Scientific Research Publishing

Advances in Infectious Diseases, 2023, 13, 355-374
https://www.scirp.org/journal/aid
ISSN Online: 2164-2656
ISSN Print: 2164-2648

Malaria Retinopathy among Under-Five Children with Severe and Uncomplicated Malaria in a Tertiary Health Institution in Southwest Nigeria: A Comparative Study

Olusoji Omotayo Olayinka[1], Philip Olayele Abiodun[1], Tolulope Opeoluwa Jegede[1], Ifedayo Olabisi Fasoranti[1], Qasim Olakunle Salau[1], Abiodun John Kareem[1*], Juliet Nnenda Olayinka[2], Evbenaye Stanley Obasohan[1], Babatunde David Babalola[1], Adeoye Adeleke Ademuyiwa[1], Foluwakemi Tope Ekogiawe[1], Ikechukwu Sunday Abazu[1], Emmanuel Olasunkanmi Babalola[1]

[1]Department of Paediatrics, Federal Medical Centre, Owo, Nigeria
[2]Department of Pharmacology, Afe Babalola University, Ado-Ekiti, Nigeria
Email: *biodunkareem13@gmail.com

How to cite this paper: Olayinka, O.O., Abiodun, P.O., Jegede, T.O., Fasoranti, I.O., Salau, Q.O., Kareem, A.J., Olayinka, J.N., Obasohan, E.S., Babalola, B.D., Ademuyiwa, A.A., Ekogiawe, F.T., Abazu I.S. and Babalola, E.O. (2023) Malaria Retinopathy among Under-Five Children with Severe and Uncomplicated Malaria in a Tertiary Health Institution in Southwest Nigeria: A Comparative Study. *Advances in Infectious Diseases*, **13**, 355-374.
https://doi.org/10.4236/aid.2023.133031

Received: May 17, 2023
Accepted: July 28, 2023
Published: July 31, 2023

Abstract

Introduction: Malaria retinopathy refers to retinal abnormalities unique to malaria resulting from prolonged parasitization by *Plasmodium falciparum*. Identifying these features and treating them promptly could prevent lethal complications of malaria. Therefore, this study was conducted to identify and compare retinal findings in severe and uncomplicated malaria. **Methods:** A cross-sectional study of 260 subjects was equally divided into two groups of severe and uncomplicated malaria. Direct ophthalmoscopy was done at recruitment for all subjects. Information on sociodemographics, physical examination, nutritional status, and retinal abnormalities were recorded. A p-value <5% was considered significant. **Results:** There were 141 (54.2%) males and 70 (26.9%) aged between 13 - 24 months. Severe anaemia, multiple convulsions, prostration, and cerebral malaria were the predominant forms of severe malaria. Twenty-three (17.7%) subjects with severe malaria and none with uncomplicated malaria had retinopathy. Retinal whitening (17.7%), vessel changes (16.2%), and retinal haemorrhages (5.4%) were the major forms of retinopathy. Retinopathy occurred in 43.8% of those with cerebral malaria. Retinal whitening and vessel changes were significantly associated with multiple convulsions, cerebral malaria, and metabolic acidosis; retinal haemorrhage was associated with cerebral malaria and haemoglobinuria (p = 0.022) and vessel changes with hypoglycaemia (p = 0.037). Cerebral malaria was an independent predictor of retinal whitening (p = 0.004) and vessel changes (p

= 0.008) while haemoglobinuria was an independent predictor of retinal haemorrhages (p = 0.007). **Conclusion:** Ophthalmoscopy is an important examination in children with severe malaria which could assist in early detection and with prompt treatment, reduce morbidities and mortalities.

Keywords

Children, Malaria, Nigeria, Ophthalmoscopy, Retinopathy

1. Introduction

Malaria is a parasitic infection that is caused by the *Plasmodium* species which is transmitted through a bite of the female *Anopheles* mosquito [1]. The five common species of the *Plasmodium spp* that cause malaria in humans are *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium vivax*, *Plasmodium malariae*, *and Plasmodium knowlesi* [2]. Among these, *Plasmodium falciparum* and *Plasmodium vivax* are associated with severe forms of malaria, the former being the most lethal [2]. *P. falciparum* accounts for 80% - 90% of cases of malaria in Africa while the remaining 8% and 2% - 3% are caused by *P. ovale* and *P. malariae* respectively [3].

Malaria affects over 55% of the world's population which cuts across 124 countries, 90% - 95% of which are in Sub-Saharan Africa [4] [5]. Recent World Health Organisation (WHO) data in 2020 estimated 241 million cases of malaria worldwide with Africa accounting for about 96% of all the cases and over 627,000 deaths occurring annually from malaria worldwide of which about 95% were from the African region [4] [5]. About one out of every five deaths of under-five children worldwide is due to malaria [4]. In Nigeria, malaria affects up to 97% of the population with 100 million cases and up to 300,000 deaths annually [4] [6]. The majority of these deaths occur in under-five children [7]. Malaria also accounts for up to 60% of outpatient visits and 30% of hospitalizations among under-five children [5]. The Southwestern region of Nigeria accounts for the highest number of malaria cases among under-five children in Nigeria with a prevalence of 50.3% compared to Southeastern Nigeria which has the lowest prevalence of 27.6% [5].

Malaria could either be uncomplicated when an individual presents with symptoms suggestive of malaria and a positive parasitologic test or severe when it is accompanied by or leads to complications that are life-threatening [8]. The complications include severe anaemia, cerebral malaria, hypoglycaemia, acute kidney injury, pulmonary oedema, haemoglobinuria, metabolic acidosis, algid malaria, and hyperparasitemia [9] [10] [11]. Severe anaemia and cerebral malaria are however the most common severe forms of malaria among children with cerebral malaria being responsible for the highest proportion of malaria mortality [12] [13].

Studies have consistently documented some ophthalmologic findings in cere-

bral malaria which include absence of corneal reflex, pupillary constriction, poor reaction to light, and retinal changes [14] [15]. These retinal changes were found to be of prognostic value in children with severe malaria. Some of these retinal changes include whitening of the retina and macula, orange discolouration of retinal vessels, papilloedema, and retinal haemorrhages [16] [17]. Oluwayemi *et al.* [18] in a study in Nigeria reported that retinal haemorrhage was significantly associated with higher mortality in cerebral malaria subjects. Similarly, Essuman *et al.* [19] in a study in Ghana concluded that the severity of retinal haemorrhages and papilloedema may be useful in predicting the likelihood of death in cerebral malaria. Singh *et al.* [17] in a study in India observed that papilloedema and retinal haemorrhages were predictors of mortality. Maude *et al.* [20] believed that the retinopathy seen in cerebral malaria and other forms of severe malaria are manifestations of the same pathophysiological mechanisms occurring at different anatomical sites. Therefore, it is possible that these retinal changes could also be occurring in other forms of severe malaria apart from cerebral malaria and could probably precede the clinical manifestations of severe malaria [20] [21].

Identification of the ophthalmoscopic changes in severe malaria as well as uncomplicated malaria could heighten the alertness of clinicians in children and therefore the need for early and appropriate interventions to prevent mortality. There is a dearth of studies on ophthalmoscopic changes in severe malaria and uncomplicated malaria in this environment which is an endemic region for malaria. This study was, therefore, carried out to identify and compare the ophthalmoscopic changes between severe malaria and uncomplicated malaria and also to determine the factors associated with the ophthalmoscopic changes. This study will, therefore, help to determine the importance of fundoscopy in all patients with severe and uncomplicated malaria to engender early treatment and better outcomes. Findings from this study will provide additional information on the ophthalmoscopic features of a wider range of malaria which may then inform the need for the inclusion of ophthalmoscopy in the assessment of all cases of malaria.

2. Methodology

Study design: This was a hospital-based comparative cross-sectional study.

Study site: This study was carried out at the Children Emergency Room (CHER) and Children Out-patient (CHOP) units of the Paediatrics Department, Federal Medical Centre (FMC), Owo, Ondo state. The FMC, Owo is a tertiary hospital that serves as the referral centre for Ondo state as well as some adjoining states of Edo, Osun, Ekiti, and Kogi. Owo is a semi-urban town with a population of about 300,000 people according to the National Population Commission [22]. Owo town is located within the south-west geo-political zone of Nigeria and lies within latitude 7.1833˚N and longitude 5.5833˚E which is within the malaria endemic belt of the world [22] [23]. The people of the town are mostly traders,

farmers, and civil servants.

Study population: The case group was children between the ages of six months and five years that were admitted to the CHER with features of severe malaria including palor, convulsions, loss of consciousness, the passage of coke-coloured urine, prostration, jaundice, shock, abnormal bleeding caused by asexual forms of *P. falciparum* while the control group were age and sex-matched children with uncomplicated malaria caused by asexual forms of *P. falciparum* seen at the CHOP. Children with chronic illnesses like sickle cell disease, diabetes, and hypertension that affect the eyes were excluded from the study.

Study duration: November 2020 to August 2021.

Ethical consideration: Approval for the study was obtained from the Federal Medical Centre, Owo Ethics and Research Committee with number FMC/OW/380/VOL.CXXXVL/98. Written informed consent was obtained from the caregiver of each of the subjects that were recruited for the study

Sample size estimation

The sample size for this study was determined using the formula by Charan and Biswas [24].

$$N = \frac{\left(Z_\alpha + Z_\beta\right)^2 \left\{p_1\left(1-p_1\right) + p_2\left(1-p_2\right)\right\}}{\left(p_1 - p_2\right)^2}$$

N = Minimum sample size.

P_1 = Proportion with malaria retinopathy in severe malaria group is 0.70.

P_2 = Proportion of malaria retinopathy in uncomplicated malaria is 0.50.

Z_α = Standard normal deviate corresponding to level of significance (usually 5%) *i.e.* 1.96.

Z_β = Standard normal variate for power of 90% is 1.28.

$$N = \frac{\left(1.96+1.28\right)^2 \left\{0.7\left(1-0.7\right)+0.5\left(1-0.5\right)\right\}}{\left(0.7-0.5\right)^2}$$

N = 120.7.

Applying an attrition rate of 5%, the minimum sample size was 130 for each of the severe and uncomplicated malaria groups.

Sampling technique: All consecutive admissions into the children's emergency room and visits to the children's outpatient clinics were noted. Those whose ages were between six months to five years and who met the inclusion criteria for severe malaria were recruited into the severe malaria group. They were tested for the presence of an asexual form of *Plasmodium falciparum* using the microscopy method. Those that tested positive for the asexual form of *Plasmodium falciparum* and whose parents had given consent were recruited into the study until the sample size was completed.

For the uncomplicated malaria group, all children between the ages of six months and five years presenting at the Children's outpatient with fever and any other symptoms related to malaria were tested for the asexual form of *Plasmodium falciparum* using the microscopy method. Only those in whom the parasite

was detected on microscopy were recruited.

2.1. Study Procedure

For all recruited subjects, information was obtained from the caregiver. The information included socio-demographic data such as age in months, gender, parents' level of education and occupation; symptoms and duration, treatment given, and type. The socio-economic classes of all the parents of the subjects were assessed using the socio-economic classification of children in Nigeria by Ogunlesi *et al.* [25]. All data obtained were entered into the questionnaires specifically designed for the study.

General physical and systemic examination was done on all subjects recruited. Features of severe malaria that were not captured from the symptomatology were identified such as palor, jaundice, level of consciousness, splenic span, liver span, as well as respiratory and neurological examinations.

Weight (in kilograms to the nearest 0.1 kg) was measured using a *Bassinet Weighing Scale*® (which measures to the nearest 0.05 kg) for children less than one year while *Hana Weighing Scale*® (which measures to the nearest 0.1 kg) was used for subjects one year and above. For unconscious subjects, approximate weights were obtained from the deduction of the weight of the caregiver from the combined weight of both the caregiver and the subject.

Height (in centimetres, cm) was assessed for the subjects above two years using a stadiometer (to the nearest 0.1 cm) while length (in centimetres, cm) was assessed for the subjects below two years using an infantometer (to the nearest 0.1 cm). For the unconscious, length was estimated using a measuring tape.

All subjects had ophthalmoscopic assessments done at recruitment using a Riester Ophthalmoscope. This was a hand-held direct ophthalmoscopic device that uses low-emission diode (LED) technology. For the conscious subject, the child was made to sit upright on a chair and to look straight ahead while the examiner standing on one side and facing the child shines the light from the ophthalmoscope into the dilated pupil. For the unconscious subject, the examination was done with the subject lying supine. With the aid of the Riester ophthalmoscope, the fundus of the subject was examined with a focus on the retina and its surrounding structures including the vessels. The eyelid was manually opened to make the palpebral fissure wide enough for examination. For those in whom the retina was difficult to visualise because of pupillary constriction, a short-acting mydriatic agent (1% tropicamide) was applied to the eyes to dilate the pupils. This was allowed to stay for about thirty minutes after which the pupils were well dilated and allowed for visualisation of the retina.

The pupillary dilatation lasted for about 90 minutes before the pupils returned to their normal sizes. The possibility of side effects of the tropicamide was explained to the parents before the application was done. These side effects include stinging of the eyes, blurring of vision, and sensitivity of the eyes to light. Some caregivers, especially those whose children had uncomplicated malaria, declined

the application of the tropicamide hence they were excluded from the research.

Repeat ophthalmoscopic examination was done at 24 and 48 hours to identify new and evolving retinal abnormalities. Those with persisting malaria retinopathy were counseled to re-present for follow-up at the children's outpatient department once weekly for two consecutive weeks after discharge and thereafter referred to Ophthalmology Department for continued follow-up if malaria retinopathy persisted.

Retinal/macular whitening was identified when there was patchy opacification of the retinal, lateral to the disc [26]. When it occurred around the macula, it was referred to as macular whitening, whereas it was called peripheral whitening when seen outside of the macula [26]. Vessel changes were reported when there was whitish or orange discolouration of retinal vessels. It involved discrete sections of vessels or peripheral trees and capillary whitening which was the whitening of retinal capillaries and post-capillary venules making them to be prominent against the choroidal background [26]. Retinal haemorrhages were white-centred, intra-retinal haemorrhage which could be numerous or overlapping and could sometimes extend to pre-retinal space [26].

2.2. Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 23. Results were expressed as means and standard deviation for normally distributed continuous variables. Categorical variables were compared using the Chi-square test and Fisher's exact test as applicable. Means of continuous variables were compared using the Student *t-test* for two groups. Multivariate analysis was used to analyze factors associated with ophthalmoscopic findings and a p-value of < 0.05 was regarded as statistically significant.

3. Results

Two hundred and six patients were admitted for different forms of severe malaria during the study period out of which one hundred and thirty (63.1%) that met the inclusion criteria were recruited into the severe malaria group. The demographic distribution and nutritional status of the study participants is as shown in **Table 1**. The predominant age group was age 13 - 24 months (26.9%) while only 12.3% were age group 37 - 48 months. The overall mean age of all participants was 30.1 (±18.1) months. About two-thirds (66.1%) of subjects in the severe malaria group were below 36 months. The mean ages of uncomplicated and severe malaria groups were 29.5 (±18.0) months and 30.8 (±18.4) months respectively. There was no statistically significant difference in the mean ages of the two groups ($t = 0.556$, $p = 0.578$). The male to female ratio was 1.2:1 for the study participants, but slightly higher (1.3:1) for the severe malaria group. Majority of the study participants have normal weight (72.7%) and height (79.2%). There were no statistically significant differences in the age, gender and nutritional status of the subjects in the two study groups.

Table 1. Demographic distribution and nutritional status of the study participants.

Variable	Severe Malaria n = 130(%)	Uncomplicated Malaria n=130(%)	Total n=260(%)	Chi-square	*p*-value
Age group (months)					
6 - 12	28 (21.5)**	30 (23.1)	58 (22.3)	0.609	0.965
13 - 24	35 (26.9)	35 (26.9)	70 (26.9)		
25 - 36	23 (17.7)	24 (18.5)	47 (18.1)		
37 - 48	18 (13.9)	14 (10.8)	32 (12.3)		
49 - 59	26 (20.0)	27 (20.7)	53 (20.4)		
Gender					
Males	72 (55.4)	69 (53.1)	141 (54.2)	0.139	0.803
Females	58 (44.6)	61 (46.9)	119 (45.8)		
Weight for age (z score)					
Normal	90 (69.2)	99 (76.1)	189 (72.7)	2.693*	0.471
Underweight	25 (19.3)	23 (17.7)	48 (18.5)		
Severely underweight	13 (10.0)	7 (5.4)	20 (7.7)		
Overweight	2 (1.5)	1 (0.8)	3 (1.1)		
Height for age (z score)					
Normal	98 (75.4)	108 (83.1)	206 (79.2)	2.342	0.311
Stunted	23 (17.7)	16 (12.3)	39(15.0)		
Severely stunted	9 (6.9)	6 (4.6)	15(5.8)		
Weight for height/length (z score)					
Normal	100 (76.9)	89 (68.4)	189 (72.7)	3.058*	0.548
Obese	12 (9.2)	17 (13.1)	29 (11.2)		
Overweight	6 (4.6)	6 (4.6)	12 (4.6)		
Moderately wasted	4 (3.1)	8 (6.2)	12 (4.6)		
Severely wasted	8 (6.2)	10 (7.7)	18 (6.9)		

*Fischer's Exact test was used; **Figures in parenthesis are percentages of column total.

3.1. Forms of Severe Malaria

Table 2 shows the forms of severe malaria among the subjects in the severe malaria group. The most frequent form of severe malaria was severe anaemia seen in 76 (58.5%) subjects while the least frequent forms were jaundice and hypoglycaemia which were seen in 12 (9.2%) and 9 (6.9%) of the subjects respectively.

3.2. Ophthalmoscopic Findings among Subjects with Uncomplicated Malaria

None of the 130 subjects with uncomplicated malaria had any ophthalmoscopic finding.

3.3. Ophthalmoscopic Findings among Subjects with Severe Malaria

Abnormal ophthalmoscopic findings were present in 23 of the 130 subjects with severe malaria giving the prevalence of malaria retinopathy as 17.7%. The most common retinopathy was retinal whitening which was present in all the 23 subjects that had retinopathy (equivalent to 17.7% of all subjects in the severe malaria group) while retinal haemorrhage was the least common, being present in 7 (5.4%) of all the subjects. Figure 1 shows the overlap of the occurrence of the different forms of retinopathy. Fourteen subjects had only vessel changes in addition to the retinal whitening while seven had retinal haemorrhage and vessel changes in addition to the retinal whitening. None had retinal haemorrhage alone while only two had retinal whitening in isolation.

3.4. Comparison of Retinopathy between Uncomplicated and Severe Malaria

Table 3 shows the comparison of retinopathy between severe and uncomplicated malaria. The occurrence of the different forms of retinopathy among subjects with severe malaria was statistically significant ($p < 0.001$ for retinal whitening, $p < 0.001$ for vessel changes, and $p = 0.007$ for retinal haemorrhages).

Table 2. Forms of severe malaria.

Form of severe malaria	Frequency (n = 130)*	Percentage (%)
Severe anaemia	76	58.5
Multiple convulsions	61	46.9
Prostration	50	38.5
Cerebral malaria	32	24.6
Haemoglobinuria	24	18.5
Metabolic acidosis	13	10.0
Jaundice	12	9.2
Hypoglycaemia	9	6.9

*Subjects had more than one form of severe malaria.

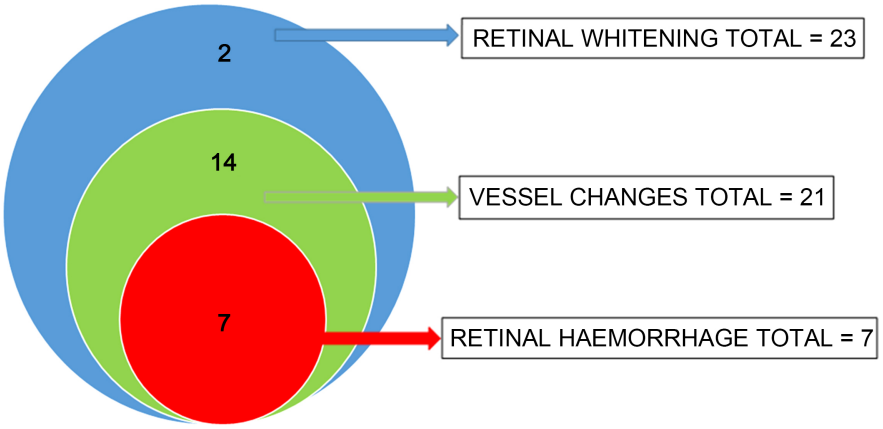

Figure 1. Stacked venn diagram showing the distribution and overlap of ophthalmoscopic findings in severe malaria.

Table 3. Ophthalmoscopic findings in children with severe malaria and uncomplicated malaria.

Ophthalmoscopic findings	Uncomplicated Malaria n = 130 (%)	Severe Malaria n = 130 (%)	Fisher's Exact test	*p*-value
Retinal whitening				
Present	0 (0.0)	23 (17.7)	25.232	<0.001
Absent	130 (100.0)	107 (82.3)		
Vessel changes				
Present	0 (0.0)	21 (16.2)	22.845	<0.001
Absent	130 (100.0)	109 (83.8)		
Retinal haemorrhages				
Present	0 (0.0)	7 (5.4)	7.194	0.007
Absent	130 (100.0)	123 (94.6)		

*Figures in parentheses are percentages of column total.

3.5. Relationship between the Forms of Severe Malaria and Occurrence of Retinal Whitening (RW)

Table 4 shows the relationship between the forms of severe malaria and presence of retinal whitening. A higher proportion of patients with cerebral malaria (43.8%), metabolic acidosis (46.2%) and hypoglycaemia (44.4%) had retinal whitening while it was less common among patients with jaundice (16.7%) and prostration (16.0%). However, the relationship between forms of severe malaria and retinal whitening was statistically significant in patients with multiple convulsions (χ^2 = 5.752; p = 0.016), cerebral malaria (χ^2 = 19.737; p = 0.001) and metabolic acidosis (χ^2 = 8.035; p = 0.005).

Table 4. Relationship between retinal whitening and forms of severe malaria.

Severe malaria		Retinal whitening		Chi-square	*p*-value
Type	Frequency	Present n = 23	Absent n = 107		
Multiple convulsion					
Yes	61 (100.0)	16 (26.2)	45 (73.8)	5.752	0.016
No	69 (100.0)	7 (10.1)	62 (89.9)		
Severe anaemia					
Yes	76 (100.0)	16 (21.1)	60 (78.9)	1.419	0.234
No	54 (100.0)	7 (13.0)	47 (87.0)		
Cerebral malaria					
Yes	32 (100.0)	14 (43.8)	18 (56.2)	19.737	0.001
No	98 (100.0)	9 (9.2)	89 (90.8)		
Prostration					
Yes	50 (100.0)	8 (16.0)	42 (84.0)	0.160	0.815
No	80 (100.0)	15 (18.8)	65 (81.2)		
Haemoglobinuria					
Yes	24 (100.0)	7 (29.2)	17 (70.8)	2.661	0.103
No	106 (100.0)	16 (15.1)	90 (84.9)		
Metabolic acidosis					
Yes	13 (100.0)	6 (46.2)	7 (53.8)	8.035	0.005
No	117 (100.0)	17 (14.5)	100 (85.5)		
Jaundice					
Yes	12 (100.0)	2 (16.7)	10 (83.3)	0.100	0.922
No	118 (100.0)	21 (17.8)	97 (82.2)		
Hypoglycaemia					
Yes	9 (100.0)	4 (44.4)	5 (55.6)	4.752	0.052
No	121 (100.0)	19 (15.7)	102 (84.3)		

3.6. Relationship between the Forms of Severe Malaria and Occurrence of Vessel Changes (VC)

Table 5 shows the relationship between the forms of severe malaria and presence of vessel changes in the retinal. A higher proportion of patients with cerebral malaria (43.8%), metabolic acidosis (46.2%) and hypoglycaemia (44.4%) had vessel changes in the retinal while it was less common among patients with

jaundice (16.7%) and prostration (14.0%). However, the relationship between forms of severe malaria and vessel change was statistically significant in patients with multiple convulsions ($\chi^2 = 8.614$; $p = 0.003$), cerebral malaria ($\chi^2 = 23.867$; $p = 0.001$), metabolic acidosis ($\chi^2 = 9.598$; $p = 0.002$), and hypoglycaemia ($\chi^2 = 5.714$; $p = 0.037$).

Table 5. Relationship between vessel changes and forms of severe malaria.

Severe malaria		Vessel changes		Chi-square	*p*-value
Type	Frequency	Present n = 21	Absent n = 109		
Multiple convulsion					
Yes	61 (100.0)	16 (26.2)	45 (73.8)	8.614	0.003
No	69 (100.0)	5 (7.2)	64 (92.8)		
Severe anaemia					
Yes	76 (100.0)	14 (18.4)	62 (81.6)	0.694	0.405
No	54 (100.0)	7 (13.0)	47 (87.0)		
Cerebral malaria					
Yes	32 (100.0)	14 (43.8)	18 (56.2)	23.867	0.001
No	98 (100.0)	7 (7.1)	91 (92.9)		
Prostration					
Yes	50 (100.0)	7 (14.0)	43 (86.0)	0.278	0.598
No	80 (100.0)	14 (17.5)	66 (82.5)		
Haemoglobinuria					
Yes	24 (100.0)	7 (29.2)	17 (70.8)	3.680	0.055
No	106 (100.0)	14 (13.2)	92 (86.8)		
Metabolic acidosis					
Yes	13 (100.0)	6 (46.2)	7 (53.8)	9.598	0.002
No	117 (100.0)	15 (12.8)	102(87.2)		
Jaundice					
Yes	12 (100.0)	2 (16.7)	10 (83.3)	0.003	0.960
No	118 (100.0)	19 (16.1)	99 (83.9)		
Hypoglycaemia					
Yes	9 (100.0)	4 (44.4)	5 (55.6)	5.714	0.037
No	121 (100.0)	17 (14.1)	104 (85.9)		

*Figures in parentheses are percentages of total along the row.

3.7. Relationship between the Forms of Severe Malaria and Occurrence of Retinal Haemorrhages (RH)

Table 6 revealed the relationship between the forms of severe malaria and presence of retinal haemorrhages. Retinal haemorrhage was mostly seen among patients with cerebral malaria (21.9%), jaundice (16.7%), and haemoglobinuria

Table 6. Relationship between retinal haemorrhage and forms of severe malaria.

Severe malaria		Retinal haemorrhage		Chi-square	*p*-value
Type	Frequency	Present n = 7	Absent n = 123		
Multiple convulsion					
Yes	61 (100.0)	7 (11.5)	54 (88.5)	8.369	0.004
No	69 (100.0)	0 (00.0)	69 (100.0)		
Severe anaemia					
Yes	76 (100.0)	4 (5.3)	72 (94.7)	0.005	0.942
No	54 (100.0)	3 (5.6)	51 (94.4)		
Cerebral malaria					
Yes	32 (100.0)	7 (21.9)	25 (78.1)	22.658	0.001
No	98 (100.0)	0 (00.0)	98 (100)		
Prostration					
Yes	50 (100.0)	1 (2.0)	49 (98.0)	1.827	0.176
No	80 (100.0)	6 (7.5)	74 (92.5)		
Haemoglobinuria					
Yes	24 (100.0)	4 (16.7)	20 (83.3)	7.354	0.022
No	106 (100.0)	3 (2.8)	103 (97.2)		
Metabolic acidosis					
Yes	13 (100.0)	2 (15.4)	11 (84.6)	2.835	0.092
No	117 (100.0)	5 (4.3)	112 (95.7)		
Jaundice					
Yes	12 (100.0)	2 (16.7)	10 (83.3)	3.303	0.690
No	118 (100.0)	5 (4.2)	113 (95.8)		
Hypoglycaemia					
Yes	9 (100.0)	1 (11.1)	8 (88.9)	0.622	0.402
No	121 (100.0)	6 (5.0)	115 (95.0)		

*Figures in parentheses are percentages of total along the row.

(16.7%) while it was barely seen among patients with prostration (2.0%). However, the relationship between forms of severe malaria and retinal haemorrhage was statistically significant in patients with multiple convulsions (χ^2 = 8.369; p = 0.004), cerebral malaria (χ^2 = 22.658; p = 0.001), and haemoglobinuria (χ^2 = 7.354; p = 0.022).

3.8. Association between Retinal Whitening, Vessel Changes, Retinal Haemorrhages and the Forms of Severe Malaria Using Multivariate Analysis

Table 7 shows the association between retinal whitening, vessel changes, retinal haemorrhages and the forms of severe malaria using multivariate analysis. Cerebral malaria was found to be an independent predictor of retinal whitening (OR = 7.7, p = 0.004, 95% CI = 0.019 - 0.475) and vessel changes (OR = 10.1, p = 0.008, 95% CI = 0.022 - 5.71) while haemoglobinuria was an independent predictor of retinal haemorrhages (OR = 6.9, p = 0.007, 95% CI = 0.003 - 0.380). The odds of patient with cerebral malaria developing retinal whitening is about eight times other forms of sever malaria and 10 times in having vessel changes. Children with haemoglobinuria have an odd of seven times other forms of severe malaria in developing retinal haemorrhages.

Table 7. Association between retinal whitening, vessel changes, retinal haemorrhages and the forms of severe malaria using multivariate analysis.

Severe malaria	Coefficient of regression	Standard Error (S.E)	Exp (B)	*p*-value	Odd ratio	95% *CI	
						Lower	Upper
Retinal Whitening							
Metabolic acidosis	−0.326	0.836	0.722	0.697	5.042	0.140	3.717
Cerebral malaria	−2.341	0.815	0.096	0.004	7.691	0.019	0.475
Multiple convulsions	0.451	0.837	1.570	0.590	3.149	0.304	8.107
Vessel Changes							
Cerebral malaria	−2.181	0.827	0.113	0.008	10.111	0.022	0.571
Multiple convulsions	−0.044	0.875	0.957	0.960	4.551	0.172	5.318
Hypoglycaemia	1.089	0.828	2.970	0.189	0.502	0.586	15.056
Retinal haemorrhage							
Multiple convulsions	−0.976	8036.266	0.377	1.000		0.000	
Cerebral malaria	−20.075	6779.795	0.000	0.998		0.000	
Haemoglobinuria	−3.466	1.118	0.031	0.007	6.867	0.003	0.380

*CI = Confidence interval.

4. Outcome

Three (2.3%) subjects died among the severe malaria group during the course of the study of which one (0.8%) had cerebral malaria while two (1.5%) had severe anaemia. One of the severe anaemia subjects had retinal whitening (0.8%) while the remaining two had no retinopathy. All three subjects died within 24 hours of hospital presentation.

None of the twenty three subjects with malaria retinopathy had resolution at 24 hours of treatment while eighteen (78.3%) had resolution at 48 hours of admission. The remaining five (21.7%) were discharged home with retinopathy but were lost to follow-up.

5. Discussion

This study was undertaken to identify and compare malaria retinopathy in different forms of severe malaria and uncomplicated malaria as well as to determine the factors associated with the occurrence of malaria retinopathy.

None of the children with uncomplicated malaria in this study had malaria retinopathy. While studies on malaria retinopathy in severe malaria abound, there are only a few available studies of the phenomenon in uncomplicated malaria. Maude *et al.* [27] in a study in Bangladesh reported a prevalence of 12% among uncomplicated malaria and the forms of malaria retinopathy were retinal whitenings and vessel changes [27]. The reason for the difference in the prevalence of retinopathy in uncomplicated malaria in the present study could be due to the age differences of the subjects of the studies. The current study focused on children below five years while the other study was done among adults. Similarly, the utilization of the indirect ophthalmoscopy method supplemented by a fundus camera that was used by Maude *et al.* [27] which has a better sensitivity in identifying the mildest form of retinopathy could also have accounted for the very high prevalence that was reported in that study. Nevertheless, this current study has further demonstrated that malaria retinopathy is almost exclusive to severe malaria hence; its presence should heighten the alertness of the clinician for early and appropriate interventions.

The prevalence of malaria retinopathy among children with severe malaria in this study was 17.7%. This prevalence was lower than the 37% reported by Mohammed *et al.* [28] in Kano, Nigeria; and 73% reported by Essuman *et al.* [19] in Ghana. The lower prevalence observed in the current study could be attributed to the diversity in the forms of severe malaria that constituted the study population. While the three earlier studies focused predominantly on cerebral malaria and severe anaemia which have been more consistently associated with malaria retinopathy the current study included other forms of severe malaria which were less associated with retinopathy. This may thus have a dilutional effect on the observed prevalence. In addition, the use of direct ophthalmoscopy in this study as against indirect ophthalmoscopy or a combination of both (which has a higher sensitivity) used in the earlier studies could also have contributed to the re-

ported lower prevalence. Although indirect ophthalmoscopy would be more desirable for better accuracy it is not practicable for routine bedside clinical practice and also not readily available in resource-poor settings including the site of the current study.

Retinal whitening was the most common form of retinopathy observed in the current study while retinal haemorrhage was the least common. This pattern is similar to what has been observed previously by Beare *et al.* [16] and Essuman *et al.* [19] who documented that retinal whitening was the most frequent form of retinopathy. This was further corroborated by the finding of cytoadherence erythrocytes within the retinal vessels of subjects who had retinal whitening as well as the predominance of receptors within the retina which allows for attachment of the parasite [29]. It is important to note that the prevalence of retinal whitening though, the highest among the other forms of retinopathy in the current study is much lower compared to those earlier reported by Essuman *et al.* [19] and Beare *et al.* [16] in studies where fundoscopy was done by the ophthalmologist using indirect ophthalmoscopy method which are factors that could independently or jointly increase the sensitivity of the fundoscopy.

The current study has been able to identify that malaria retinopathy does not only occur in cerebral malaria as it was observed in children with other forms of severe malaria. It was however observed that malaria retinopathy was more significantly associated with cerebral malaria, metabolic acidosis, multiple convulsions, and haemoglobinuria. Being the most lethal form of severe malaria, cerebral malaria retinopathy has received the greatest attention. Studies on cerebral malaria have observed a high prevalence of retinopathy ranging between 44% - 73%. Oluwayemi *et al.* [18] reported a prevalence of 44.0% in Ekiti, Essuman *et al.* [19] reported 73% in Ghana, while Beare *et al.* [26] and Burton *et al.* [30] reported 61% and 66.7% respectively. In the same vein, cerebral malaria retinopathy prevalence in the current study was 43.8%, half of whom had retinal haemorrhages. Examination of the fundus should therefore be considered important when cerebral malaria is being suspected in a child as the presence of retinopathy could support the diagnosis. In this study, the prevalence of malaria retinopathy was significantly high among subjects with cerebral malaria, similar to what has been observed in other studies [19] [26] [30]. The pathogenesis and pathologic changes of retinopathy although, not completely understood have been said to be similar to those that occur in the brain in cerebral malaria while receptors responsible for attachment and cytoadherence of the *Plasmodium* species are said to be equally predominant in the brain and retina [14]. It is therefore not unexpected that cerebral malaria will be more associated with retinopathy than other non-cerebral forms of severe malaria.

While the overall prevalence of retinal haemorrhage in this study was 5.4%, it was significantly more common among those with cerebral malaria, multiple convulsions, and heamoglobinuria. The 21.9% prevalence of retinal haemorrhages in cerebral malaria was similar to the 23.3% that was reported by Olumese

et al. [31] in Ibadan. Both studies were carried out among children of similar age groups within the same geographical location and using a similar method of fundoscopy. Mohammed *et al.* [28] and Oluwayemi *et al.* [18] however, documented a very low prevalence of retinal haemorrhage in children with cerebral malaria in Ekiti and Kano states of Nigeria respectively, while the prevalences reported by Beare *et al.* [16] and Essuman *et al.* [19] were almost double that of the current study. Rather than just attributing this difference to geographical location or method of fundoscopy, a more detailed multicentre study involving ophthalmologists might be useful to further highlight the relationship of retinal haemorrhage to cerebral malaria.

In keeping with previous studies [19] [26], it was noted in the current study that all the observed types of malaria retinopathy were significantly associated with the two forms of severe malaria that affect the brain (cerebral malaria and multiple convulsions). This further provides evidence that retinopathy is more associated with certain forms of severe malaria especially those with pathologic changes within the brain. Some authors have further documented the usefulness of malaria retinopathy in prognosticating cerebral malaria [16] [17]. Beyond this, however, this study documented an association between retinal whitening and metabolic acidosis similar to the findings of Maude *et al.* [27] between vessel changes and hypoglycaemia as well as between retinal haemorrhage and haemoglobinuria. This indicates that retinopathy is not limited to cerebral malaria.

To the best of our knowledge, the association of haemoglobinuria and hypoglycaemia with malaria retinopathy has not been reported previously. Metabolic acidosis causes endothelial dysfunction and hence affects vascular integrity [32]. This may increase the risk for ischaemia, localised tissue hypoxia, and haemorrhage leading to retinopathy [27]. With increased intravascular haemolysis resulting in haemoglobinuria, the free serum haemoglobin scavenges nitric oxide which is a potent vasodilator [33]. This decreased nitric oxide may predispose to ischaemia of the retina. Also, free haemoglobin has been shown to cause oxidative damage by lipid peroxidation and loss of vascular integrity. This predisposes to vasoconstriction, and thus possibly contributes to retinopathy [34]. Therefore, it is prudent that all children with severe malaria be examined for retinopathy. A longitudinal study of patients with these other forms of severe malaria who have retinopathy may be desirable. This will assist in determining the prognostic values of retinopathy in them just as has been severally done for cerebral malaria.

It is noteworthy that despite being the most common form of severe malaria in this study, there was no significant association between severe anaemia and any form of malaria retinopathy. This was contrary to the observation of Beare *et al.* [16] in Malawi and Essuman *et al.* [19] in Ghana who found a significant association between malaria retinopathy and severe anaemia. The exact reason for the difference is unknown. However, the retinopathy associated with severe anaemia in malaria has been described as being mild, which is best detected by the more sensitive indirect ophthalmoscopy used by the authors compared to

the direct ophthalmoscopy used in the present study [16] [19]. Although, there was no direct significant association between retinal haemorrhage and severe anaemia on one hand, the importance of the presence of retinal haemorrhage in severe anemia as a possible indicator of severe haemolysis could be observed in this study. The only four subjects who had retinal haemorrhage among a large number of subjects with severe anaemia were the same as the only four who had retinal haemorrhage among the few with haemoglobinuria which showed significant association. This suggests that the presence of retinal haemorrhages could serve as an indicator of massive haemolysis with subsequent haemoglobinuria (and the possibility of kidney injuries from the toxic effects of haemoglobin contact with the renal tubules) which therefore calls for closer attention when found. A longitudinal study to further document the presence of such a relationship is however advocated.

The limitation of this study was the inability to perform post-mortems for patients that died because of the refusal to give consent and aversion by the pathologists to conduct post-mortems due to the Corona Virus pandemic. Post-mortem is the confirmatory test to diagnose cerebral malaria.

6. Conclusion

In conclusion, the current study showed the presence of retinopathy in all forms of severe malaria and was not limited to cerebral malaria as speculated by other studies; it also revealed that cerebral malaria and haemoglobinuria were predictors of retinopathy. This, therefore, calls for routine fundoscopic examination in all children with severe malaria and the need for ophthalmoscopic examination training for all health care workers.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Pinault, L.L. and Hunter, F.F. (2011) New Highland Distribution Records of Multiple Anopheles Species in the Ecuadorian Andes. *Malaria Journal*, **10**, 238-243. https://doi.org/10.1186/1475-2875-10-236

[2] Tedrow, R.E., Rakotomanga, T., Nepomichene, T., Howes, R.E., Ratovonjato, J., Ratsimbasoa, A.C., *et al.* (2019) *Anopheles* Mosquito Surveillance in Madagascar Reveals Multiple Blood Feeding Behavior and *Plasmodium* Infection. *PLOS Neglected Tropical Diseases*, **13**, e0007176. https://doi.org/10.1371/journal.pntd.0007176

[3] Crawley, J., Chu, C., Nosten, F. and Mtove, G. (2010) Malaria in Children. *The Lancet*, **375**, 1468-1481. https://doi.org/10.1016/S0140-6736(10)60447-3

[4] World Health Organization (2020) World Malaria Report 2020: 20 Years of Global Progress and Challenges. World Health Organization, Geneva. https://apps.who.int/iris/handle/10665/337660

[5] WHO Malaria Policy Advisory Committee and Secretariat (2016) Malaria Policy

Advisory Committee to the WHO: Conclusions and Recommendations of Eighth Biannual Meeting. *Malaria Journal*, **15**, Article No. 117. https://doi.org/10.1186/s12936-016-1169-x

[6] World Health Organization. Fact Sheet on Malaria 2022. https://www.who.int/news-room/fact-sheets/detail/malaria

[7] Mwangome, M.K. and Berkley, J.A. (2014) The Reliability of Weight-for-Length/ Height Z Scores in Children. *Maternal & Child Nutrition*, **10**, 474-480. https://doi.org/10.1111/mcn.12124

[8] World Health Organization (2015) Guidelines for the Treatment of Malaria. 3rd Edition, WHO Press, Geneva. https://apps.who.int/iris/handle/10665/162441

[9] Mishra, S. (2012) Update on Management of Severe Malaria. *International Journal of Infectious Diseases*, **16**, e43-e44. https://doi.org/10.1016/j.ijid.2012.05.110

[10] Ogah, A.O., Ezeonwumelu, J.O.C., Okoruwa, A.G., Adiukwu, C.P., Ajayi, A.M. and Akib, S.S. (2013) Manifestations of Severe Malaria among the under-Five Children Attending Kampala International University Teaching Hospital, Bushenyi, Western Uganda: Pilot Study. *British Journal of Pharmacology and Toxicology*, **4**, 128-135. https://doi.org/10.19026/bjpt.4.5390

[11] Gbotosho, G.O., Okuboyejo, T.M., Happi, C.T. and Sowunmi, A. (2011) *Plasmodium falciparum* Hyperparasitaemia in Nigerian Children: Epidemiology, Clinical Characteristics, and Therapeutic Responses to Oral Artemisinin-Based Combination Treatments. *Asian Pacific Journal of Tropical Disease*, **1**, 85-93. https://doi.org/10.1016/S2222-1808(11)60043-1

[12] Edelu, B.O., Ndu, I.K., Igbokwe, O.O. and Iloh, O.N. (2018) Severe Falciparum Malaria in Children in Enugu, South East Nigeria. *Nigerian Journal of Clinical Practice*, **21**, 1349-1355.

[13] (2014) Severe Malaria. *Tropical Medicine & International Health*, **19**, 7-131. https://doi.org/10.1111/tmi.12313_2

[14] MacCormick, I.J.C., Beare, N.A.V., Taylor, T.E., Barrera, V., White, V.A., Hiscott, P., *et al.* (2014) Cerebral Malaria in Children: Using the Retina to Study the Brain. *Brain*, **137**, 2119-2142. https://doi.org/10.1093/brain/awu001

[15] Bruneel, F. (2019) Human Cerebral Malaria: 2019 Mini Review. *Revue Neurologique*, **175**, 445-450. https://doi.org/10.1016/j.neurol.2019.07.008

[16] Beare, N.A., Southern, C., Chalira, C., Taylor, T.E., Molyneux, M.E. and Harding, S.P. (2004) Prognostic Significance and Course of Retinopathy in Children with Severe Malaria. *Archives of Ophthalmology*, **122**, 1141-1147. https://doi.org/10.1001/archopht.122.8.1141

[17] Singh, J., Verma, R., Tiwari, A., Mishra, D. and Singh, H.P. (2016) Retinopathy as a Prognostic Marker in Cerebral Malaria. *Indian Pediatrics*, **53**, 315-317. https://doi.org/10.1007/s13312-016-0844-x

[18] Oluwayemi, O.I., Brown, B.J., Oyedeji, O.A., Adegoke, S.A., Adebami, O.J. and Oyedeji, G.A. (2013) Clinical and Laboratory Predictors of Outcome in Cerebral Malaria in Suburban Nigeria. *The Journal of Infection in Developing Countries*, **7**, 600-607. https://doi.org/10.3855/jidc.2769

[19] Essuman, V.A., Ntim-Amponsah, C.T., Astrup, B.S., Adjei, G.O., Kurtzhals, J.A., Ndanu, T.A., *et al.* (2010) Retinopathy in Severe Malaria in Ghanaian Children-Overlap between Fundus Changes in Cerebral and Non-Cerebral Malaria. *Malaria Journal*, **9**, 232-242. https://doi.org/10.1186/1475-2875-9-232

[20] Maude, R.J., Dondorp, A.M., Abu-Sayeed, A., Day, N.P., White, N.J. and Beare, N.A. (2009) The Eye in Cerebral Malaria: What Can It Teach Us? *Transactions of*

the Royal Society of Tropical Medicine and Hygiene, **103**, 661-664. https://doi.org/10.1016/j.trstmh.2008.11.003

[21] Harding, S.P., Lewallen, S., Beare, N.A.V., Smith, A., Taylor, T.E. and Molyneux, M.E. (2006) Classifying and Grading Retinal Signs in Severe Malaria. *Tropical Doctor*, **36**, 1-13. https://doi.org/10.1258/004947506776315781

[22] National Population Commission (NPC) and ICF (2019) Nigeria Demographic and Health Survey 2018. NPC and ICF, Abuja and Rockville. https://dhsprogram.com/pubs/pdf/FR359/FR359.pdf

[23] Oyinloye, M.A. (2013) Using GIS and Remote Sensing in Urban Waste Disposal and Management: A Focus on Owo L.G.A, Ondo State, Nigeria. *European International Journal of Science and Technology*, **2**, 106-118.

[24] Charan, J. and Biswas, T. (2013) How to Calculate Sample Size for Different Study Designs in Medical Research? *Indian Journal of Psychological Medicine*, **35**, 121-126. https://doi.org/10.4103/0253-7176.116232

[25] Ogunlesi, T.A., Dedeke, I.O. and Kuponiyi, O.T. (2008) Socio-Economic Classification of Children Attending Specialist Paediatric Centres in Ogun State, Nigeria. *Nigerian Medical Practitioner*, **54**, 21-25. https://doi.org/10.4314/nmp.v54i1.28943

[26] Beare, N.A.V., Taylor, T.E., Harding, S.P., Lewallen, S. and Molyneux, M.E. (2006) Malarial Retinopathy: A Newly Established Diagnostic Sign in Severe Malaria. *The American Journal of Tropical Medicine and Hygiene*, **75**, 790-797. https://doi.org/10.4269/ajtmh.2006.75.790

[27] Maude, R.J., Beare, N.A.V., Sayeed, A.A., Chang, C.C., Charunwatthana, P., Faiz, M.A., *et al.* (2009) The Spectrum of Retinopathy in Adults with Plasmodium Falciparum Malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **103**, 665-671. https://doi.org/10.1016/j.trstmh.2009.03.001

[28] Mohammed, I., Ibrahim, U.Y., Mukhtar, M., Farouq, Z., Obiagwu, P.N. and Yashua, A.H. (2010) Malarial Retinopathy in Northern Nigerian Children. *Tropical Doctor*, **40**, 50-52 https://doi.org/10.1258/td.2009.080420

[29] Storm, J. and Craig, A.G. (2014) Pathogenesis of Cerebral Malaria-Inflammation and Cytoadherence. *Frontiers in Cellular and Infection Microbiology*, **4**, Article 100. https://doi.org/10.3389/fcimb.2014.00100

[30] Burton, M., Nyong'O, O., Burton, K., John, W., Inkoom, E., Pinder, M., *et al.* (2004) Retinopathy in Gambian Children Admitted to Hospital with Malaria. *Tropical Doctor*, **34**, 214-218. https://doi.org/10.1177/004947550403400409

[31] Olumese, P.E., Adeyemo, A.A., Ademowo, O.G., Gbadegesin, R.A., Sodeinde, O. and Walker, O. (1997) The Clinical Manifestations of Cerebral Malaria among Nigerian Children with the Sickle Cell Trait. *Annals of Tropical Paediatrics*, **17**, 141-145. https://doi.org/10.1080/02724936.1997.11747877

[32] Govindasamy, G., Barbe,r B.E., Ghani, S.A., William, T., Grigg, M.J., Borooah, S., *et al.* (2016) Retinal Changes in Uncomplicated and Severe Plasmodium Knowlesi Malaria. *The Journal of Infectious Diseases*, **213**, 1476-1482. https://doi.org/10.1093/infdis/jiv746

[33] de Jesus Trovoada, M., Martins, M., Mansour, R.B., do Rosário Sambo, M., Fernandes, A.B., Gonçalves, L.A., *et al.* (2014) NOS2 Variants Reveal a Dual Genetic Control of Nitric Oxide Levels, Susceptibility to Plasmodium Infection, and Cerebral Malaria. *Infection and Immunity*, **82**, 1287-1295. https://doi.org/10.1128/IAI.01070-13

[34] Barber, B.E., Grigg, M.J., William, T., Yeo, T.W. and Anstey, N.M. (2016) Intravascular Haemolysis with Haemoglobinuria in a Splenectomized Patient with Severe *Plasmodium knowlesi* Malaria. *Malaria Journal*, **15**, 203-210. https://doi.org/10.1186/s12936-016-1514-0