of the optic cup to the longest vertical diameter of the optic disk, was determined for all participants and recorded. All estimates were recorded to the nearest 0.1. Where the VCDR was more than 0.5, the participant was referred to undergo further tests (central visual field and optical coherence tomography for glaucoma evaluation) as a standard of care. The diagnosis of NPSCR was based on the presence of characteristic signs in sickle cell disease, such as angioid streaks, retinal hemorrhages 'Salmon patches' or black sunburst spots. In contrast, PSCR was defined as the presence of at least one of the following features: peripheral arteriolar occlusions, arteriovenous anastomoses, 'sea fan' neovascularization, pre retinal or vitreous hemorrhage, and a tractional retinal detachment based on Goldberg's classification [8].

Sample size calculation and statistical analyses

Using Fischer's formula, we estimated a sample size of 262 sickle cell disease patients to determine the prevalence of retinopathy. The study population's baseline characteristics were summarized using frequency and percentages for categorical variables and median and interquartile ranges (IQR) for continuous variables. Comparisons of the quantitative data were done using the Mann-Whitney U test. A p value of <0.05 was considered to be statistically significant.

We performed a univariate logistic regression (Supplemental file A) and multivariate stepwise forward logistic regression with retinopathy as a dependent variable and other potential predictors [Hb level, anterior segment changes, systolic BP (SBP), and visual acuity] as independent variables. In the analysis, we considered both PSCR and NPSCR as a single outcome (retinopathy), due to the low proportion of PSCR ($n = 5$) that would not allow us to perform multinomial logistic regression. The predictors/covariates included in the model were selected based on their

relevance in the literature and using a directed acyclic graph (Supplemental file B). The final model had a likelihood ratio χ^2 of 23.15, p values (for F statistic) <0.001. Our model-fitting test demonstrated a receiver operating characteristic (ROC) of 0.68 (Supplemental file C), which approximates good discrimination. We checked for influential observations in the final model using Pearson Residuals (Supplemental file D). Adjusted odds ratios (AORs) were reported with their accompanying 95% confidence intervals (95% CIs). A p value of <0.05 was considered to be statistically significant. Data were analyzed using STATA Version 13 (STATA Corporation, College Station, TX, USA).

Results

Baseline demographic and clinical characteristics of the participants

A total of 262 adolescents and adults with sickle cell disease were included in the analysis. The median age for all participants was 20 years (17–25 years), (Table 1). A substantial proportion [21.8% (57 of 262)] of the participants were above 26 years old. The majority of the participants [69.5% (182 of 262)] were female. The median body mass index (BMI) was 16.8 (14.7–19.2). Almost all the participants had homozygous Hb S (*HBB*: c.20A>T), except for only 3.1% who had Hb S/Hb C (*HBB*: c.19G>A). Their median SBP was 100.0 mmHg (100.0–110.0), whereas 16.0 and 1.9% had SBP in the range of relative hypertension and hypertension, respectively. Some of the participants [12.6% (33 of 262)] were on hydroxyurea (HU) for different indications. Their median Hb level was 8.0 g/dL (7.1–9.1) with median Hb F and LDH of 7.4% (3.7–12.5) and 466.0 IU (344.0–622.0), respectively.

Ocular findings

Out of 262 patients, 24 (9.3%) used prescription glasses for various indications. Moderate vision loss in the better eye (eye with better visual acuity) was found in 3.8% (10 of 262) of the participants (Table 2). A sizable proportion of the participants [32.4% (85 of 262)] were found to have abnormal changes in the anterior segment of the eyes. The median IOP in the participants' right and left eyes was 14.0 mmHg (12.0–15.0) and 13.0 mmHg (12.0–15.0), respectively. Only 0.8 and 0.4% of the participants had IOP above 20.0 mmHg in the right and left eye, respectively. Moreover, the median cup-disc ratio (CDR) in the participants' right and left eyes was 0.3 (0.2–0.4) and 0.3 (0.2–0.4). Some of the participants [12.3% (32 of 262)] had an indication for optical coherence tomography and visual field assessment to rule out glaucoma.

Sickle cell retinopathy was common and was associated with visual impairment, high systolic blood pressure, and anterior segment changes

The prevalence of retinopathy (proliferative and non proliferative) was 26.3% (69 of 262), Figure 2. The majority [24.4% (64 of 69)] had NPSCR, and only 1.9% (5 of 64) had PSCR. The proportions of the subtypes of PSCR and NPSCR identified in the participants were also reported. All five

Table 1. Demographic, clinical and laboratory baseline data for 262 adolescent and adult patients with sickle cell disease.

Parameters, $n = 262$	Summary statistics
Age, years, median (IQR)	20 (17–25)
Age categories, *n* (%):	
13–16	58 (22.1)
17–25	147 (56.1)
≥26	57 (21.8)
Gender, *n* (%):	
Males	80 (30.5)
Females	182 (69.5)
BMI, median (IQR)	16.8 (14.7–19.2)
Sickle cell disease phenotype, *n* (%):	
Homozygous Hb S	254 (96.9)
Hb S/Hb C	8 (3.1)
SBP (mmHg), median (IQR)	100 (100–110)
SBP (mmHg) categories, *n* (%):	
<120.0	215 (82.1)
12.0–139	42 (16.0)
≥140.0	5 (1.9)
DBP (mmHg), median (IQR)	60 (60–70)
Pulse pressure, median (IQR)	40 (30–50)
HU, *n* (%)	
Yes	33 (12.6)
No	229 (87.4)
Hb, median (IQR)	8.0 (7.1–9.1)
Hb F, median (IQR)	7.4 (3.7–12.5)
LDH, median (IQR)	466 (344–622)

IQR: interquaterile range; BMI: body mass index; Hb S: *HBB*: c.20A > T; Hb C: *HBB*: c.19G > A; SBP: systolic blood pressure; DBP: diastolic blood pressure; HU: hydroxyurea; Hb: hemoglobin; LDH: lactate dehydrogenase.

Table 2. Eye examination findings among 262 adolescent and adult patients with sickle cell disease.

Parameters	Patients ($n = 262$) (%)
Use of eye glasses, *n* (%):	
Yes	24 (95.3)
No	235 (90.7)
Right eye vision, *n* (%):	
Normal	245 (93.5)
Mild impairment	5 (1.9)
Moderate impairment	12 (4.6)
Left eye vision, *n* (%):	
Normal	242 (92.4)
Mild impairment	5 (1.9)
Moderate impairment	15 (5.7)
Better eye, *n* (%):	
Normal	248 (94.7)
Mild impairment	4 (1.5)
Moderate impairment	10 (3.8)
Anterior segment, *n* (%):	
Normal	177 (67.6)
Abnormal	85 (32.4)
Right eye IOP, median (IQR)	14 (12–15)
Right eye IOP, *n* (%):	
≤20	257 (99.2)
≥20	2 (0.8)
Left eye IOP, median (IQR)	13 (12–15)
Left eye IOP, *n* (%):	
≤20	261 (99.6)
≥20	1 (0.4)
CDR right eye, median (IQR)	0.3 (0.2–0.4)
CDR left eye median (IQR)	0.3 (0.2–0.4)
OCT and visual field indicated, *n* (%):	
Yes	32 (12.3)
No	229 (87.7)

IOP: intraocular pressure; IQR: interquartile range; CDR: cup-disk ratio; OCT: optical coherence tomography.

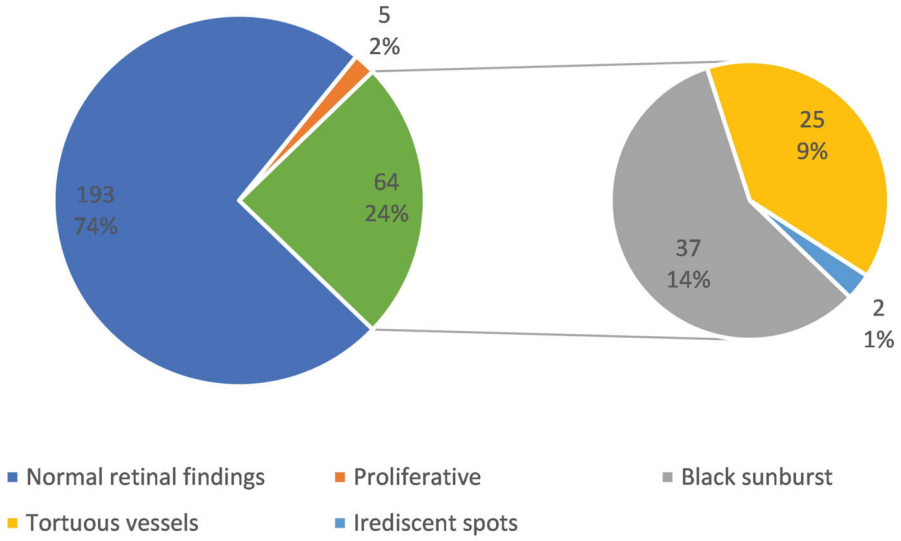

Figure 1. Retinal morphology in sickle cell disease. The primary divisions are normal, proliferative and non-proliferative retinopathy. The vast majority of participants ($n = 193$, 74.0%) had normal retinal findings. All participants with proliferative retinopathy ($n =$ five, 2.0%) had the sea fan appearance. Of the 64 participants (24.0%) with non-proliferative retinopathy ($n = 37$, 14.0%) had black sunburst appearance of retinal vessels ($n = 25$, 9.0%) had tortuous vessels, while two (1.0%) had iridescent spots lesion.

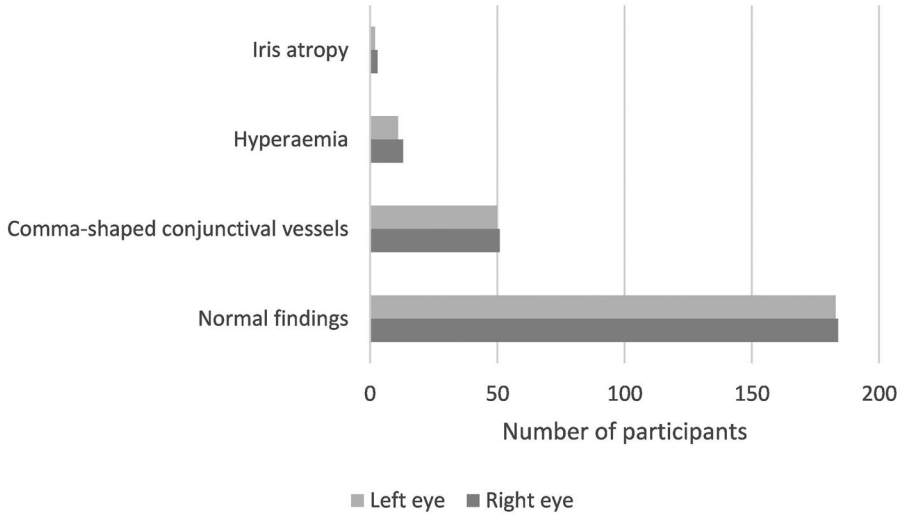

Figure 2. Anterior segment changes in the study participants. The majority of participants had normal anterior segment findings ($n = 178$, 67.9%). Other anterior segment findings include comma-shaped conjunctival vessels ($n = 51$, 19.5%), hyperemia ($n = 13$, 5.0%) and iris atrophy ($n = 3$, 1.1%). None of the participants had anterior segment cells/flare or iris neovascularization.

cases of PSCR were sea fan neovascularization based on Goldberg's staging. For the NPSCR, only three types were identified: black sunburst lesions (14.0%), tortuous vessels (9.0%), and iridescent spots (1.0%) (Figure 1). The proportion of PSCR was significantly higher among participants with Hb S/Hb C [25.00% (2/8) vs. 1.18% (3/254), $p = 0.01$ for Fischer's exact test]. The proportion of persons with retinopathy who were taking HU compared with those not taking the drug showed no significant difference between the two groups (Fisher's exact p values = 0.08).

For a moderate visual impairment, using the better eye, the odds of retinopathy were 5-times as high when compared to normal vision (AOR: 5.42, 95% CI: 1.42–20.66, $p = 0.015$) Table 3. For the observed changes in the anterior segments of the right or left eye, the odds of retinopathy were approximately 3-fold higher than normal findings in the anterior segment of the eye (AOR: 2.88, 95% CI: 1.60–5.19, $p < 0.001$). The most common anterior segment change that was identified in the participants was comma-shaped conjunctival vessels (Figure 2). High SBP was also significantly associated with retinopathy. For an SBP of $\geq$140.0 mmHg, the odds of retinopathy were almost 7-fold higher (AOR: 6.85, 95% CI: 1.05–44.45, $p = 0.059$), Table 3. High Hb count (75th percentile) was associated with lower odds of retinopathy compared to low Hb count (25th percentile), (AOR: 0.63, 95% CI: 0.35–1.14). However, this difference was not statistically significant ($p = 0.163$).

Discussion

This study reports one of the largest and comprehensive eye examination findings in persons with sickle cell disease from sub-Saharan Africa. To the best of our knowledge, this is the

Table 3. Independent predictors of sickle cell retinopathy in 262 adolescent and adult patients with sickle cell disease.

Parameters	OR (95% CI)	AOR (95% CI)	*p*-Value
Anterior segment changes	2.70 (1.52–4.78)	2.21 (1.60–5.19)	0.012
Moderate visual impairment (better eye)	4.50 (1.22–16.46)	5.21 (1.42–20.66)	0.015
SBP $\geq$ 140.0 mmHg	4.06 (0.66–24.90)	5.96 (0.35–1.12)	0.059
Hb $\geq$ 9.1 g/dL	1.31 (0.63–2.73)	0.63 (0.35–1.12)	0.116

SBP: systolic blood pressure; Hb: hemoglobin.

first study in sub-Saharan Africa to highlight the relevance and significance of anterior segment changes, visual impairment, and BP as predictors of retinopathy in adolescents and adults with sickle cell disease. This study's findings have direct implications on early screening and risk-stratification of retinopathy in this patient population.

The proportion of participants in this study who were on HU therapy was 12.6%. This is clearly at variance with the findings in developed countries where the proportion of persons taking HU for various indications is much higher. The possible reasons for the low use of HU may include: HU in our country is still prescribed only for patients with severe disease and for specific indications such as primary and secondary stroke prevention [9], recurrent painful events, recurrent acute chest syndrome, and priapism among others. Although the acceptability of HU is relatively high among this patient population [10,11], the actual number of persons on HU in practice is low. Other potential reasons for this low level of HU coverage include high cost, lack of availability, and possibly fear of side effects.

Studies have shown Nigerian patients with sickle cell disease, and indeed, the general population, have significantly lower BMI than those in more developed countries [12]. This pattern is likely to be true for other countries in sub-Saharan Africa.

Retinopathy is a leading cause of visual impairment and blindness in persons with sickle cell disease worldwide [3]. For this study, we included adolescents and adults (age $\geq$13 years) with sickle cell disease because previous studies in Nigeria had shown that retinopathy was rare in children under the age of 8 years [13]. Overall, we found the prevalence of retinopathy (both PSCR and NPSR) in individuals with sickle cell disease to be 26.3%, which is similar to other findings within and outside the sub-Saharan African region [14–18].

In this study, none of the demographic, hematological, or biochemical parameters included in the analysis was significantly associated with retinopathy in the regression model. Similar to our findings, Kent *et al.* [19] in the United Kingdom, did not find any significant associations with all the demographic and hematological variables they considered, except for low Hb F levels. Our findings are at variance with what was reported in other studies, where advancing age, male gender, higher Hb concentration, and low Hb F levels were associated with PSCR in sickle cell disease [19,20]. We believe that these differences could be the result of some nuances in these studies. The predominant outcome in our study was mainly NPSCR, which is biologically different from the PSCR considered in the other studies. Our data also did not show a significant difference in the prevalence of retinopathy between persons taking HU and those not taking the drug. This may be related to the fact that HU tends to be prescribed to individuals with apparently more severe diseases in our resource-limited settings. The fact that our data showed no difference might be due to this selection bias that is beyond the control of this study design. Appropriately controlled trials or cohort studies may turn out to show a protective effect, considering that HU is a known disease-modifying agent in sickle cell disease for many complications.

Moderate visual impairment, based on WHO criteria [7], was found to be predictive of retinopathy in this study. Earlier studies have demonstrated the association between PSCR and decreased visual acuity [16,17,21]. Progressive loss of vision may be an outcome of retinal disease, although other ocular conditions such as refractive errors could result in reduced visual acuity. In this study, we did not carry out full refraction to exclude definitive refractive errors. However, all participants known to have refractive errors had their visual acuity corrected with their prescription spectacles. We believe this approach has reduced the chances of refractive error confounding our findings. Moreover, it is known that even in the setting of severe retinal disease in sickle cell disease, the rate of vision loss might be relatively low due to the phenomena of spontaneous regression or auto infarction [4].

Anterior segment changes were found to be an independent predictor of retinopathy. Although changes in the eye's anterior segment have been well described in the literature, our study demonstrated a significant association with retinopathy. The significance of this association lies in the fact that the anterior segment of the eye is more accessible during physical examination (can be examined without dilation or administration of cycloplegic agents), and nonspecialist could easily be trained to evaluate the patient's anterior segment. Based on our results, abnormal findings in the anterior segment by the primary care physician should prompt early referral to retina specialists for a detailed evaluation of the posterior segment, including dilated fundoscopy, optical coherence tomography, wide-field imaging, and perimetry. This approach will lead to early diagnosis of the treatable stages of the retinopathy and could prevent the potential complications of blindness such as a vitreous hemorrhage or retinal detachment. The apparent drawback of this approach is that in our study, the anterior segment abnormalities are composite findings, which include comma-shaped conjunctival vessels, iris atrophy, and hyperemia. We do not know exactly which (some or all) of the findings contribute more to the significant association. Future studies should be designed to focus on the specific anterior segment findings to see which is/are predictive of retinopathy.

Although not statistically significant, our results also showed that elevated SBP above 140.0 mmHg to be a predictor of retinopathy. This finding suggests a potential synergy between sickle cell disease and elevated SBP in causing retinopathy. Systemic hypertension is a known cause of retinopathy in the general population [22]. Although our study was

not designed to explore the mechanistic relationship between systemic hypertension and sickle cell disease, we intuitively postulate that hypertension may have an additive effect on the propensity to develop retinopathy in the setting of sickle cell disease. Blood pressure measurements are generally easy, reproducible, and part of routine checks at every clinic visit for sickle cell disease patients. The lack of statistical significance of this relationship might be the result of the relatively small sample size of individuals with elevated SBP in our study sample. We recommend that the finding of elevated SBP above 140.0 mmHg in sickle cell disease should prompt a more careful assessment for the presence of retinopathy.

Our study has several strengths. We demonstrated the importance of BP, visual acuity, and anterior segment changes as predictors of retinopathy. Identifying these predictors in a clinical setting is easy and cost-effective, considering that they are part of physical examination, and no special tests are required. This is important for low-resource settings where catastrophic spending defines the health system, and the cost of doing a test can be a significant hindrance to disease risk stratification. Our study also included children and adults from both sexes, making its conclusion more generalized than other studies carried out exclusively on specific demographic groups. Our study's notable limitations include the fact that we merged both PSCR and NPSCR as a composite outcome in the analysis due to the low numbers of PSCR in our sample.

In conclusion, our data provide new insight into some important clinical and ophthalmic predictors of retinopathy in adolescents and adults with sickle cell disease in sub-Saharan Africa. These findings will form a convenient guide for screening and early detection of this predominantly asymptomatic but the potential complication of blindness in sickle cell disease, especially in resource-constrained settings. If validated in future studies, these predictors will be useful in building a single clinically relevant predictive tool for screening and early prevention of retinopathy in sickle cell disease.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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