CORRELATION BETWEEN MALARIAL RETINOPATHY AND DIAGNOSIS OF CEREBRAL MALARIA IN COMATOSE CHILDREN ADMITTED AT WEBUYE SUB COUNTY HOSPITAL

BY

DR JAMES ODUOR OTIENO

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DECLARATION

I declare that this is my original work done in partial fulfilment leading to the award of Masters in Medicine, Family Medicine. This work has not been presented for a degree in any other university.

DR. OTIENO, James Oduor _____

Family Medicine Resident

SM/PGFM/04/11

SUPERVISORS

This thesis has been presented to Moi University with approval of my supervisors

Dr. Janice Armstrong _____

Lecturer, Family Medicine Department,

School of Medicine, Moi University.

Dr. James Cheruiyot Bett _____

Ophthalmologist, Eye unit,

Moi Teaching and Referral Hospital,

Eldoret.

DEDICATION

I dedicate this work to all the children who suffer from malaria especially in sub Saharan Africa particularly those with cerebral malaria.

ABSTRACT

Background: Malaria is a common cause of morbidity in children. Cerebral malaria accounts for more than half of the children admitted in coma. In malaria endemic areas, parasitemia in a child with coma may not necessarily mean that cerebral malaria is the cause of the coma. Malarial retinopathy, detected by fundoscopy, is a "signature" of malaria that can confirm if malaria is the cause of coma(Koram K.A and Molyneux M.E, 2007).

Objective: To identify the retinal findings of children admitted with coma at Webuye sub county Hospital and describe their clinical associations.

Study design and methodology: The study was carried out at Webuye sub county hospital. Children aged 9 months to 12 years admitted to Paediatrics ward in coma were recruited into the study after guardians gave written informed consent. The study design was cross sectional. Direct fundoscopy was done within 24 hours of admission after application of tropicamide 1%. The researchers doing fundoscopy were blinded to laboratory results of the children. Laboratory work up included blood slide for malaria parasites (Bs for Mps), cerebrospinal fluid analysis, random blood sugar, sickling test, and complete blood count. The Bs for Mps slides were re-read by another microscopist. Children were treated according to WHO and Ministry of Health protocols. Data was collected using pretested interviewer administered questionnaire, entered into EPi-info v 10, cleaned and then exported to STATA v 10 where analysis was done using Fisher's exact test. Descriptive statistics were used for continuous data while frequency listings were used for categorical variables. Results were considered significant at 0.05 α-level.

Results: 51 comatose children were studied of whom 72.6% were males. Their median age was 5 years (IQR 3, 6). The mean temperature at admission was 38.0^0C. On fundoscopy, 33.3% of the children had normal retinal findings, 45.1% had retinal whitening, 25.5% had retinal haemorrhages, 13.7% had vessel changes, and 3.9% had papilledema while 3.9% had optic atrophy. Of the children with cerebral malaria, 69.5% had malaria retinopathy. Having malaria retinopathy correlated with laboratory diagnosis of malaria (p=0.005) and a final diagnosis of cerebral malaria (p=0.011). However, there was no correlation between malaria retinopathy and duration of coma (p=0.441) even though coma took longer to resolve in those who had malaria retinopathy. More children without retinopathy made complete recovery without obvious neurological sequalae (94.6% as compared to 81.3% in those with retinopathy). This rate of recovery however was not statistically significant (p=0.178). More children with retinopathy (18.8%) died as compared to those without retinopathy (5.3%). This was not statistically significant (p=0.178).

Conclusions: Malaria retinopathy occurs in 69.5% of children with cerebral malaria. There was correlation between laboratory diagnosis of cerebral malaria and malaria retinopathy.

Recommendation: There should be training for general clinicians to increase the use of direct fundoscopy to assist in diagnosis of malaria in children admitted in coma in malaria endemic area. The use of fundoscopy should be irrespective of their malaria parasitemic status.

Limitation: No indirect fundoscopy was done in this study that could lead to missing of retinal signs in the peripheral retina.

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LIST OF ABBREVIATIONS

WHO – World Health Organization

RDT – Rapid diagnostic test

Bs for mps – Blood slide for malaria parasites

LP – Lumbar puncture

CM – Cerebral Malaria

Non CM – Non cerebral malaria

NTC – Non Traumatic Coma

ABM – Acute Bacterial Meningitis

DEFINITION OF TERMS

Cerebral Malaria - a deep level of unconsciousness (inability to localize a painful stimulus 1hour in children post convulsion) in the presence of a *P.falciparum* asexual parasitaemia, after the correction of hypoglycemia and exclusion of other encephalopathies, especially bacterial meningitis and locally prevalent viral encephalitides(WHO).

Child – any patient who qualifies to be admitted to Pediatric Ward. In our hospital this is up to age 12 years.

Comatose Child – Any child presenting with Blantyre coma scale score of 2 or less; also any child with "P" or "U" on AVPU coma scale (WHO).

A positive laboratory diagnosis of malaria – identification of asexual forms in thick film done according to national guidelines.

Child with malaria retinopathy – any child with either 1 or more of the malaria retinopathy features: retinal whitening, retinal hemorrhages and vessel changes.

Delayed development – A chronological delay in the appearance of normal developmental milestones achieved during infancy and early childhood, caused by organic, psychological, or environmental factors (The American Heritage® Medical dictionary)

1 INTRODUCTION

1.1 BACKGROUND

Malaria is a common and potentially fatal protozoan infection in tropical areas. It affects three billion people and causes one to three million deaths annually. Its burden has been decreasing over the years under the roll back malaria campaigns. In Sub Saharan Africa, the prevalence rate of *Plasmodium falciparum* in children aged 2years to 10 years has decreased from 37%(1985-1997) to 17%(2000-2007)[1]. In 2010, there were approximately 216 million malaria episodes, of which 81% were in Africa. Malaria accounted for 655,000 deaths, of which 91% were in Africa. Globally in 2010, 86% of malarial deaths occurred in children less than 5 years of age[2]. Though globally malaria specific mortality has decreased by 26%, in Kenya it is still one of the leading causes of morbidity and mortality, particularly in children[2, 3, 4]. *Plasmodium falciparum* is responsible for most morbidity and mortality, with cerebral malaria being one of its serious morbidities.

Altered level of consciousness is a common feature of many different conditions. Non traumatic coma (NTC) is a common cause of morbidity and mortality in children. In a study of Iranian children, NTC accounts for 10-15% of all hospital admissions[5]. In a Kilifi study, NTC has decreased from 4.6% in 2004 to 3% in 2009[6]. Malaria contributes up to 40% of pediatric admissions in parts of Sub Saharan Africa with 10% of these being cerebral malaria (CM) [7]. In the Kilifi study above, 59% of all children admitted comatose had malarial parasitemia[6].

The study site is a malaria endemic area[3]. In such areas reliably establishing parasitemia for diagnosis of malaria can be difficult[9]. This is because in malaria endemic area,

parasitemia can be incidental to other concurrent disease[10, 11]. In addition, the clinical signs of severe malaria and other serious infectious diseases such as pneumonia, meningitis and other causes of coma, overlap and this can lead to failure to treat some of these life threatening diseases[1, 9, 12, 13]. Failure to treat other causes of fevers leads to higher mortality and morbidity as shown by studies which showed higher case fatality rates among non-malaria fevers compared to malaria fevers[1]. In areas of high transmission, the prevalence of asymptomatic parasitemia in the population may be as high as 40–70%[10.] In Coast province, Kenya, it was found to be 30% in one survey (Mwangi et. al, 2005)[4]. Therefore, parasitemia in a critically ill patient is insufficient basis for the diagnosis of severe malaria in disease-endemic areas.

Malarial retinopathy has been suggested as adjunct in diagnosis of malaria[13, 14, 15]. It has been described in literature as the "signature" that can be used with confidence to identify if malaria is the cause, rather than, an irrelevant accompaniment of an illness[13]. Severe retinopathy is highly specific for cerebral malaria (93%) [16, 17]. A study among Bangladeshi adults found that 85% of those with cerebral malaria had malarial retinopathy[16]. Studies among Malawian and Ghanaian children with cerebral malaria show that 61% to 73% of them had malarial retinopathy[9, 18]. In Kenyan children, retinal opacification is associated with higher parasite count while white centered retinal hemorrhages are significantly associated with higher parasite count[19].

The changes in malarial retinopathy can be detected by general clinicians using direct ophthalmoscopy after training[20]. Compared to indirect fundoscopy, direct fundoscopy had sensitivity of 94% and specificity of 100% for malaria retinopathy[17]. The weighted kappa values for retinal signs of malaria retinopathy indicate a high degree of inter-observer agreement in identification and grading of the signs[21]. The detection of malarial

retinopathy (especially retinal whitening and vascular changes) could therefore be a useful diagnostic tool for the clinician to confirm the diagnosis of severe malaria, particularly in a comatose parasitaemic child[12, 14, 20]. The severity of retinopathy (number of retinal hemorrhages) and papilledema may also be useful in predicting the likelihood of death in cerebral malaria[12]. Specifically, it has been suggested that ophthalmoscopy may be the most specific diagnostic tool[10], calling for widespread use in general practice. Malarial retinopathy has some predictive value on prognosis of malaria diseases. A study in Malawi found that malarial retinopathy was better than any other clinical or laboratory feature in distinguishing malarial from non-malarial coma[10].

The current Kenya guidelines on management of suspected severe malaria cases require laboratory confirmation of malaria[3, 22]. It further requires that if Rapid diagnostic tests (RDT) are negative or three blood slides for malaria taken 8hours apart are negative, then alternative cause of illness be sought. The use of malarial retinopathy could be of use in such a situation[1, 13]

Malarial retinopathy is characterized by retinal whitening, vessel changes and /or hemorrhages[14, 23, 26]. The first two are specific to malaria and are not seen in other ocular or systemic condition[10]. Papilledema may accompany any of these features when they are severe but when present without the other findings it is not specific[23]. The figure below illustrates malaria retinopathy:

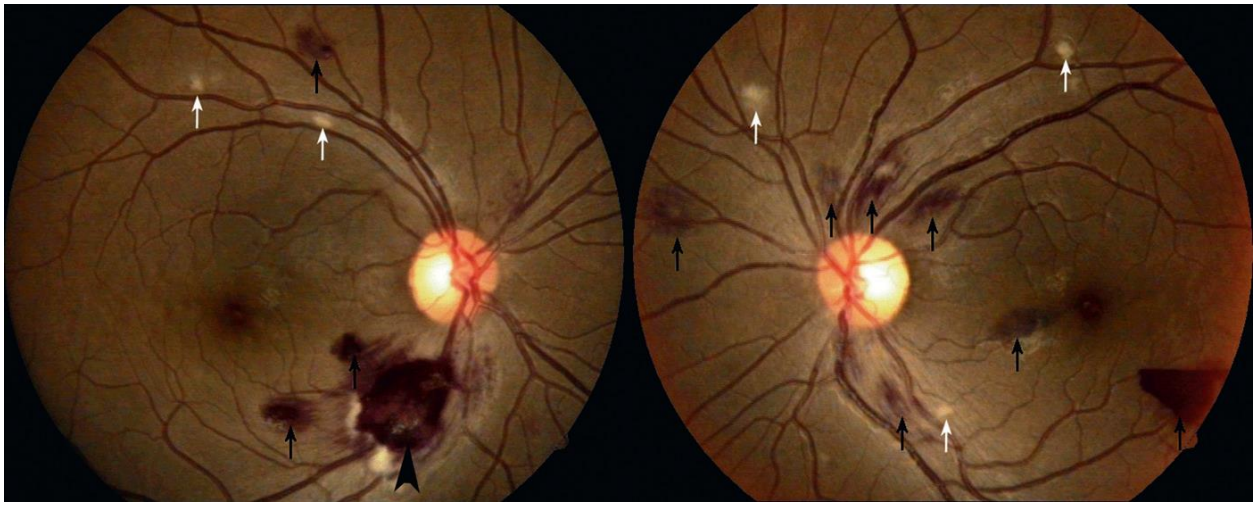

Figure 1: Fundus photographs of a patient with severe malaria showing a large white-centred haemorrhage (big black arrow), scattered patches of retinal whitening (white arrows), and haemorrhages (black arrows) in the right eye and patches of retinal whitening in the left eye.

1.2 PROBLEM STATEMENT

In malaria endemic areas, reliably establishing diagnosis of malaria is difficult because clinical signs of malaria overlap with other childhood illness while parasitemia can be incidental in these children to other concurrent illness[9, 10, 11]. Therefore, parasitemia alone in a critically ill patient is insufficient basis for the diagnosis of severe malaria in disease-endemic areas. In addition, failure to treat other causes of fevers leads to higher mortality and morbidity as shown by studies which showed higher case fatality rates among non malaria fevers compared to malaria fevers[1]. Furthermore, malarial infections range from asymptomatic parasitemia to rapid death[23]. Malarial retinopathy, detected by fundoscopy, has been suggested as adjunct for diagnosing and predicting the prognosis of cerebral malaria[13, 14, 15].

1.3 JUSTIFICATION OF THE STUDY

There is a global concerted effort to battle malaria which is a major public health problem. This will help in achieving millennium development goal number four: reduce child mortality. Coverage of at risk population with malaria prevention measures needs to be synergized with detection and treatment of malaria cases[2, 22]. Difficulty, however, arises in malaria endemic areas where a critically ill client with a positive diagnostic test does not necessarily have severe malaria[9, 10, 11]. This study will evaluate if fundoscopy done in our setting can detect malarial retinopathy in such children to ascertain if malaria is the cause of severe illness.

Furthermore, there are currently no studies evaluating the usefulness of malarial retinopathy in Webuye region in management of severely ill child.

1.4 RESEARCH QUESTION

In children admitted at Webuye sub county Hospital comatose, what are their fundoscopic findings and can these findings assist in diagnosis of cerebral malaria and predict treatment outcome in patients with cerebral malaria?

1.5 OBJECTIVES

1.5.1 BROAD

1. To identify the retinal findings of children admitted with coma at Webuye sub county Hospital and describe their clinical significance.

1.5.2 SPECIFIC

I. To describe the retinal findings of children admitted with coma at Webuye sub county Hospital.

II. To determine the frequency with which these findings meet the criteria for malarial retinopathy.

III. To correlate the presence of malarial retinopathy changes with laboratory diagnosis of cerebral malaria.

IV. To describe the correlation between malarial retinopathy with

   a. Time required for coma to resolve,
   b. Complete recovery without neurological sequelae at time of discharge.
   c. Complete recovery but with residual neurological deficit at time of discharge,
   d. Discharge outcomes: alive or dead.

2 LITERATURE REVIEW

Malaria affects infants from the age of four months as immunity acquired from mother decreases. It affects about 5% of world's population at any time[24]. It is transmitted by bite of an infected female anopheles mosquito. There are four species that cause infection – *Plasmodium falciparum, Plasmodium malarieae, Plasmodium vivax, Plasmodium ovale*; *Plasmodium falciparum* is common in Kenya and causes most morbidity and mortality[3]. Malaria occurs throughout most of tropical world. In Africa *Plasmodium falciparum* predominates; *Plasmodium malariae* is found in most endemic areas especially throughout sub Saharan Africa but is much less common.

Pathology associated with all malarial species is related to the rupture of infected erythrocytes, release of parasite material and metabolites and cellular debris. The peripheral blood parasite count is a relatively poor predictor of the size of the sequestered biomass[25]. Sequestration within the blood vessels reduces micro vascular flow [15, 23]. This occurs predominantly in the venules of vital organs.

Cerebral malaria, defined as a deep level of unconsciousness (inability to localize a painful stimulus 1hour in children post convulsion) in the presence of a *P.falciparum* asexual parasitaemia, after the correction of hypoglycemia and exclusion of other encephalopathies, especially bacterial meningitis and locally prevalent viral encephalitides[25]. In cerebral malaria, the principal neurological features are coma (Blantyre coma scale ≤2), seizures, and brainstem signs (absence of reflexes, abnormal respiratory patterns, posture abnormalities and motor abnormalities of tone and reflexes), severe anemia, hypoglycemia and kidney failure. Other signs include repeated

generalized convulsions, thrombocytopenia, pulmonary edema, haemoglobinuria, splenic enlargement, jaundice and acidosis.

Cerebral malaria primarily affects children in sub-Saharan Africa with mortality ranging from 15% to 50%[15, 18, 26]. It occurs in older children; African children with cerebral malaria are older (40–45 months of age) than children with other complications of the disease, but cerebral malaria is rarely encountered after the age of 10 years in people exposed to *P falciparum* since birth[25]. In malaria endemic areas, the falciparum malaria is the commonest cause of seizures, even though the risk of seizures decreases with age. The malaria attributable fraction for seizures, however, has decreased with the decrease in malaria prevalence[4].

Sequestration in small vessels is implicated in the pathogenesis of coma in cerebral malaria, although the mechanism remains unclear[26]. The presence of malarial retinopathy can be used to differentiate children whose comas are caused by *P.falciparum* and its attendant pathophysiologies from those with other reasons for their abnormal mental status[10, 26]. However, children with retinopathy-negative cerebral malaria share a common clinical phenotype but with lower rates of mortality compared with those who have malarial retinopathy[27].

Eye abnormalities have been described in malaria by various authors since 1879. These abnormalities include keratitis, uveitis, retinitis pimentosa, optic neuritis and ocular muscle pareses. These changes have either been found to be of great prognostic significance or indicators of severity of malarial infections[28].

Embryologically, the eye is an extension of the brain tissue. Both of them are of ectodermal in origin and they therefore share structural and functional similarities[14, 23].

The eye thus acts as the window to the brain as it contains one of the few capillary networks that can be observed in life. Malarial retinopathy has been described by Dr. Lewallen et. Al (1992) which consists of four features, two of which are unique to malaria and two of which are independently associated with poor outcome[14]. Papilledema is the swelling of the optic disc which occurs due to raised intracranial pressure, generally due to brain edema. It is seen in up to 8 to 10% of patients with cerebral malaria. Presence of papilledema is associated with a 6-7 fold increase in the relative risk of death[14, 26]. Its presence alone without the other features of retinopathy is not specific for malaria[23]. Presence of hemorrhages is indicative of malaria and is present in 35-40% of patients with severe malaria[14]. Fifty percent of hemorrhages may be white centered. The presence of hemorrhages is not an independent predictor of a worse outcome in malarial infection. Vessel changes are observed in up to 25% of patients with cerebral malaria[14]. These changes are either white or orange colored and are observed in the optic fundi. This finding is unique to malaria and is associated with poor outcome even though it is not an independent predicator [14]. Often, only a single segment of a vessel will be affected, and frequently, the phenomenon begins at a branch point. Retinal whitening is also unique to severe malaria and occurs in about 50% of patients[14, 23]. It's an independent predictor of mortality, and cerebral malaria patients with whitening are three times more likely to die than are patients are without.

In autopsy studies, the patients who had retinal hemorrhages in life have been found to have cerebral hemorrhages. These hemorrhages were easily seen in the white matter of the cerebral hemispheres. Both brain and retinal hemorrhages were typically "ring hemorrhages"[14], in which unparasitized red cells escape into the brain parenchyma, usually surrounding a vessel in which a fibrin thrombus has formed.

Histological examination of optic fundi demonstrate that vessels which are orange or white upon fundoscopic examination during life are the same vessels which contain dehemoglobinized red blood cells and mature pigmented parasites. There is a statistically significant correlation between the predominant stage of the parasites in the optic fundi and the predominant stage of the parasites in the brain[14]. Thus, the vessel changes visible in the optic fundus reflect the sequestration of parasitized red cells in the brain.

In malaria, the blood retina barrier and retinal vascular flow remain substantially normal despite widespread pathological features[19]. Retinal features in children with severe malaria are consistent with cellular hypoxia, nutritional deficiency, or both rather than vascular occlusion. A study by Mark Hero et. al of the retina in Kenyan children with severe malaria found that retinal opacification was significantly associated with a higher parasite count ($p<0.2$) while white centered hemorrhages are significantly associated with a higher parasite count ($p<0.5$), severe disease ($p<0.5$) and severe anemia ($p<0.2$)[19].

Other than malarial retinopathy, other neuro-ophthalmic effects that can occur in malaria are visual field defects, cortical blindness (due to transient ischemia), optic neuritis, papilledema and optic atrophy[22]. These occur mainly in cerebral malaria clients. These effects are due to anemia, vascular occlusion, inflammation and increased intracranial pressure. Visual field defects are due to oculomotor and trochlear nerve pareses due to either ischemia or inflammation.

Retinal changes in cerebral malaria are significantly associated with a poor outcome. These changes take longer to resolve than the clinical episode and vascular changes can persist for many weeks[22]. It is also noteworthy that treatment with quinine especially if there is overdose may have ocular side effects but these are different from malarial

retinopathy. These side effects include decreased vision, retinal or macular degeneration and pigmentary changes, distortion due to flashing lights, color vision defects(red-green or blue-yellow defect) and mild scotomas to a constricted visual field.

A study among Ghanaian children with severe malaria found that 73% of cerebral malaria children, 54% of severe malaria anemia and 50% of malarial children with respiratory distress had malarial retinopathy[9]. Sixty eight percent of children with cerebral malaria and convulsions and 100% of those with cerebral malaria but no convulsions had malarial retinopathy. Comparison between cerebral malaria and non cerebral malaria groups showed a significant risk relationship between retinal whitening and cerebral malaria; however, no such significant association was found with papilledema, macular whitening, macular hemorrhage, retinal hemorrhage and vessel abnormalities. The study concluded that retinal whitening was significantly more common in cerebral than non cerebral syndromes. Nonetheless, it noted that any retinopathy in the non cerebral malaria syndrome suggests that the brain and the retina may be suffering from ischemia in both cerebral and non cerebral malaria.

Beare et. al (2004) studied the prognostic significance and cause of retinopathy in Malawian Children found that in cerebral malaria patients, 61% had some retinopathy while 53% of those with severe malaria anemia had retinopathy. In cerebral malaria, retinopathy was associated with subsequent death (RR 3.7, 95% CI 2.7 – 7.6) and papilledema conferred the highest risk[18]. Increasing severity of retinal signs was related to increasing risk of fatal outcome independent of papilledema. These retinal signs were associated with prolonged time to recover consciousness. Patients who had severe malarial anemia had better outcomes and less severe retinopathy than those who had cerebral malaria.

A study by Richard J.M et. al (2010) on Bangladeshi adults found that 85% of those with cerebral malaria, 67% of those with non cerebral malaria and 47% of those with uncomplicated malaria had retinal changes. In the control groups, less than 1/3 had mild retinal changes[16]. Moderate to severe retinopathy was found in 67% of those with fatal, 62% of cerebral, 41% of non cerebral malaria and 12% of uncomplicated malaria. Other than papilledema, moderate to severe retinopathy was highly specific for malaria (98%) and for cerebral malaria in comatose patients (93%). Resolution of signs took a median of 14days and visual function 3-4 days. Severity of retinopathy correlated with severity of malaria and coma recovery time. Moderate to severe retinopathy as assessed by non-ophthalmologists was found to be an independent predictor of mortality of malaria. Although indirect ophthalmoscopy was more sensitive, it provided minimal additional prognostic information compared to direct opthalmoscopy[16, 17]. This study concluded that malarial retinopathy has potential as bedside adjunct to diagnosis and prognosis in adults with malaria and this finding is similar to results in children[16, 17]. An earlier study by the same author (2009) concluded that retinal changes were common in adults with severe falciparum malaria and correlated with disease severity and coma[15, 29].

Lewallen S. et.al (1993) in a Malawian study[30] examined the fundi of children with cerebral malaria. Those with papilledema had a relative risk of poor outcome 5.2 times greater than those without this finding. They thus concluded that fundus findings are useful as predictors of outcome in children with cerebral malaria.

Olumese P.E et.al(1997)[31] in a study of retinal hemorrhages in cerebral malaria in children found that 52.1%, 24.7% and 23.3% respectively had normal fundi, papilledema and retinal hemorrhages with mortality rates between the 3 groups being 16%, 22% and 47% respectively. In this study, retinal hemorrhages was found to be significantly associated

with death even after adjusting for other known risk factors for mortality such as age, sex, acidosis, parasite density, anemia, deep coma and hypoglycemia[31]. This study concluded that fundoscopic examination is not just useful to rule out increased intracranial pressure but also can be used as a measure of assessing prognosis in children with cerebral malaria.

3 METHODOLOGY

3.1 STUDY AREA

The study was carried out at Webuye sub county hospital which is on a 37 acre piece of land in Webuye town, Bungoma East Sub County in Bungoma County along the Eldoret-Bungoma highway, just below the Chetambe Hills. The peak malaria period is between March and July which coincides with heavy rains. The main economic activity is farming of sugarcane and maize. The hospital was built by the African Development Bank under the rural health services fund and started functioning in 1991 being officially opened in 1996.

Webuye sub county hospital is centrally placed with an immediate catchment population of 87,257 people. Children less than 5 years of age constitute 16.9% of population while those less than 15years of age constitute 42.3%. The male to female ratio is 47:53.

Webuye sub county hospital is a high volume level 4 hospital and a referral centre for several other level 4 hospitals surrounding it. The hospital has a bed capacity of 217 beds and bed occupancy of up to 150 percent. On average 150-200 patients are seen on a daily basis. It offers in and outpatient services. The pediatric ward has a bed capacity of 46 beds catering for both surgical and medical cases, with an average occupancy rate of 97%. The children are seen in Pediatric casualty in the MCH department from where those who require admission proceed to the ward after stabilization in the casualty. The casualty operates on weekdays between 8am to 5pm.

3.2 STUDY POPULATION

Children who were admitted to the Pediatrics casualty and Pediatric ward comatose were recruited into the study.

3.2.1 Inclusion criteria

1. Children whose guardians gave consent to be included in the study.
2. Children who had altered consciousness: AVPU = P or less, Blantyre coma scale ≤2 (Appendix 4).
3. Age: 9 months to 12 years. Children are protected from severe malaria in the first 4-6 months of life. A previous study had showed that direct fundoscopy is more easily done in children older than 9 months old.

3.2.2 Exclusion criteria

1. Children with obvious eye abnormalities e.g. corneal or lens opacity, red eye or proptosis
2. Children involved in acute trauma care.

3.3 STUDY DESIGN

Cohort prospective study design was used. Participants in the study were recruited upon admission to the hospital and then followed up in the ward until they were discharged at which point they were evaluated for any neurological deficit or died.

3.4 SAMPLING TECHNIQUES

Consecutive sampling technique was used in this study. As children came to Pediatrics triage and ward, those that fulfilled the inclusion criteria were recruited into the study during the study period until sample size was achieved.

3.5 SAMPLE SIZE DETERMINATION

Sample size was calculated based on Fisher's exact formula. A study on Ghanaian children in 2010 found the prevalence of malaria retinopathy do be 73% among children with cerebral malaria[9]. Setting the confidence level at 95% with a 5% sampling error, the sample size was determined by:

$$n = \frac{Z^2\ \hat{p}(1-\hat{p})}{e^2}$$

p=73%, e=5%

$n= (1.96^2*0.73*0.27)/0.05^2 = 302.8$

= 303.

At Webuye sub county Hospital, an average of 2 comatose children per week, translating to 48patients in 6 months. Adjusting for finite population,

$n_f=n_o/(1+((n_o-1)/N))) = 303/(1+(303-1)/48))$ where n_f is the actual sample size, n_o(303) is the sample size without considering the finite population and N(48) is the finite population

n_f =41.5

n_f=42

The sample size for this study was 42. Adding 10% for drop outs from the study gave a minimum sample size of 47.

3.6 DATA COLLECTION TECHNIQUES

A Pretested Interviewer administered questionnaires was administered to care takers of the children to collect social demographics, clinical and laboratory presentations (Appendix 3). The study was carried out over a six months period because the time available for doing the masters in medicine was limited. A pilot study was carried out at the outpatient department of Webuye sub county hospital before actual study was undertaken. A total of 10 participants had the questionnaire administered to them and results were recorded.

At each step of data collection, the questionnaire was checked for errors and inconsistencies.

3.7 Study procedures

Before commencement of the study, the principal investigator underwent a two week training by an experienced ophthalmologist in order to be able to identify malaria and other retinal signs in the fundus. He was supervised during the period and at the end of the training was certified to be able to identify the above (Appendix 7). The ophthalmologist was also his supervisor during the study.

The children who were recruited were those who presented to the hospital on week days. This was because one of the research assistants, the clinical officer ophthalmologist, was available only during week days. Hypoglycemia and postictal state were excluded as the

cause of coma. Only those children who remained comatose 1 hour postictal or after correction of hypoglycemia were included in the study. All the children recruited had a direct fundoscopy done on them within 24 hours of admission by the principal investigator as well as by research assistant who was a clinical officer ophthalmologist. The eyes of the children were dilated using tropicamide 1% 2 drops per eye at least 20 minutes before fundoscopy was done. Since the severity of malaria retinopathy is similar in both eyes[10], fundoscopic exam did not differentiate between the left and right eye findings. Both the principal investigator and the ophthalmologist were blinded to laboratory results before the fundoscopy was done. This was done by ensuring that both of them were not directly involved in care of patients and the laboratory results were not disclosed to them till after the fundoscopy was done and recorded. Laboratory data was recorded by the other research assistant and included taking blood slide for malaria parasites, lumbar puncture unless it was contraindicated, random blood sugar, complete blood count and sickling test. They were followed in the course of the admission to ascertain if their laboratory diagnosis was supported by the fundoscopic findings. Time of follow up was during period of admission up to a maximum of 14 days of admission or till discharge or death whichever was earlier. This period of follow up was decided upon from a study that showed that malaria retinopathy signs took a median of 14days to resolve[16]. The children were be treated according to Ministry of Health – Kenya Basic Pediatrics protocols – Revised 2010, National Guidelines for the Diagnosis, Treatment and Prevention of Malaria in Kenya 2010 and Pocket Handbook of hospital care for children: guidelines for the management of common illnesses with limited resources, WHO 2005. The children were divided into those with malaria (based upon a positive blood slide for malaria) and those without malaria. The two groups were evaluated for

the presence of malarial retinopathy to assess the usefulness of this retinopathy in differentiating those with malaria from those without.

Children were further followed up in the ward till end point of their treatment. They were evaluated for the study's endpoints. This was to assist in correlating the malarial retinopathy findings to prognosis of children with retinopathy. No follow up fundoscopy was done in participants because as children's consciousness improved doing fundoscopy became difficult and would have needed examination under anesthesia which was not be available during the study period.

Laboratory results (results of blood slide for malaria parasites, Lumbar puncture results, Complete blood count, and sickling test) and final diagnosis were retrieved from the file of the patient. When the initial blood slide for malaria parasite was negative, a repeat one was done every eight hours up to the third one. If all the three were negative, the child was assumed to be malaria negative and alternative source of coma was actively investigated for. All the blood slides were re-read by another microscopist to confirm the reading.

3.8 DATA ANALYSIS AND PRESENTATION

Following the completion of data collection process, questionnaires were coded and entered in computerized database designed in EPi-info v 10. This was then exported to STATA v 10 where analysis was done. Descriptive statistics such as mean, median, standard deviation and interquartile range (IQR) were used for continuous data. While frequency listings were used for categorical variables. Results were considered significant at 0.05 α-level. The findings were presented tables and graphs.

3.9 STUDY VARIABLES

Independent variable in this study was malarial retinopathy:

- The retinal whitening and vessel changes which are specific to malaria and not seen in any other ocular or systemic condition were independent variables in diagnosis of malaria.
- Presence of papilledema and retinal hemorrhages are indicators of poor outcome in severe malaria; thus these two were the independent variables in analyzing the prognosis of these patients.

Dependent variables were:

- Ability to make diagnosis of malaria on the basis of presence of malarial retinopathy.
- Treatment outcome of children with severe malaria and malarial retinopathy:
    - Time for coma to resolve
    - Complete recovery with no neurological deficit
    - Complete recovery with neurological deficit[1]
    - Death

3.10 LIMITATIONS

1. Direct fundoscopy was done and no indirect fundoscopy. Though indirect fundoscopy gives a wider view of the retina especially in the peripheral retina where retinal whitening and vessel changes do occur, this has been found in

studies not to increase the ability of the researcher to identify the features of malarial retinopathy though the rate it is picked is higher.

2. PCR for *Plasmodium falciparum* was not carried out as the gold standard in diagnosis of malaria. This is because PCR was not available in our locality, was expensive and was not available in the course of the study. The researcher used blood slide for malaria parasites to diagnose malaria as recommended by WHO and the WHO features of cerebral malaria to note children to be admitted to the study. Further, the blood slides used in this study were reread by another microscopist.

3.11 ETHICAL CONSIDERATION

Approval from the Institutional Research and Ethics Committee (IREC) from Moi University was obtained after the research proposal had been ratified before the research commences (**IREC approval number:** 000964). Thereafter authority from the administration of Webuye sub county hospital was sought to allow research to take place in the institution (Ref: WBY/DH/GA/8B/VOL.111). Written informed consent was obtained from the guardians of the children who agreed to participate in the study. Participant's confidentiality was observed by not using any form of participant identity on the data collection tool (using only serial numbers). The questionnaires were kept under lock and key in a place accessible only to the researcher. Data entered in the computer was protected by use of password. The children were treated according to Kenya Pediatric Protocol 2010. They were treated as per norms and standard without unnecessary influence or discrimination because they were in the study or not.

4 RESULTS

4.1 Study participants recruitment

The study was conducted as from May 2013 to December 2013. A total of 64 children meeting the inclusion criteria were treated in the hospital during the study period. The recruitment schema for the study is shown below:

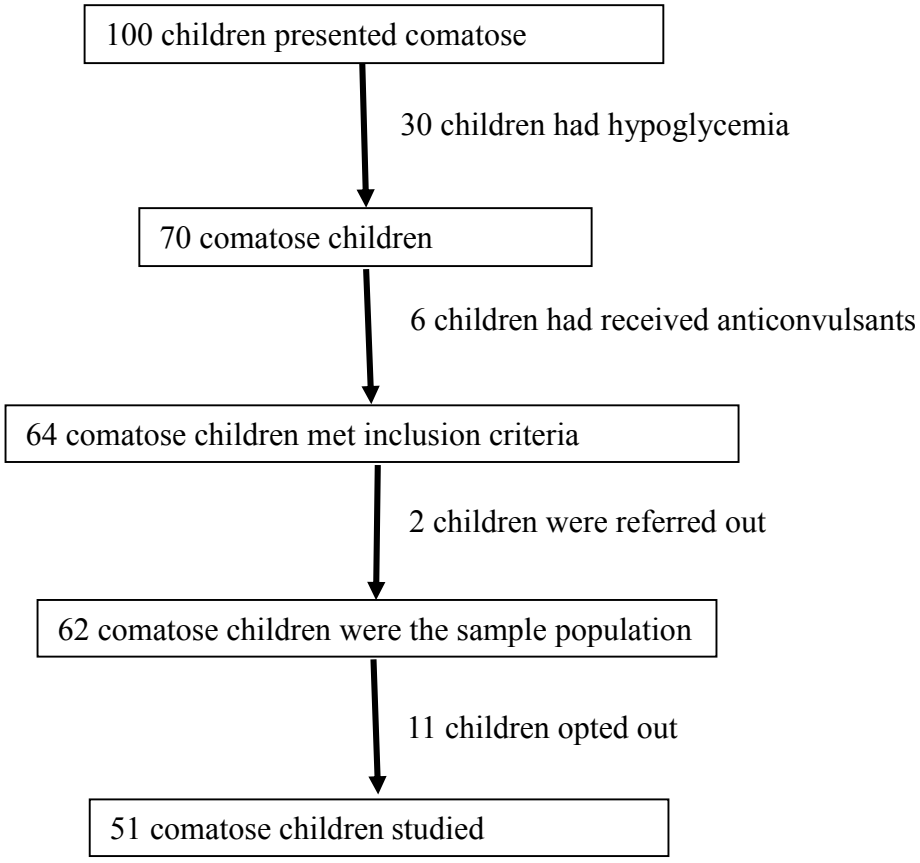

Figure 2: Recruitment Schema for the comatose children

4.2 Baseline characteristics of study participants

Of the 51 children recruited into the study, 31(72.6%) were males. The median age of the study subjects was 5 years (IQR3, 6). The median duration of illness for the children was 2 days (IQR of 2, 4). The mean temperature at admission was 38.0^{o}C (s.d 1.04). The baseline characteristics of the children is shown in table 1 below.

Variable	N Freq (%)
Age(yrs.) Median (IQR)	N=51 5 (3,6)
Gender Male Female	N=51 37 (72.55) 14 (27.45)
Weight in kg Median (IQR)	N=51 14.50 (11.50, 18.00)
Development assessment Delayed Appropriate	N=51 2 (3.92) 49 (96.08)
Immunization up-to-date Yes	N=51 49 (96.08)
Duration of illness before coming to hospital(days) Median (IQR)	N=51 2 (2,4)
Temperature(^{0}C) Mean (std)	N=51 37.97 (1.04)

Table 1: Baseline characteristics of the children

4.2.1 Presentation characteristics of the children

The most common presenting symptoms before the children lost consciousness was convulsions with 62.8 % of children having history of convulsions. The children had a combination of more than 1 presenting symptom. The presenting symptoms in children in this study is shown in the bar graph below:

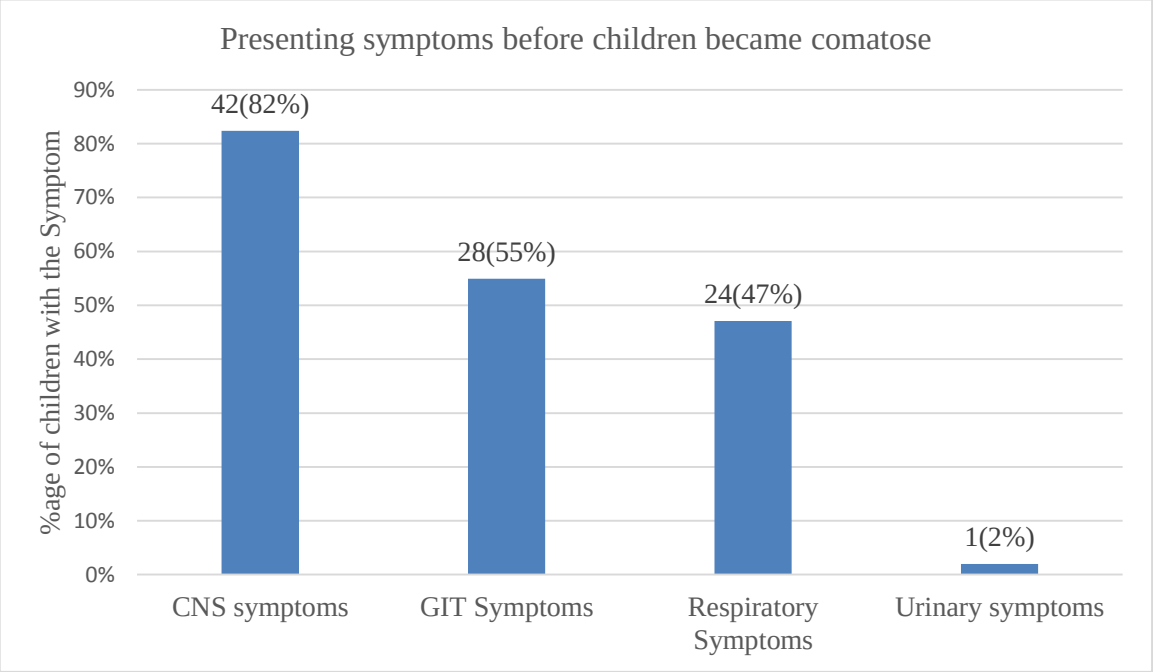

Figure 3: Presenting Symptoms of children before being comatose

The respiratory symptoms included cough, difficulty in breathing, or runny nose. The gastrointestinal symptoms included diarrhea and vomiting while central nervous system symptoms included headache, convulsions or lethargy. Forty eight (94%) of the children were febrile at presentation.

Twenty seven children (52.9%) had been pretreated with oral medications (majorly antimalarials) before coming to the hospital with worsening of the symptoms. The pie chart below shows the pretreatment the children used:

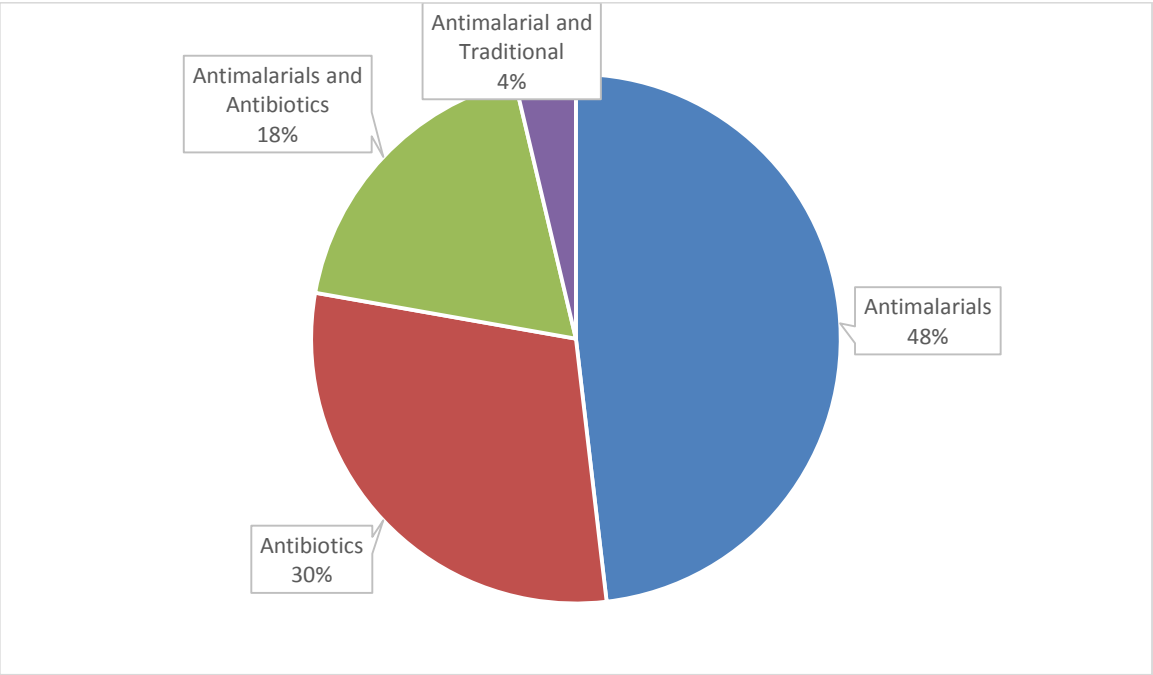

Figure 4: Treatment Received by children prior to coming to Webuye Sub County Hospital; N=27

4.2.2 Physical Examination Findings

The summary of physical exam findings is in the table below:

Variable	N Freq (%)
Coma scale at admission (AVPU)	N=51
P	44 (86.27)
U	7 (13.73)
Blantyre coma scale	N=25
1	7 (28.00)
2	18 (72.00)
Child is pale	N=51
Yes	25 (49.02)
No	26 (50.98)
Pupillary light reflex	N=51
Bilaterally equally reactive	50 (98.04)
Peripheral lymphadenopathy	N=51
Yes (Inguinal)	1 (1.96)
Presence of neurological signs	N=51
Yes	8 (15.69)
Type of neurological sign	N=8
Cranial nerves abnormalities	1 (12.50)
Bruxism	2 (25.00)
Opisthotonus	3 (37.50)
Motor abnormalities	2 (25.00)
Kerning's sign	N=51
Positive	3 (5.88)
Brudzinki's sign	N=51
Positive	2 (3.92)

Table 2: Physical Examination Findings of the children

4.2.3 The laboratory examination

Of the 51 children, 46(90%) had a positive Bs for mps. The summary of the laboratory findings are shown in the table below:

Variable		Freq (%)
RBS Mean (std)		N=51 6.32 (3.00)
BS for Mps Positive		N=51 46 (90.20)
Cerebrospinal fluid analysis	**Gram stain** Positive	N=51 4 (7.84)
	Ziehl Neelsen stain Positive	N=51 0(0.00)
	Indian Ink Positive	 0(0.00)
	Cell count Less than 5 5-10 More than 10	N=51 45 (88.24) 4 (7.84) 2 (3.92)
	Pandy test Positive	N=51 4 (7.84)
Complete blood count	**Total Leukocyte Count** Normal Leukopenia Leukocytosis	N=51 17 (33.33) 1 (1.96) 33 (64.71)
	Neutrophils count Normal Neutropenia Increased	N=51 41 (80.39) 1 (1.96) 9 (17.65)
	Hemoglobin Normal Anemic(mild or mod.) Severe anemia	N=51 18 (35.29) 17 (33.33) 16 (31.37)
Sickle cell test Positive		N=51 3 (5.88)

Table 3: Summary of Laboratory Findings

4.2.4 Final Diagnosis

Of the 51 children:

- 43(84%) had cerebral malaria
- 3(6%) had both cerebral malaria and acute bacterial meningitis
- 2(4%) had acute bacterial meningitis
- 3(6%) had encephalopathies of undetermined origin

For children who had encephalopathies of undetermined origin, 1 was suspected to have sickle cell encephalopathy while the other 2 were suspected to have viral encephalopathy.

4.3 Fundoscopic Examination

The mean time taken to do fundoscopy was 38 minutes (s.d=16.38). On fundoscopic exam, 17(33%) of the children had normal fundoscopic exam. For the 66.7% of children with retinal findings, most had more than one retinal finding. The findings are illustrated in the pie charts and bar graphs below:

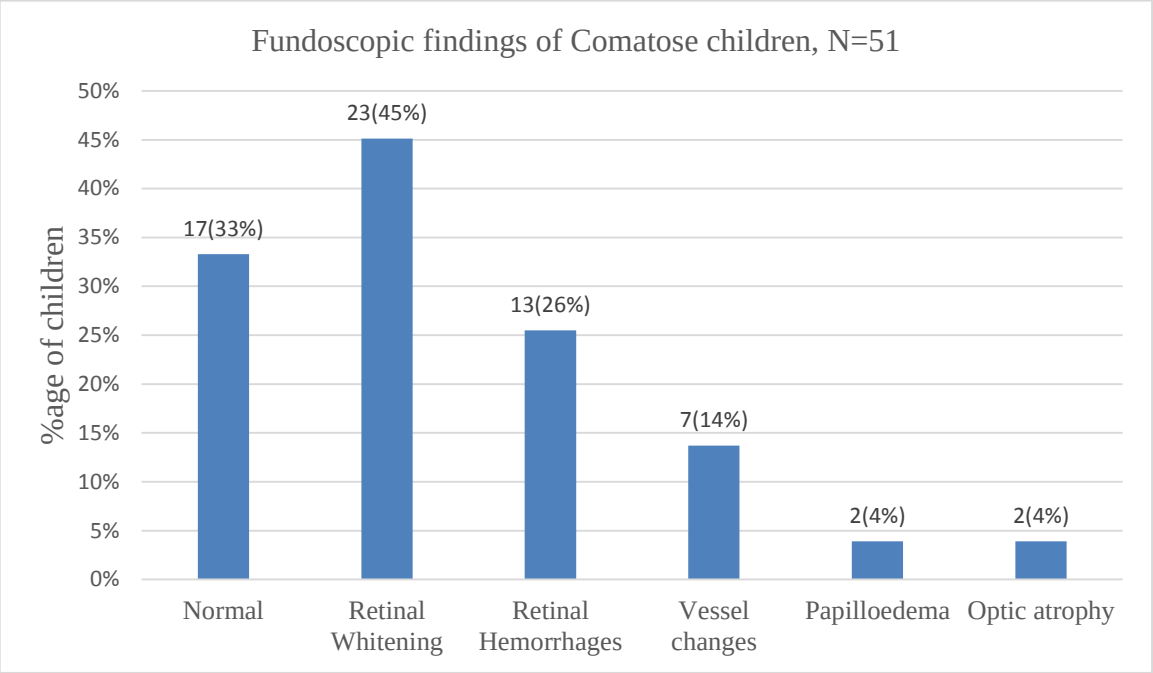

Figure 5: Retinal Findings of Comatose Children

4.4 Correlation of Retinal Findings and Malaria Retinopathy

Thirty two (63%) children had malaria retinopathy. This finding is represented in the chart below:

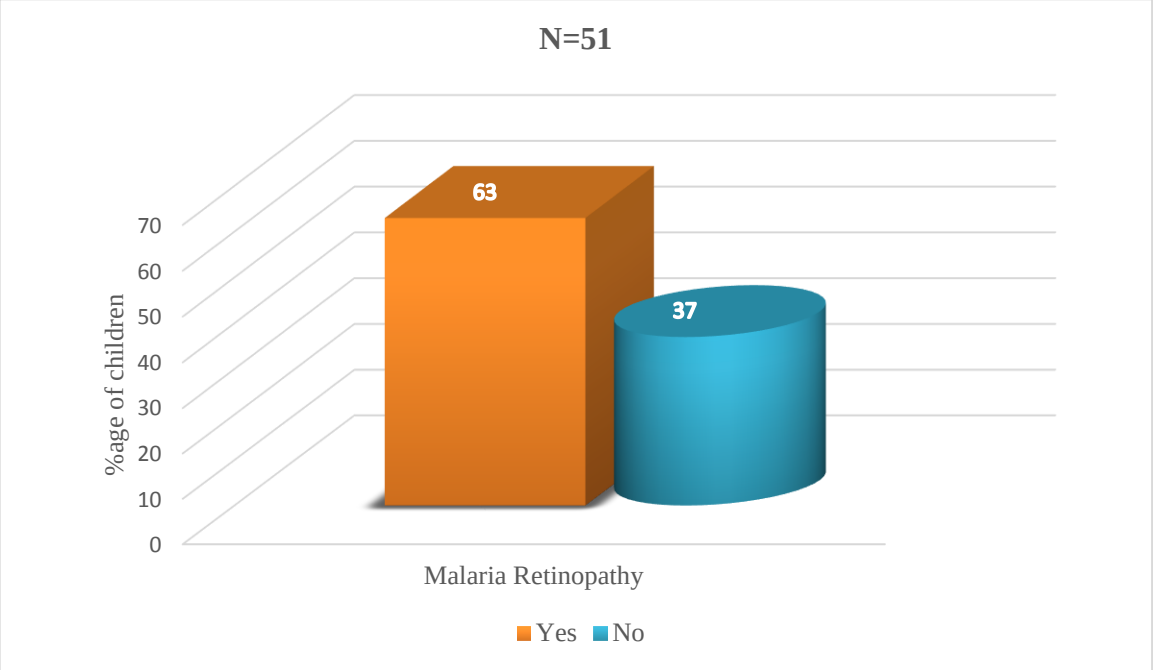

Figure 6: Proportion of children fulfilling Malaria Retinopathy criteria

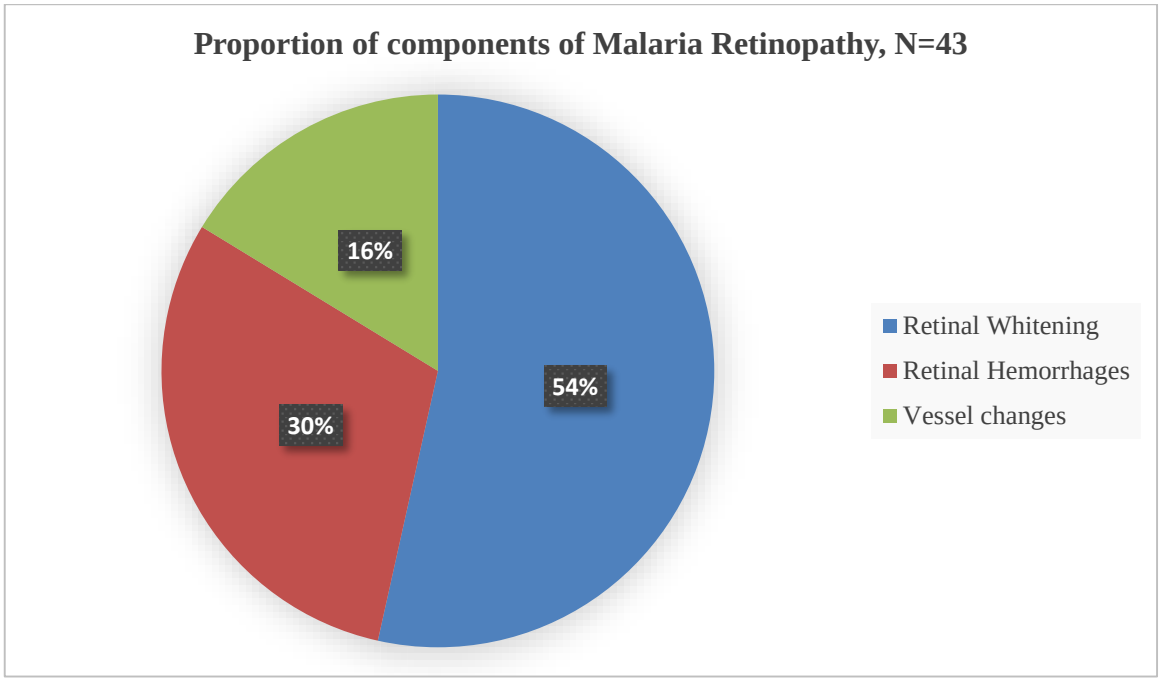

Figure 7: Proportion of various components of Malaria Retinopathy

Note: 32 children had malaria retinopathy but some children had one or more components of malaria retinopathy hence N in figure 7 is 43.

4.5 Treatment outcomes

4.5.1 Duration before coma resolution

In 33 children (65%), coma resolved within 24 hours. The pie chart below shows the summary of time it took for coma to resolve in the children:

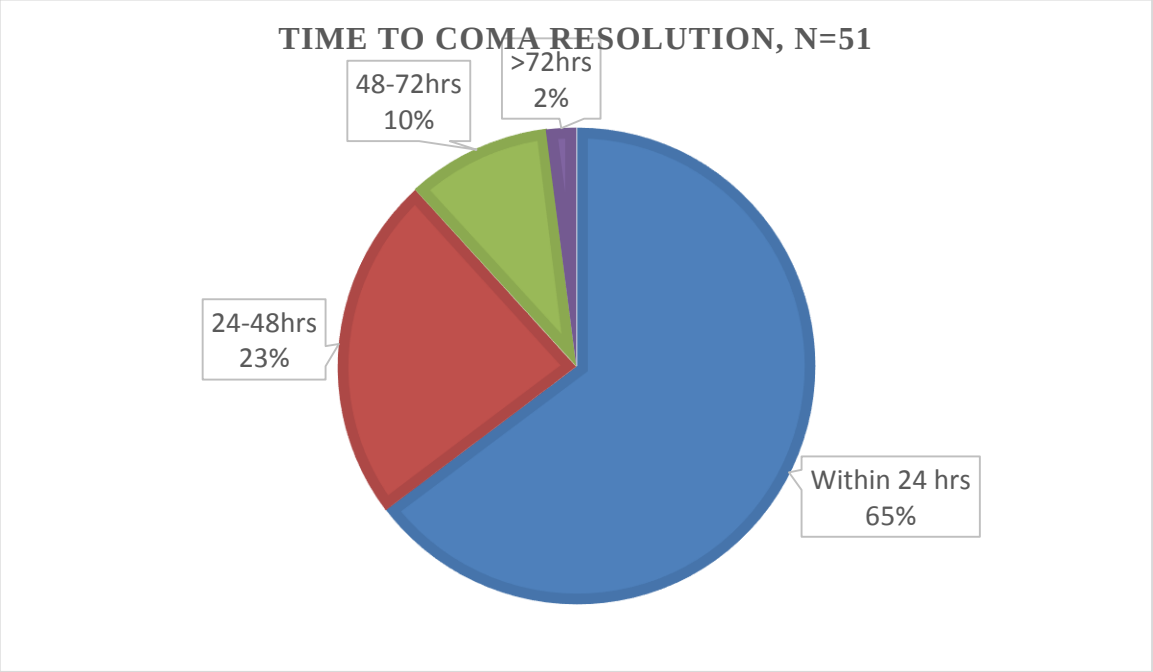

Figure 8: Duration of coma before resolution

4.5.2 Treatment outcomes

Of the 51children involved in the study, 44(86%) made complete recovery from their illness without any neurological deficit.

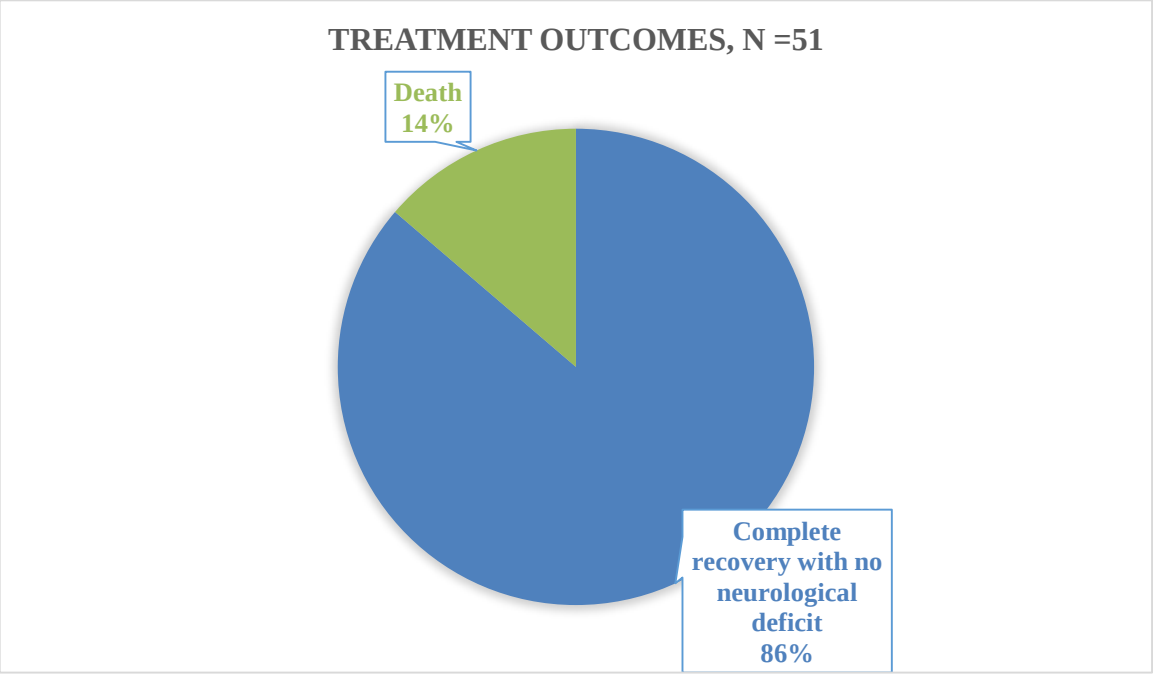

Figure 9: Pie Chart of Treatment Outcomes of children admitted comatose

4.6 Correlation of Malaria Retinopathy and Treatment Outcomes

Variable	Malaria retinopathy		Fishers' exact
	Yes	No	p-value
Bs for Mps			
Positive	32 (100)	14 (73.68)	0.005
Negative	0 (0)	5 (26.32)	
Time to coma resolve			
<24 hours	18 (56.25)	15 (78.95)	0.441
24-48 hours	9 (28.13)	3 (15.79)	
48-72hrs	4 (12.50)	1 (5.26)	
>72hours	1 (3.13)	0 (0)	
Complete recovery without neurological sequel			
Yes	26 (81.25)	18 (94.74)	0.178
No	6 (18.75)	1 (5.26)	
Death			
Yes	6 (18.75)	1 (5.26)	0.178
No	26 (81.25)	18 (94.74)	
Final diagnosis			
Cerebral Malaria(CM)	30 (93.75)	13 (68.42)	
Acute bacterial meningitis(ABM)	0	2 (10.53)	
Encephalopathies of undetermined origin	0	3 (15.79)	
CM and ABM	2 (6.25)	1 (5.26)	0.011

Table 4: Malaria Retinopathy and Treatment Outcomes

4.6.1 Correlation of malaria retinopathy with laboratory diagnosis of malaria

All the 32 children who had malaria retinopathy had a positive blood slide for malaria. For the 19 children who did not have malaria retinopathy, 73.7% had a positive blood slide for malaria. On analysis using Fisher's exact test, having malaria retinopathy correlated with laboratory diagnosis of malaria (p=0.005).

4.6.2 Correlation of Malaria Retinopathy and Final Diagnosis

Using Fisher's exact test it was statistically significant that those with malaria retinopathy to have cerebral malaria as their final diagnosis (P=0.011).

4.6.3 Correlation of malaria retinopathy with duration of coma

It took longer for the coma to resolve in children who had malaria retinopathy as compared to those without malaria retinopathy. More children without malaria retinopathy had their coma resolve within 24hours compared to those with malaria retinopathy (79% vs. 56%). However, on analysis using Fisher's exact test, the time required for coma to resolve between those with and those without retinopathy was not statistically significant (p=0.441).

4.6.4 Correlation of the malaria retinopathy and treatment outcomes

More children without malaria retinopathy (18[95%]) made complete recovery with no neurological sequalae compared to 26(81%) children with malaria retinopathy. On analysis using Fisher's exact test, however, it was not statistically significant whether a child recovered completely with no neurological sequealae between those with malaria retinopathy and those without (p=0.178).

4.6.5 Correlation of Malaria Retinopathy and Death

For the 7 deaths in this study, 86% of them had malaria retinopathy. Even though more children with malaria retinopathy died (18.8% compared to 5.3% of those without malaria retinopathy), this was not statistically significant (p=0.178).

For the children with retinopathy, all had cerebral malaria as their final diagnosis. All of them except 1 child had retinal hemorrhages and 2 of them had papilledema in addition. For the child without malaria retinopathy, it was a case of suspected sickle cell encephalopathy and had normal fundi.

5 DISCUSSION

Malaria incidence is decreasing in Sub Saharan Africa but it still constitutes up to 40% of pediatric hospital admissions. Cerebral malaria account for up to 10% of these admissions and the rate of neurological complications is up to 24%. Approximately 20% of cerebral malaria patients die during the course of admission[7].

5.1 Etiology of coma

In our study, of the comatose children admitted, cerebral malaria accounted for 84.3% of their diagnosis, 3.9% of them had acute bacterial meningitis, 5.9% had both CM and ABM while 5.9% had encephalopathies of undetermined origin. A cross sectional study by Ahmed S et al on non-traumatic coma in children admitted in Pediatric department of Civil Hospital Karachi showed that cerebral malaria occurred in 29.3% of children with infective cause of coma while acute bacterial meningitis was more common infective cause of coma with 31% of children being diagnosed with it. In that same study, viral encephalitis, tuberculous meningitis, sepsis and Reye's syndrome accounted for 18%, 12%, 8% and 1% of infective cause of non-traumatic coma[8]. The difference between this study and our study in terms of etiology of non-traumatic coma in children could be due to the differences in endemicity of malaria in the 2 regions: Bungoma East Sub County is largely rural area where malaria is endemic while Karachi is an urban area in which malaria is not endemic.

A review by Gwer S. et al (2013) showed that cerebral malaria was the most common cause of coma in most African studies while acute bacterial meningitis was the second most common cause of coma in 7 African studies[35]. The same review showed that in India

and Japan encephalitides were the most common cause of non-traumatic coma while in Pakistan acute bacterial meningitis was more common. These findings are similar to our study findings which showed that cerebral malaria was the most common cause of coma in children. An Iranian study by Fariba K. and Najmeh N. did confirm the review by Gwer by showing that 32.2% of all non-traumatic coma in children was due to infective process with meningitis, encephalitis, respiratory and systemic being the main causes[5].

A study by Gwer S et al on children admitted comatose in Kilifi, Kenya, 59% of patients had malaria parasitemia, and 36% had encephalopathies of undetermined origin while the rest (5%) had acute bacterial meningitis (ABM), most of whom had ABM and malaria parasitemia[6]. The difference in proportions of the final diagnosis between this study and our study could be because of duration of study. Our study was done during over 6 months covering mostly peak malaria season between May and December while the Kilifi study was done over 5 years.

5.2 Fundoscopic Exam Findings

In this study, 33.3% of the children had a normal fundoscopic examination, 3.9% of the children had optic atrophy, 3.9% had papilledema, 45.1% had retinal whitening, 13.7% had vessel changes while 25.5% had retinal hemorrhages. A study by Essuman et al in Ghanaian children showed that those who had cerebral malaria had the following opthalmoscopic findings: retinal whitening was 22%, macular whitening was 33%, macular hemorrhages was 9% and retinal hemorrhages were 35%. Papilledema was seen in 21% of the children, cotton wool spots in 5% of the children and vessel abnormalities in 28% of the children[9]. The difference between our study findings and those of the Ghanaian study could be because they used both indirect and direct opthalmoscopic

examination which can detect higher proportions of retinal whitening and retinal hemorrhages especially in the peripheral retina.

Other studies also do show higher proportion of the retinal findings. For example, Lewallen et al showed that between 35-40% of patients had retinal hemorrhages while 25% of patients had vessel changes. She also found that retinal whitening occurred in 50% of the patients[14]. A study by Baere et al showed that 39% of the children had normal fundi[18].

In adults, however, the retinal findings proportion was different from the ones in children. A study by Kochar et al of adults admitted at PBM hospital India showed that retinal hemorrhages were the most common opthalmoscopic findings at 9.3% followed by papilledema at 6.7% while the other findings being less than 1%[28]. In that study up to 65.9% with cerebral malaria had normal fundus. The findings in this adult population however cannot be generalized to the children population as the study was done in Asia and during a season of low malaria transmission and secondly adults tend to have herd immunity to malaria hence are unlikely to have malaria as the cause of their coma.

Retinal Finding	**Our Study**	**Essuman et.al[9]**	**Lewallen et al[14]**	**Baere et.al[18]**
Normal	33.3%	38%		39%
Retinal whitening	45.1%	55%	50%	90%
Retinal hemorrhages	25.5%	44%	35-40%	46%
Vessel changes	13.7%	28%	25%	32%
Papilledema	3.9%	21%	-	15%

Table 5: Discussion: comparison of retinal findings

The most easily recognizable retinal change was retinal hemorrhage and this finding is consistent with other studies from Asia[17].

5.3 Malaria retinopathy

In our study, 69.5% of the cerebral malaria children had opthalmoscopic findings satisfying criteria for malaria retinopathy. This is slightly lower than the rate seen in the Ghanaian children with cerebral malaria which was 73%[9]. In our study, in those patients with cerebral malaria and convulsions, malaria retinopathy was found in 46.4% of them while in the Ghanaian study 68% of similar patients had malaria retinopathy. In Malawi, Beare et al showed that 61% of the children with cerebral malaria had malaria retinopathy[18].

The difference in the rates seen in the other studies and our study could be due to the fact that in our study direct fundoscopy was carried out while in the other studies employed both direct and indirect fundoscopy was done. Despite the fact that indirect fundoscopy gives better peripheral visualization of retina leading to higher detection rate of retinal whitening and vessel changes, this has been found not be significant in terms of detecting and grading of severity of the malaria retinopathy in patients with cerebral malaria[17]. Furthermore, since a large proportion of retinal changes in malaria are in the peripheral retina, the use of direct opthalmoscopic may account for low incidences by non-expert which is approximately 50%[17]. In our study however, one of the research assistant was a clinical officer ophthalmologist and this could explain why our findings are slightly higher than that by non-experts but lower than that done by experienced ophthalmologists. Finally, the almost similar rates of malaria retinopathy could be because the studies were done in malaria endemic zones.

In our study, the proportion of children who did not have malaria retinopathy yet fulfilled WHO criteria for cerebral malaria was 73.7%. This represented 30.4% of all cerebral

malaria children. This finding was a puzzle as sequestration of parasitized red cells in cerebral microvasculature is hypothesized as the pathogenic mechanism leading to cerebral malaria. An autopsy study showed that 23% of children who fulfilled the cerebral malaria criteria lacked autopsy evidence of *Plasmodium falciparum* sequestration. In that study, the children who lacked the evidence of typical cerebral malaria neuropathology had other identifiable cause of death including Reye's syndrome and severe pneumonia on autopsy[11]. A study by Postels D.G found 19.5% of cerebral malaria patients fulfilling WHO criteria for cerebral malaria were retinopathy negative on fundoscopy[27].

A later study by Postels D.G et al in a study of Malawian children with cerebral malaria did corroborate the above findings by the same author. They hypothesized that retinopathy negative cerebral malaria is unlikely to be associated with acute infection with malaria parasite[36]. Alternatively, it was hypothesized that it could be due to malaria infection with a cofactor (possibly co infection). In that study by Postels D.G et al, retinopathy negative cerebral malaria was more common in period when malaria transmission was low.

These findings could possibly explain why in our study those who had cerebral malaria and yet were retinopathy negative constituted 30.4% of all cerebral malaria patients. Since in our study, all comatose children were treated with parenteral Quinine and parenteral antibiotics, this could explain why these patients did not suffer excess morbidity and mortality in the course of their admission, hence no statistically significant difference in treatment outcomes between retinopathy-positive and retinopathy–negative cerebral malaria children. Moreover, because our study span a period of both low malaria transmission and high malaria transmission season, this could explain the high incidence of retinopathy negative cerebral malaria patients. Admittedly, the use of direct

ophthalmoscopy leading to missing of retinopathy changes in peripheral retinal could have contributed to this.

5.4 Treatment outcomes

5.4.1 Coma resolution

In our study, there was no statistically significant difference between the duration it took coma to resolve between those with malaria retinopathy and those without. More patients without retinopathy recovered within 24 hours while 15% of those with malaria retinopathy had coma lasting more than 48hours. This is in keeping with other African studies in which children with cerebral malaria recovered their consciousness within 48-72hours of starting treatment. The median time taken for recovery of consciousness in these studies was 32.3 hours (95% CI 23.4 – 41.1)[26]. A study by Baere et al did show however that coma took longer in children with malaria retinopathy to resolve compared to those without retinopathy. The median time to coma resolution in patients with retinopathy was 42 hours compared to 29 hours for those without retinopathy[18]. The difference between how frequent patients were assessed for coma resolution in Baere's study and our study may be responsible for the difference between the 2 studies. In our study, by the 48th hour, 94.7% of patients without malaria retinopathy would have had their coma resolved while 84.4% of patients with malaria retinopathy would have had their coma resolved. Thus in our study, coma did last longer in patients with retinopathy compared to those without retinopathy.

5.4.2 Recovery from the illness

The rate of neurological sequel in children with cerebral malaria is documented at 12% at the time of discharge[15]. In our study, the rate of complete recovery with no neurological sequel was almost the same in those who were retinopathy-positive and retinopathy–negative children with rate being 81.3% and 94.6% respectively. The difference in the rates of full recovery with no neurological sequel was not statistically significant between those with and those without retinopathy in our study with a p value of 0.178. This probably is because our study subjects were slightly older than other studies (the mean age in our study was 4.96years) hence they could "accommodate small silent infarcts" due to redundancy of cerebral vasculature[15].

In our study, none of the children developed any neurological sequel. Previous studies, however, have shown that 25% of cerebral malaria children have long term neurological deficits[37]. In a Ugandan study, children presenting to neurology clinic, only 23 children out of 835 incident to the clinic had neurological deficit secondary to cerebral malaria over 2 year study period[32]. A study by Baere N.A et al on Malawian children, 6.1% of children admitted and treated for cerebral malaria had neurological deficit[18]. In that study too it was found that the frequency of retinopathy in those who developed neurological sequel and those who fully recovered was not statistically significant. A study carried out in Mali involving 101 children with mean age of 5.6 years+/-3.6yrs, 27.7% of them had persistent neurological sequel: 7.9% of the children had neurological deficit at discharge while 19.8% developed this a few months later[38]. A further study by Postels D.G et al assessing neurologic outcomes in retinopathy negative cerebral malaria survivors showed that children surviving retinopathy- negative or –positive cerebral malaria are at similar risk for adverse neurological outcomes[39].

In our study, no long term follow up of the children was done; if this had been done then probably the rate of neurological sequel that develop months later after cerebral malaria would have been detected. In the Ghanaian study, the rate of neurological deficit in children post cerebral malaria was also low with only 2 children out of 26(7.7%) had transient neurological deficit[9]. In a Gambian study, however, the rate was 12%[40]. A Nigerian study, 13.7% of cerebral malaria survivors had neurological sequel at discharge and 4.6% at follow up[41]. The lower rate of neurological sequel in African studies could possibly be due to improvement in the treatment protocols so that the sequel is reduced compared to the rate in literature.

5.4.3 Death

In our study, there were 7 deaths with more deaths occurring in those with malaria retinopathy (18.8%) than those without (5.3%). However, this was not statistically significant with p value of 0.178. Other studies have shown increased mortality and a positive predictive value of retinal hemorrhage and papilledema for fatality[18]. In our study, 5 out 6 children who died and had malaria retinopathy had retinal hemorrhages and 2 had papilledema. A study by Baere N.A et al showed that retinopathy was present significantly higher in those who died compared to survivors with relative risk of 3.7 of death in those with any abnormality on fundus exam and also increased in presence of papilledema, retinal hemorrhage or vessel changes[18]. Studies have shown that deep coma and hypoglycemia (these 2 mainly but also respiratory distress) are predictive of death[18, 42, 43]. A study of Gambian children showed that 14% of children with cerebral died and these had the above presenting symptoms at admission[40]. A study among Nigerian children with cerebral malaria, 18.1% died during their admission closely mirroring the results of our study. This could be because all the studies were performed in malaria

endemic area and where the presentation to health facility can be delayed as client tries over the counter medications before coming for evaluation when symptoms worsens.

6 CONCLUSIONS

The following conclusions were made from this study:

- Of the children admitted comatose at Webuye sub county hospital, a third of them had normal retinal findings. For those with retinal findings, retinal whitening was the most common finding occurring in nearly half of them, followed by retinal hemorrhages in a quarter of them while vessel changes occurred in only 10% of the children. Papilledema was relatively uncommon.
- In this study, 69.5% of the cerebral malaria children had malaria retinopathy
- There was correlation between malaria retinopathy and laboratory confirmed cerebral malaria in this study. Therefore, malaria retinopathy is a useful adjunct in diagnosis of cerebral malaria
- Coma took longer to resolve in children with malaria retinopathy compared to those who were retinopathy negative even though this was not statistically significant.
- Regardless of their malaria retinopathy status, all children who survived in this study recovered completely with no neurological deficit as a result of their illness.
- More children with malaria retinopathy died in this study as compared to those who were retinopathy negative though this was not statistically significant.

7 RECOMMENDATIONS

- There should be training for general clinicians to increase the use of direct fundoscopy to assist in diagnosis of children admitted comatose in malaria endemic area. The use of fundoscopy should be irrespective of their malaria parasitemic status.
- Further studies to assess the malaria retinopathy and treatment outcomes in our settings. These studies could also assess the prognostic factors that make children with malaria retinopathy to have prolonged coma and higher death rate than those who do not have malaria retinopathy in our setting.

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9 APPENDIX

9.1 APPENDIX 1: CONSENT

INTRODUCTION AND CONSENT

Hello. I am Dr James Oduor and I am a student at Moi University School of Medicine. I am conducting a survey on the usefulness of changes in the eye that can help us in diagnosing malaria in a child. We hope to use this information to assist fellow doctors decide if it can be used to treat children and in the process avoid delay in initiating treatment. I am doing this research in Webuye District Hospital and will compare it with results from other surveys done earlier. I request your permission to allow your child to be involved this study. The study involves dilating your child's eyes by putting drops of drugs and looking into them to see the different types of changes that have occurred.

Whatever information you gathered will be kept confidential and will not be shared with anyone other than members of our study team. Also neither your identity nor that of your child will be revealed to others. Your participation in this study is entirely **voluntary** and you can stop me anytime for any clarification you might need or if uncomfortable to continue. However, I hope that you will participate in this study to the end.

At this time, do you want to ask me anything about this study?

Consent:

I,_____being the parent/guardian of a sick child and having been informed about this study to my satisfaction and all my questions and concerns having been addressed, do give consent for my child to participate in the study.

Signed:_____Date_____

Signature of interviewer: _____ Date: _____

KISWAHILI VERSION FOR CONSENT

Habari yako. Mimi ni daktari James Oduor, mwanafunzi katika chuo kikuu cha Moi. Nafanya utafiti kuhusu yale mabadiliko ambayo malaria inaleta ndani ya macho. Hii inaweza kutusaidia pamoja na madaktari wengine wakati tunapotibu watoto ili tusichelewe kuanza dawa. Nafanya utafiti huu hapa katika hospital ya Webuye. Nakuomba uhurusu mtoto wako awe mmoja wa wale tutakaofanyia utafiti hii. Tutaweka dawa ambayo itafanya macho ya motto yapanuke ili tuweze kuangalia ndani ili tuone kama yale mabadaliko yako.

Ile habari utatupatia itakuwa siri yetu na itatumika na sisi peke yetu. Wewe wala motto wako atajulikana. Kushiriki kwako ni kwa hiari yako. Nakuomba ukubali mtoto wako afanyiwe utafiti huu.

Unamaswali yoyote ungependa kuuliza?

Mimi,_____, mzazi/mchungaji wa motto huyu mgonjwa, baada ya kuelezewa juu ya utafiti huu na maswali yangu yote kujibiwa vizuri, nakubali motto wangu awe mmoja wa wale wanaokuwa katika utafiti huu.

9.2 Appendix 2: Approvals from IREC and Webuye sub county hospitals

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2012/218
Approval Number: 000964

21st March, 2013

Dr. Otieno James Oduor,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

Dear Dr. Oduor,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee have reviewed your research proposal titled:-

"Correlation between Malarial Retinopathy and Diagnosis of Cerebral Malaria in Children Admitted Comatose at Webuye District Hospital."

Your proposal has been granted a Formal Approval Number: **FAN: IREC 000964** on 21st March, 2013. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 20th March, 2014. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

26/03/2013
DR. W. ARUASA
VICE-CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc: Director - MTRH
Principal - CHS
Dean - SOM
Dean - SPH
Dean - SOD
Dean - SON

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
APPROVED
21 MAR 2013

MINISTRY OF MEDICAL SERVICES

Telegram: "MEDICAL",- Webuye
TEL/FAX: 020 2625315
TELNO: 055-41066/41314

When Replying please quote

WEBUYE DISTRICT HOSPITAL
P.O. BOX 25
WEBUYE

REF: WBY/DH/GA/8B/VOL.111

24th May, 2013

Dr. Otieno James Odour,
Family Medicine Department - Moi University,
WEBUYE DISTRICT HOSPITAL.

RE: STUDY APPROVAL: CORRELATION BETWEEN MALARIAL RETINOPATHY AND DIAGNOSIS OF CEREBRAL MALARIA IN CHILDREN ADMITTED COMATOSE AT WEBUYE DISTRICT HOSPITAL

Following your request to conduct the aforementioned research in our facility, I am glad to inform you that approval has been granted by the relevant hospital committee.

On perusal of your abstract, it was noted that there was no similar on-going study in the facility. Likewise, there were no unaddressed ethical concerns.

We look forward to a mutually beneficial engagement.

DR. MUNYENDO W. A
MEDICAL SUPERINTENDENT
WEBUYE DISTRICT HOSPITAL

c.c.
The Medicines and Therapeutics Committee,
Webuye District Hospital,
P.O. Box 25,
WEBUYE

9.3 Appendix 3: Questionnaire

Patient code……

PART A: SOCIAL DEMOGRAPHICS

1. Age:_____ Date of Birth:_____
2. Sex: [1] ○ Male [2] ○ Female
3. Weight:_____
4. In the assessment of Developmental milestones of the child, are they:

   [1]○Delayed [2]○Appropriate for age [3]○Regressed

5. Is the Immunization of the child up to date according to KEPI schedule:

   [1]○Yes [2]○No

PART B: CLINICAL AND LABORATORY PRESENTATION

6. Temperature at time of admission(^{0}C):_____
7. Duration of illness(days): _____
8. Convulsions(History of convulsions, observed at admission or in the course of inpatient stay):

   [1]○ Yes(*if yes, go to 11*) [2] ○No(*go to 12*)

9. If Yes, what were the type of convulsions:

   [1]○Focal [2]○ Generalized

10. Presenting Symptoms(*Tick those which apply)*:

[1]□ Respiratory symptoms (cough, Difficulty in breathing, wheeze, runny nose),

[2]□ Urinary symptoms (dysuria, hematuria),

[3]□ Gastrointestinal symptoms(diarrhea, vomiting),

[4]□ HoB

[5]□ CNS systems(headache, convulsions, altered level of conscious/lethargic)

11. Treatment before presenting to the hospital(*Tick all that apply):*

[1]□ Antimalarials

[2]□ Antibiotics

[3]□ Traditional treatment

[4]□ Faith based treatment

12. Coma scale score at admission(*Choose one):*

a. AVPU: [1] A [2]V [3]P [4]U
b. Blantye coma scale_____

13. Dehydration status of the child(*Choose one):*

[1]○None [2]○Some [3]○Severe [4]○Shock

14. Is the child pale(*Choose one):* [1] ○Yes [2] ○No
15. What was the pupillary light reflex (*Choose one):*

    [1]○Bilaterally equally reactive to light [2]○Abnormal light reflex

16. Is there peripheral lymphadenopathy? [1] ○Yes [2] ○No
17. If there is lymphadenopathy in 16 above, is it [1] ○ Cervical [2] ○ Axillary [3] ○ Inguinal
18. In Head, Ear, Nose and Throat exam, is there(*Tick all that apply)*: [1] ○ Otitis media [2] ○Pharyngitis [3] ○None of the above [4] All of the above
19. Presence of neurological signs:

    [1]○ Yes [2]○No

If Yes, Specify(*Tick all that apply)*: [1] cranial nerves abnormalities[2] bruxism [3] opisthotonus[4] motor abnormalities [5] Other *specify*_____

Kernig's sign: [1]○Positive [2] ○ Negative

Brudzimki's sign : [1]○Positive [2] ○ Negative

20. Laboratory work up
    - RBS(at admission, *mmol/L*): _____
    - Blood slide for malaria parasites(*up to a maximum of 3 done 8hours apart*): [1] Positive [2] Negative
    - Lumbar puncture results: Gram Stain *[1] Positive [2] Negative,* Ziehl Nelsen Stain *[1] Positive [2] Negative* Indian Ink *[1] Positive [2] Negative* Cell count *[1]*less than 5 [2] 5-10 cells [3] more than 10

- Complete blood count and differentials: TLC: [1] Normal [2]Leukopenia [3] Leukocytosis; Neutrophils count [1] Normal[2] Neutropenia [3] Increased; Hb [1] Normal [2] Anemic(*mild or moderate*) [3] Severe anemia
- Sickle cell test: [1] Positive [2] Negative
- Urinalysis(Positive will either with leukocytes, nitrites or proteins on dip stick): [1] Positive [2] Negative

21. Final diagnosis(to be filled at time of discharge/death): [1] Cerebral Malaria [2] Acute bacterial meningitis [3] Encephalopathies of undetermined origin [4] Other(*Specify*)_____
22. FUNDOSCOPY EXAMINATION FINDINGS(*to be carried out within 24 hours of admission*)

    Time Started:

    Findings

    [1]Optic neuritis □

    [2]Papilledema □

    [3]Optic atropy □

    [4]Retinal whitening □

    [5]Vessel changes (either white or orange) □

    [6]Retinal hemorrhages □

[7]Others (specify)_____

Challenges met during the examination_____

Time finished

EVALUATION OF TREATMENT OUTCOMES

23. Time to coma resolution: [1] <24 hours [2] 24-48 hours [3]48-72hrs [4]>72hours
24. Complete recovery with no neurological deficit: [1] Yes [2] No
25. Complete recovery with neurological deficit: [1] hemiplegia [2] focal seizures [3]quadriparesis [4]movement disorders [5] cognitive impairment [6] blindness [7]loss of social skills [8]speech [9] hearing impairment
26. Death: [1] Yes [2] No

9.4 Appendix 4: The Coma Scales

Blantyre coma scale (from NHS clinical knowledge summaries – clinical topic – malaria… Glasgow and Blantyre coma scales)

Eye movement

1 - Watches or follows e.g watches mother's face

0 - Fails to watch or follow

Best motor response

2 - Localizes painful stimulus

1 - Withdraws limb from painful stimulus

0 - No response or inappropriate response

Best verbal response

2 - Cries appropriately with pain, or, if verbal, speaks

1 - Moan or abnormal cry with pain

0 - No vocal response to pain

Any score less than 4 is abnormal. A score of 2 or less indicates 'unrousable coma'. The maximum score is 5.

9.5 Appendix 5: Work Plan

January 2012 to November 2012 – writing research proposal and defense of the proposal at departmental level

November 2012 – January 2013 – submitting research proposal to IREC for approval

January 2013 – February 2013 – Training and certification of the researcher by ophthalmologist on doing fundoscopy and to be able to identify retinal changes in various conditions

March 2013 – pilot study and submission to IREC any alteration to questionnaire for approval

June 2013 to December 2013 – data collection, editing and entry into Epi info

January 2014 to June 2014 – Data analysis using STATA v 10

July 2014 to August 2014 – Presentation to department, mock defense

August 2014 – correction and finalizing of the thesis

August 2014 – Submission of the thesis manuscript

February 2015 – Defense of the thesis

February 2015 – correction and submission of bound thesis document

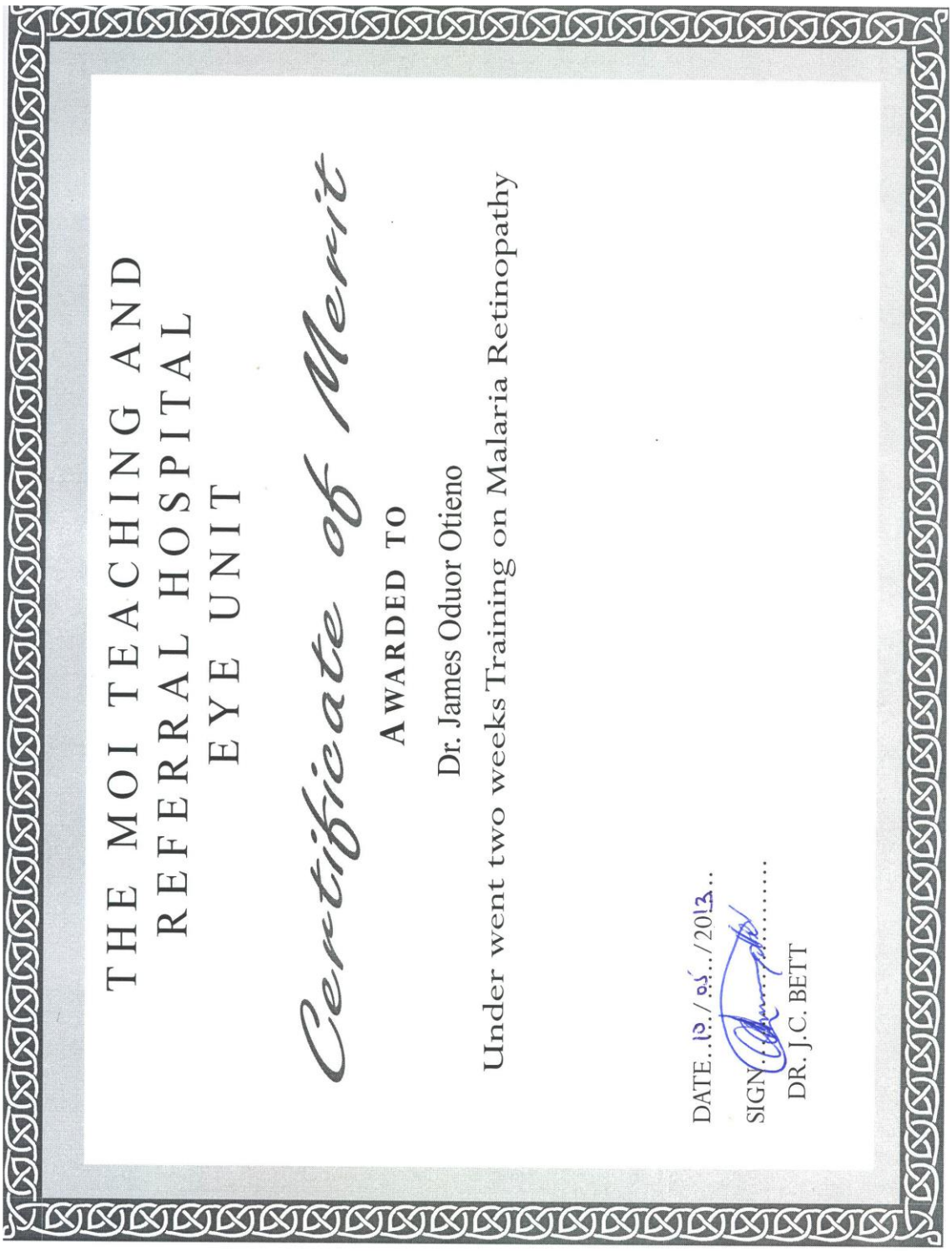
9.6 Appendix 6: Budget

ITEM	COST
Research assistants(3)	6,000
Laboratory reagents(Field stain A and B)	6,000
Biostastician	35,000
Stationery and Printing costs	16,000
SUBTOTAL	**63,000**
Contingency(10% subtotal)	6,300
TOTAL	**69,300**

The study was funded by the principal investigator. The cost of all laboratory investigations were met by the patients. However, the cost of re-reading the blood slides for malaria parasites was met by the principal investigator.

The clinical officer ophthalmologist participated in the research on voluntary basis.

9.7 Certification



THE MOI TEACHING AND
REFERRAL HOSPITAL
EYE UNIT

Certificate of Merit

AWARDED TO

Dr. James Oduor Otieno

Under went two weeks Training on Malaria Retinopathy

DATE..19./04.../2013..

SIGN:.....

DR. J.C. BETT