Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Original Article

A Study of the Prevalence and Pattern of Sickle Cell Retinopathy among Eye Clinic Attendees in a Nigerian Tertiary Hospital

***Adetunji Olusesan Adenekan[1,2], Adegboyega Sunday Alabi[2], Olubanke Theodora Ilo[1,2], Judith Ogechi Anikwenwa[1], Omolola Olayemi Adisa[2], Folasade Bolanle Akinsola[1,2]**

[1]Guinness Eye Centre, Lagos University Teaching Hospital, Lagos, Nigeria. [2]Department of Ophthalmology College of Medicine, University of Lagos, Idi-Araba, Lagos, Nigeria.

Abstract

Background: Sickle Cell Disease (SCD) is the first and the most common group of haemoglobinopathies in the world. It affects virtually all body systems including the eyes. Proliferative Sickle cell Retinopathy (PSR) is a cause of visual loss in the working age group which has an impact on the economy and quality of life. This study aimed to describe the pattern of presentation of Sickle Cell Retinopathy (SCR)to improve understanding of the disease presentation.

Methodology: The ophthalmic surgical records of patients diagnosed with sickle cell disease at the retinal unit, department of Ophthalmology at the Lagos University Teaching Hospital between the year 2011-2020 were reviewed retrospectively.

Results: A total of 64 patients (108 eyes) records were reviewed in this study. The Prevalenceof sickle cell retinopathy was 5.4% of all retina cases within the study period. Age ranged from 10-70 years; the mean age was 36.28 years ± 13.66. There were 25 females and 39 males (F:M= 1:1.6). SCR was most common in patients with HbSC 40 (62.5%). Common presenting symptoms were loss of vision34 (53.1%) and floaters 34 (53.1%). Goldberg stage III 26 (20.3%) and stage IV 27 (21.1%) were the most common stages of proliferative disease at presentation. A significant association was seen between Haemoglobin genotype SC and the occurrence of sickle cell retinopathy with 90% of the patients with Haemoglobin genotype SC having had PSR. The majority of the patients25 (39.1%) had no treatment, and 13 (20.3%) had laser photocoagulation only.

Conclusion: Sickle cell retinopathy is not uncommon in Nigeria and many patients only present in tertiary health facilities when they have severe symptoms such as loss of vision. This may be attributed to the late diagnosis and referral. Routine screening is recommended to ensure early detection and treatment to prevent avoidable blindness.

Keywords: Sickle Cell; Proliferative Retinopathy; Symptoms; Visual Loss; Screening; Treatment.

Corresponding Author: *Adetunji Olusesan Adenekan, Department of Ophthalmology, College of Medicine, University of Lagos, Idi-Araba, Lagos, Nigeria. Email: aadenekan@unilag.edu.ng

How to cite this article: Adenekan AO, Alabi AS, Ilo OT, Anikwenwa JO,Adisa OO, Akinsola FB.A Study of The Prevalence and Pattern of Sickle Cell Retinopathy Among Eye Clinic Attendees in a Nigerian Tertiary Hospital. Niger Med J 2023;64(2):193 –201

Quick Response Code:

Introduction

Sickle cell disease, an autosomal recessive disorder of haemoglobin, is caused by the inheritance of an altered beta-globin chain gene. In individuals with defective haemoglobin, the abnormal Hb undergoes a conformational change under conditions of hypoxia, acidosis, oxidative stress, and infection, changing the erythrocytes into rigid sickle-shaped (sickled) cells called drepanocytes. These cells, which are less flexible, are more prone to hemolysis than normal red blood cells, with their formation leading to various clinical manifestations of anaemia and vaso-occlusive events. [1-4]

Every tissue of the body including the retina is affected by the vaso-occlusion caused by the sickling of red blood cells in sickle cell disease.[5] Sickle cell retinopathy (SCR), the most common -ocular complication of haemoglobinopathies, is a sight-threatening condition because of the retinal ischaemia caused by vaso-occlusive changes.[6] Sickle cell retinopathy results from the stasis and occlusion of small retinal vessels in theperiphery. Although among the forms of SCD, homozygous SS patients have the most severe systemic clinical form of the disease, ocular occlusive effects resulting in proliferative SCR are more predominant and severe in heterozygous SC. [5,6]

Sickle cell retinopathy can be classified into proliferative and non-proliferative, according to Goldberg.[6] The most common non-proliferative lesions are the increase in vascular tortuosity, black sunburst and retinal haemorrhage like salmon patches.[7] The stages of proliferative disease correlate chronologically with the appearance of proliferative changes, from the appearance of peripheral arteriolar occlusions to retinal detachment. [6,7]

Proliferative Sickle Retinopathy (PSR), the major vision-threatening complication of sickle cell disease, was classified by Goldberg into five stages:(I) Peripheral arteriolar occlusion, (II)Peripheral arteriovenous anastomosis proximal to the non-perfused area, (III) 'Sea fan'neovascularization occurring at the posterior border of non-perfusion, (IV) Vitreous haemorrhage from the new vessel sand (V) Rhegmatogenous or tractional retinal detachment. [8,9]

Ocular symptoms of sickle cell retinopathy include reduction in vision, flashes, floaters, and metamorphopsia.[10,11]Many of these tend to occur in the later stage of the disease with an immediate need for an intervention to restore vision or mitigate visual loss.[10] Available treatment options include observation, laser or cryotherapy, intravitreal anti-Vascular Endothelial Growth Factor (Anti-VEGF) injections, pars plana vitrectomy and retina surgery.[7,10,11]

In this study, we retrospectively describe the presentation, severity, and treatment modalities of sickle cell retinopathy at a tertiary eye health institution in Lagos, Nigeria, to understand the pattern of SC Retinopathy in our environment.

Methods

This was a retrospective study of all patients diagnosed with sickle cell retinopathy who presented to the retinal unit of the Department of Ophthalmology at Lagos University Teaching Hospital from 2011 to 2020.
Case files were retrieved from the records department and the information required was extracted with the aid of a data extraction form. Retrieved information included the patient's age, sex, chief presenting complaints, systemic diagnosis (Hb genotype), use of hydroxyurea medications, anterior and posterior segment findings, retinopathy types and stage and mode of treatment.

The inclusion criteria for patients enrolled for the study were patients with laboratory evidence of genotype electrophoresis confirming the diagnosis of Hb SS, Hb SC, Hb AS, Hb AA and adequate data in case notes. Patients who did not fulfill the above-listed requirements were exempted from the study.

The data were entered into a database and statistical analysis was performed using IBM Statistical Package for the Social Sciences software, version 26 (IBM SPSS, IBM Corp., Armonk, New York). Data were expressed as frequency tables and cross-tabulations.

Ethical approval was obtained from the Health Research Ethics Committee (HREC) of the Lagos University Teaching Hospital, Idi-araba, Lagos.

Results

A total case of 64 patients representing 5.4% of the total number of retinal disease cases (1,194) was seen within the study period. (Table 1).

The age range of these patients was from 10 years to 70 years, and a mean age of36.28 years ± 13.66. There were more males 39 (60.9%) than females 25(39.1%), with a male-to-female ratio M: F= 1.6:1. The age and gender distribution of the patients is depicted in (Table2).

The most common presenting symptoms recorded were loss of vision and floaters, 34 (53.1%) each and other symptoms of presentation were as documented in Figure 1.

No visual impairment was noted in 67 (52.3%) eyes with visual acuity better than or equal to 6/12; 10 (7.8%) eyes between 6/12 – 6/18. Visual acuity of 6/18- 6/60 was reported in 19 (14.8%) eyes while 32 (25%) eyes had worse than 3/60. (Table 3).

The majority of the patients 51 (79.7%) had visible clinical features of sickle cell retinopathy whereas 13 (20.3%) did not have visible evidence.

Forty (62.5%) of the cases reviewed had Haemoglobin SC genotype, followed by Haemoglobin SS with 15 (23.4%), and 6 (9.4%) had Haemoglobin AS. Fischer's exact test showed no significant association between the genotype and sex (p= 0.444).

No clinical features of sickle cell retinopathy were noted in 42 (32.8%) eyes. The Non-Proliferative type was seen in 11 (8.6%) eyes which were black sunbursts, salmon patch and iridescent spots. The Goldberg PSR stage III 26 (20.3%) and stage IV 27 (21.1%) were the most common stages of the disease at presentation. Other presentations were 6 (4.7%) stage 1; 3(2.3%) stage II and 13 (10.2%) stage V. (Table 4).

Fifty-one(79.7%) had documented retinal features of sickle cell retinopathy, with 39 (97.54%) seen in patients with Haemoglobin SC and only 5(33.3%) with Haemoglobin SS. Forty-four(68.8%) had proliferative sickle cell retinopathy, with 36(90.0.%) seen in patients with Haemoglobin SC, 4 (66.7%) seen in haemoglobin AS and only 1(2%) in haemoglobin SS. Out of the 13 (20.3%) reviewed cases with no evidence of retinal features of sickle cell retinopathy, 10 (66.7%), were haemoglobin SS, constituting the majority. The result showed that there is an association between the Haemoglobin genotype and the occurrence of proliferative sickle cell retinopathy {P= 0.000} (Table5).

Twenty-five (39.1%), constituting the majority, did not receive any treatment, and 13 (20.3%) had laser only. These were followed by 8 (12.5%) that had a combination of laser and intravitreal anti-Vascular Endothelial Growth Factor (anti-VEGF) injections and 11(17.2%) with a combination of laser and pars plana vitrectomy. Furthermore, pars plana vitrectomy alone; the combination of laser, intravitreal anti-VEGF injection and pars plana vitrectomy; and the combination of intravitreal anti-VEGF injection and pars plana vitrectomy were the treatment modalities received by 2 (3.1%) each. Only 1(1.6%) had intravitreal anti-VEGF injection only. (Table6)

Only 3(4.7%) of the patients were on regular use of hydroxyurea and all had evidence of sickle cell retinopathy. The study did not find a significant association between the use of hydroxyurea and the development or otherwise of sickle cell retinopathy.

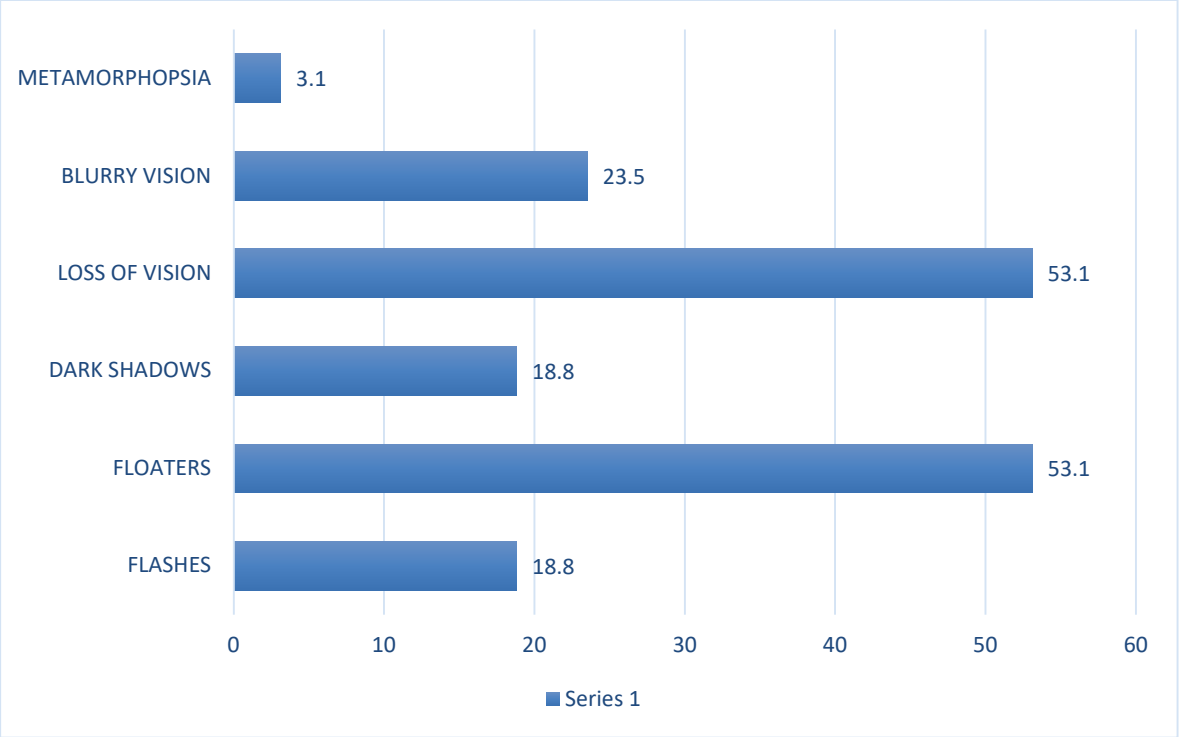
Retinal Diseases	**Frequency**	**Percentage (%)**
Diabetic Retinopathy	259	21.7
Hypertensive Retinopathy	92	7.7
Sickle Cell Retinopathy	64	5.4
Retinopathy of Prematurity	29	2.4
Retinal Vascular Occlusions	122	10.2
Age Related Macular Degeneration	101	8.5
PolypoidalChoroidal Vasculopathy	23	1.9
Vitreous Haemorrhage	66	5.5
Posterior Uveitis	82	6.9
Retina/Macular Dystrophies (Retinitis Pigmentosa, Stargardt etc)	43	3.6
Retinal Detachment	151	12.6
Macula Hole	49	4.1
Chorioretina/Macula scars	61	5.1
Others (Coats Disease, Central Serous Retinopathy,)	42	3.5
Total	1, 194	100

Table 1: Distribution of retinal cases seen at the retinal clinic.

Age	**Frequency (n = 64)**	**Percentage (%)**
0-10	4	6.3
11-20	4	6.3
21-30	10	15.6
31-40	21	32.8
41-50	19	29.7
51-60	3	4.7
61-70	3	4.7
Total	**64**	**100.0**
Gender	**Frequency (n = 64)**	**Percentage (%)**
Female	25	39.1
Male	39	60.9
Total	64	100.0

Table 2: Age and Sex Distribution of Patients

Figure 1: Presenting symptoms of patients with SCR



SCR- Sickle Cell Retinopathy

*Category of visual impairment	Frequency (n = 128, eyes	Percentage (%)
No vision impairment (VA better than or equal to 6/12)	67	52.3
Mild impairment (VA worse than 6/12)	10	7.8
Moderate impairment (VA worse than 6/18)	19	14.8
Severe impairment (VA worse than 6/60)	0	0.0
Blindness (VA worse than 3/60)	32	25

Table 3: Presenting Visual Acuity of Patients.
*ICD-11 for Mortality and Morbidity Statistics (Version: 09/2020)

Stage of Disease	Frequency (n = 124 eyes)	Percentage (%)
NPSR	11	8.6
PSR I	6	4.7
PSR II	3	2.3
PSR III	26	20.3
PSR IV	27	21.1
PSR V	13	10.2
None	42	32.8

Table 4: Distribution of types and stages of sickle cell retinopathy amongst patients
NPSR-Non-Proliferative Sickle Retinopathy, PSR- Proliferative Sickle Retinopathy

Haemoglobin Genotype	SCR (%)	Does not have SCR (%)	Total (%)
AA	1 (100.0)	0 (0.0)	1 (100.0)
AS	5 (83.3)	1 (16.7)	6 (100.0)
SC	39 (97.5)	1 (2.5)	40 (100.0)
SS	5 (33.3)	10 (66.7)	15 (100.0)
Not recorded	1 (50.0)	1 (50.0)	2 (100.0)
Total	51 (79.7)	13 (20.3)	64 (100.0)
Haemoglobin Genotype	PSR (%)	Does not have PSR (%)	Total
AA	1 (100.0)	0 (0.0)	1 (100.0)
AS	4 (66.7)	2 (33.3)	3 (100.0)
SC	36 (90.0)	4 (10.0)	40 (100.0)
SS	2 (13.3)	13 (86.7)	15 (100.0)
Not recorded	1 (50.0)	1 (50.0)	2 (100.0)
Total	44 (68.8)	20 (31.3)	64 (100.0)

Fischer's exact test 116.542 (p= 0.000)

Table 5: Association between Haemoglobin genotype and Proliferative Sickle Retinopathy

Stage of Disease	Frequency (n = 64)	Percentage (%)
None	25	39.1
Laser	13	20.3
Anti-VEGF	1	1.6
Vitrectomy	2	3.1
Laser + Anti-VEGF	8	12.5
Laser + Vitrectomy	11	17.2
Anti-VEGF + Vitrectomy	2	3.1
Laser + Anti-VEGF + Vitrectomy	2	3.1

Table 6: Distribution of treatment modalities received by the patients.
Anti-VEFG: Anti Vascular Endothelial Growth Factor

Discussion

Sickle cell disease is common in the West African sub-region. However,64 cases of sickle cell retinopathy, were found in a ten-year review, resulting in a prevalence of 5.4% of all retina cases at the Lagos University Teaching Hospital, Lagos, Nigeria, West Africa. The explanation for this low number of cases may include poor health-seeking behaviours, lack of knowledge of the ocular complications of sickle cell disease, the asymptomatic nature of SCR at the early stage, and the epidemiological distribution of the SCD itself.

The majority of the patients with proliferative sickle retinopathy, in our study, were within the age group 31 years to 40 years and we had more male patients recorded. These findings were similar to several other studies including a retrospective study conducted in the University College Hospital, Ibadan where sickle cell retinopathy was found to be more in ages 31-40years and was more in males than females (76% and 24% respectively). [12-14] The explanation could be the sociodemographic similarity of the two locations, being in the South-west zone of Nigeria. The presentation of patients in this age group could also be connected to poor health-seeking behaviour, poor understanding of ocular features of SCR and symptomless nature of the disease at the early stage and thus leading to late presentation, referral and diagnosis.

Findings that showed sickle cell retinopathy and the proliferative type are most common in haemoglobin SC, in our study, and are like findings in several other studies. [12-17] Explanation for the higher prevalence of SCR and PSR amongst Hb SC patients compared to Hb SS patients could be because of the lower hematocrit in Hb SS, due to many circulating sickled red cells, thus, providing relative protection from vaso-occlusion in the small-calibre vessels of the retina.[18]

Furthermore, the literature description of retinal vascular occlusions in HbSS disease as being a complete one that total infarction and retinal necrosis occur, with no viable tissue remnant that can stimulate an angiogenic vascular endothelial growth factor (VEGF) response. This is contrary to the retinal vascular occlusions in HbSC disease, which is often less severe, resulting in chronic ischemia, instead of complete infarction, and therefore promoting the continuous secretion of angiogenic substances by the damaged tissues.[7,11,18]Finally, the argument that HbSS patients, perhaps due to their severe systemic complications, do not live long enough to develop retinopathy when compared to the HbSC patients, whose systemic complications are less comparable to the HbSS patients, may support the higher prevalence of SCR and PSR in Hb SC.[7,18]

The most common ocular symptoms in our study, sudden vision loss and floaters were similar to those reported in studies conducted in Ibadan and Lagos. [12,13] Perhaps, the adverse effect of these symptoms on the patient's activity of daily living could explain why they are obliged to present once these symptoms occur compared to other symptoms.

The majority of patients are within stages III and stages IV of proliferative retinopathy, 20.3% and 21.1% respectively, using Goldberg's classification. This was like another study in Lagos that reported the majority of patients presenting with stages III and 1VPSR,27.9% and 44.2% respectively. [10] The lack of symptoms at the onset of SCR and low referral for ophthalmic evaluation and screening amongst managing physicians resulting in the late patient presentation may explain this finding. Sight-threatening PSR occurred more in patients of increasing age and in patients with HbSC.

The treatment modalities were observation, laser, vitrectomy and anti-VEGF injections which were done singly or in different combinations, the highest modalities being observation (39.1%), laser alone (20.3%). Others were laser and anti-VEGF (12.5%), laser and vitrectomy (17.2%), and other combinations with little percentage. The availability of Laser therapy, minimal complications, and its relative affordability in our facility, being a federal government institution, compared to the other few eye care facilities where it is available in Lagos, which are mainly privately owned, could explain why it has become the mainstay of treatment as discovered by this study. In Ibadan, the combination of laser/cryotherapy +/- intravitreal anti-VEGF accounted for 70% of the treatment modalities for proliferative retinopathy and vitrectomy alone accounted for 30%.[17]

Laser treatment for PSR prevents visual loss and vitreous haemorrhage, however, it does not appear to have a significantly different effect on other clinical outcomes such as regression of proliferative sickle retinopathy and development of new ones.[19]

The use of hydroxyurea by patients with SCD has been reported to reduce vaso-occlusive changes, hence the idea to report its use among our patients. However, as only three of the patients used it, it was difficult to make any inference as to the benefit or otherwise of hydroxyurea in the development of sickle cell retinopathy. TheDisease-modifying effect of hydroxyurea has been reported to increase the production of foetal Hb which reduces the tendency for red blood cells to sickle and reduces the production of white blood cells that contribute to inflammation, thus, controlling vaso-occlusive complications.[20,21] Contrary to the practice of routine use of hydroxyurea, amongst individuals with sickle cell disease in developed societies, the usage in most resource-limited societies such as ours is less, hence the difficulty in assessing the evidence that suggested treatment with hydroxyurea may confer protection from Sickle cell retinopathy.[19,20]

Conclusion

Sickle cell retinopathy is not uncommon in Nigeria and is known to be more common in the South-Western part of the country. It is most prevalent in the Haemoglobin genotype SC. Many patients only present in tertiary health facilities when they have severe symptoms such as loss of vision and they present at stage 1V. This may be attributed to the late diagnosis and referral. Screening is recommended for all patients with sickle cell disease and traits, especially those with heterozygous SC, to ensure early detection and treatment of proliferative changes with a view to preventing avoidable blindness.

Limitations

The challenge of patients being lost to follow-up and others not showing up for treatment which is likely due to financial constraints explained the inadequate data. The other limitations of the study, which are methodology-related, include small sample size, retrospective design and lack of randomization.

Financial Support and sponsorship

None

Conflict of Interest

The authors have no conflict of interest.

References

1. Steinberg NH, Forget GE, Higgs RD, Nagel RL. Disorders of haemoglobin: genetics, pathophysiology, and clinical management. *Cambridge University Press*. 2001; **653:**775-781.
2. Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (Hb S) allele and sickle cell disease: a HuGE review. *American Journal of Epidemiology.* 2000; **151**:839–845.
3. Ingram VM. Abnormal human haemoglobins. III. The chemical difference between normal and sickle cell haemoglobins. *Biochim Biophys Acta.* 1959; **36**:402–11.
4. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet.* 2010; **376**:2018–31.
5. Abdalla Elsayed ME, Mura M, Al Dhibi H, Schellini S, Malik R, Kozak I, et al. Sickle cell retinopathy. A focused review. *Graefes Arch Clin Exp Ophthalmol*. 2019; **257**:1353-64.
6. Goldberg MF. Classification and pathogenesis of proliferative sickle retinopathy. *Am J Ophthalmol.* 1971; **71**:649-65.
7. Scott AW. Ophthalmic manifestations of sickle cell disease. *South Med J.* 2016 Sep 1; **109**:542-8.
8. Fox PD, Dunn DT, Morris JS, et al. Risk factors for proliferative sickle retinopathy. *Br J Ophthalmol* 1990; **74**:172–176.

9. Downes SM, Hambleton IR, Chuang EL, et al. Incidence and natural history of proliferative sickle cell retinopathy: observations from a cohort study. *Ophthalmology* 2005; **112**:1869–1875.
10. AO Hassan, O Oderinlo, O Okonkwo, FO Oluyadi, AO Ogunro, SA Oke. Pattern of presentations seen in sickle cell retinopathy patients at eye foundation hospital Lagos, Nigeria. *Nigerian Journal of Ophthalmology* 2005; **13**:17-20.
11. American Academy of Ophthalmology 2022-2023 Basic and Clinical Science Course. Retina and Vitreous. Chapter 7 pg 167-174.
12. Oluleye TS. Pattern of presentation of sickle cell retinopathy in Ibadan. *J Clin Exp Ophthalmol* 2012; **3**:9.
13. Akinsola FB, Kehinde MO (2004) Ocular findings in Sickle Cell Disease Patients in Lagos. *The Niger Postgrad Med J*. 2004; **11**:203-206.
14. Eruchalu UV, Pam VA, Akuse RM (2006) Ocular findings in children with severe clinical symptoms of homozygous sickle cell anaemia in Kaduna, Nigeria. *West Afr J Med.* 2006; **25**:88-91.
15. Babalola OE, Wambebe CO (2006) Ocular morbidity from sickle cell disease in a Nigerian cohort. *Niger postgrad Med J.* 2006; **12**:241-244.
16. Fadugbagbe AO, Gurgel RQ, Mendonça CQ, Cipolotti R, dos Santos AM, et al. (2010) Ocular manifestations of sickle cell disease. *Ann Trop Paediatr.* 2010; **30**:19-26.
17. Oluleye TS, Babalola YO, Majekodunmi OI, Ijaduola MA. Sickle cell retinopathy: patient awareness, mode of presentation, and treatment modalities in Ibadan, South-west, Nigeria. *Nigerian Journal of Medicine* 2021; **30**:481-486.
18. Aguiar AG, Aguiar LP, Santos VL, Oliveira DC. Sickle cell retinopathy: characterization among patients over 40 years of age. *Revista Brasileira de Oftalmologia*. 2020 Jun 3; **79**:118-2.
19. Myint, Kay & Sahoo, Soumendra & Moe, Soe & Ni, Han. (2013). Laser therapy for retinopathy in sickle cell disease (Protocol). Cohrane Database of Systematic Reviews. 2013. Art. No.: CD010790. 10.1002/14651858.CD010790.
20. Estepp JH, Smeltzer MP, Wang WC, Hoehn ME, Hankins JS, Aygun B. Protection from sickle cell retinopathy is associated with elevated HbF levels and hydroxycarbamide use in children. *Br J Haematol*. 2013; **161**:402–5.
21. National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: *expert panel*. 2014; **1**–161.