Published in final edited form as:

Trans R Soc Trop Med Hyg. 2008 November ; 102(11): 1089–1094. doi:10.1016/j.trstmh.2008.06.014.

Using malarial retinopathy to improve the classification of children with cerebral malaria

Susan Lewallen^{a,b,*}, Rachel N. Bronzan^{c,d}, Nicholas A. Beare^{e,f}, Simon P. Harding^f, Malcolm E. Molyneux^{f,g}, and Terrie E. Taylor^{c,d}

^aKilimanjaro Centre for Community Ophthalmology, Tumaini University/KCMC, Moshi, Tanzania

^bBritish Columbia Centre for Epidemiologic and International Ophthalmology, University of British Columbia, Vancouver, Canada

^cBlantyre Malaria Project, University of Malawi College of Medicine, Blantyre, Malawi

^dDepartment of Internal Medicine, College of Osteopathic Medicine, Michigan State University, East Lansing, MI, USA

^eSt Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, UK

^fMalawi-Liverpool-Wellcome Trust Clinical Research Programme, College of Medicine, University of Malawi, Blantyre, Malawi

^gSchool of Tropical Medicine, University of Liverpool, Liverpool, UK

Summary

The mechanisms leading to death in cerebral malaria (CM) remain unclear. We compared clinical and laboratory data among children with CM, categorized by ocular fundus findings, to elucidate differences that suggest different underlying pathological processes. From 1999–2005, standard examinations, treatment and record keeping were used for children with a clinical diagnosis of CM. Children were divided into ocular subgroups: normal fundus (N), malarial retinopathy (R), or papilloedema alone (P) and appropriate statistical tests were used to compare clinical and laboratory findings among groups. Eight hundred and eighty children who had eye examinations within 6 h of admission were included in the analysis. The groups differed significantly in case-fatality rates: Group P, 44.4% (95% CI 25.3–63.2), Group R, 18.0% (95% CI 15.6–22.3) and Group N, 7.0% (95% CI 4.2–9.8). There were also significant differences among the groups in blood pressure, prevalence of deep breathing, haematocrit, parasite density, platelet concentration and, among survivors, hours taken to recover from coma. Differences among groups suggest that different underlying pathophysiological processes are operating in children with CM defined by existing criteria. Our proposed classification, by improving the specificity of diagnosis, would enhance consistency among different study sites and prove useful in future research studies.

© 2008 Royal Society of Tropical Medicine and Hygiene. Published by Elsevier Ltd. All rights reserved.

*Corresponding author. Present address: P.O. Box 2254, Moshi, Tanzania. slewallen@kcco.net (S. Lewallen).

Authors' contributions: SL conceived and designed the overall study; SL conceived the concepts of the classification described here, in consultation over several years with all other authors; NAB, SPH and TET made significant contributions to the concepts in the classification scheme; RNB, MEM and TET examined the patients; SL and NAB performed the ophthalmological examinations; TET collected data; RNB designed the database and provided support with statistical analysis; MEM and TET helped to develop the database; SL analyzed the data and took primary responsibility for writing the manuscript; NAB, MEM and TET made significant contributions to the final manuscript. All authors read and approved the final manuscript. SL is guarantor of the paper.

Conflicts of interest: None declared.

Ethical approval: Granted by the Malawi College of Medicine Research Committee, Blantyre, Malawi.

Keywords

Cerebral malaria; Children; Retinopathy; Pathophysiology; Papilloedema; Malawi

1. Introduction

The standard clinical case definition for the syndrome known as cerebral malaria (CM) in children includes coma (Blantyre Coma Score ≥ 2), *Plasmodium falciparum* parasitaemia and no other identifiable cause of coma (WHO, 2000). The case-fatality rate in the group at highest risk, African children, is 15–30%, even with good treatment (Newton et al., 1998). In addition, up to 24% of survivors suffer long-term neurological sequelae (Carter et al., 2005). Furthermore, the inability to exclude other causes of coma in a parasitaemic child may limit the accuracy of the diagnosis of CM in malaria-endemic areas. Much remains unknown about CM, including the mechanisms that lead to death.

Examination of the ocular fundus by binocular indirect ophthalmoscopy in patients with malaria and coma has yielded new findings in recent years, and their usefulness as prognostic indicators has been demonstrated (Beare et al., 2004; Lewallen et al., 1993, 1996, 1999). The fundus abnormalities in CM consist of four distinct features: haemorrhages, retinal whitening, vessel abnormalities and papilloedema. Haemorrhages have been recognized for many years in CM, and are round, predominately have white centres, and may number from one to more than 50 in the retina. Retinal whitening, originally referred to as retinal oedema (Lewallen et al., 1993) is a patchy opacification of the retina, most common around the fovea or in the temporal posterior pole (macular whitening) but also occurring in the peripheral retina (peripheral whitening). Retinal whitening is distinct from cotton wool spots, which also occur, but less frequently. Vessel abnormalities are discolorations in small vessels and capillaries, which appear orange or white rather than red. The colour changes are often present in a segmental fashion, usually on the venous side of the circulation. Papilloedema (bilateral optic disc swelling) has also been recognized as a feature in CM. It may occur alone or in combination with the first three signs.

Papilloedema and retinal haemorrhages are not unique to CM, although white-centred haemorrhages are only occasionally seen in other conditions. The vessel abnormalities and the pattern of retinal whitening, however, have never been described in any disease other than malaria. The abnormal retinal vessels are associated with sequestration of parasitized dehaemoglobinized red blood cells on histopathological examination (Lewallen et al., 2000). The pathogenesis of retinal whitening has recently been shown to be due to local tissue hypoxia (Beare et al., 2008). There is a positive correlation between the numbers of retinal and brain haemorrhages in patients undergoing autopsy (White et al., 2001). Taken together, these associations suggest that retinal findings reflect pathological processes occurring in the brain. Given that the retina is an embryonic outgrowth of neural ectoderm, this is not an unreasonable hypothesis.

A histopathological study of fatal malaria in Malawian children has demonstrated the importance of retinopathy as a clinical sign in severe malaria (Taylor et al., 2004). In that study, 23% of children who died with a clinical diagnosis of CM actually had other non-malarial causes of death discovered on autopsy. The absence of malarial retinopathy on fundus examination before death proved to be the most accurate way to identify the cases with non-malarial causes of death.

Our observation that children with clinically defined CM fall into several distinct groups defined by the ocular fundus signs led us to hypothesize that these groups might represent

different pathophysiological processes. Using data collected in a standard fashion from 1999 to 2005 in the paediatric research ward in Blantyre, Malawi, we compared clinical and laboratory features of patients according to fundus findings.

2. Methods

Enrolled patients included all those admitted to the paediatric research ward at the Queen Elizabeth Central Hospital in Blantyre, Malawi from 1999 to 2005 who satisfied the standard clinical case definition of CM (WHO, 2000): *P. falciparum* parasitaemia, a coma score of 2 or less on the Blantyre Coma Scale maintained for at least 4 h after admission, and no other explanation for altered consciousness, e.g. hypoglycaemia or meningitis. Informed consent to be part of ongoing studies was obtained from guardians according to procedures approved by the Malawi College of Medicine Research Committee. All children underwent a standardized history and physical examination and were managed according to standard protocols. Blood culture and lumbar puncture, unless contraindicated, were performed on admission. All children were treated with intravenous quinine with a loading dose of 20 mg/kg given over 4 h followed by 10 mg/kg every 12 h for at least 24 h and a single oral dose of sulfadoxine-pyrimethamine. Glucose, blood transfusions and anticonvulsants were administered if clinically indicated. Antibiotic coverage was provided when a lumbar puncture was clinically contraindicated or when the patient's clinical condition was consistent with septic shock (cool extremities, delayed capillary refill, or hyperlactataemia).

Fundus examinations were conducted using direct and indirect ophthalmoscopy through fully dilated pupils, by trained ophthalmologists who recorded their findings on a standard form. Fundus examinations were carried out as soon as possible after admission, once the patient was clinically stabilized and the pupils were dilated with short-acting mydriatic drops. Haemorrhages, retinal whitening and abnormal vessels were graded for severity (Harding et al., 2006). The ophthalmologist was not aware of laboratory findings (including parasitaemia) at the time of the admission examination. Patients admitted in 1999 and 2000 (276 in total) were the subjects of a previous report (Beare et al., 2004) in which we described the predictive value of individual eye signs for outcome, and followed the signs over several weeks.

Data were entered into SPSS version 10 (SPSS Inc., Chicago, IL, USA). We calculated case-fatality rates (with 95% CIs) and mean values (with SDs) or frequencies of other variables for each of three funduscopically-defined groups. Differences in clinical and laboratory parameters among the three groups were tested by Pearson's χ^2 tests for binary outcomes, or nonparametric tests (Mann-Whitney *U* or Kruskal-Wallis) for continuous variables. $P < 0.05$ was considered to be statistically significant.

3. Results

During the period of study, 1191 children with clinically defined CM were admitted and 879 had an eye examination by an ophthalmologist, once they were stable, within 6 h of admission. Comparing the group who were examined to those not examined, there was no difference in age or gender. Unexamined children were significantly more likely to die than those who were examined (odds ratio = 1.8, 95% CI 1.3–2.5, $P = 0.001$) and their mean time from admission to death was 10.7 h compared to 20.8 h in examined children ($P < 0.001$, Mann-Whitney *U*).

Children who satisfied the standard clinical case definition of CM were classified into one of three groups on the basis of their funduscopic findings: Group N ($n = 327$) had normal fundi,

Group R ($n = 526$) had malarial retinopathy (typical malaria haemorrhages, retinal whitening of any degree or abnormal vessels) and Group P ($n = 27$) had papilloedema only, without any of the other features of malarial retinopathy. Group R was further subdivided into R1 ($n = 427$), without papilloedema, and R2 ($n = 99$), with papilloedema.

There were significant differences in case-fatality rates among the groups (Table 1). Group P had the highest fatality rate (44.4%), followed by Group R (18.9%) and Group N (7.1%). Within Group R, the case fatality rate for R2 (those with papilloedema) was significantly higher than for R1 (those without papilloedema) ($P < 0.001$).

Significant differences among Groups N, R and P were found for the number of hours taken to recover from coma (among survivors), admission blood pressure, opening cerebrospinal fluid pressure (when measured), parasite density, haematocrit and platelet count (Table 1). Lactate values could not be measured in all cases due to equipment failure. There were significant differences between Group R2 and Group P (both with papilloedema) in haematocrit ($P < 0.001$, Mann-Whitney U), platelets ($P = 0.001$, Mann-Whitney U) and blood pressure ($P = 0.003$, Mann-Whitney U).

Post-hoc pairwise comparisons in the variables between each main group (N vs. R, N vs. P and R vs. P) are also shown in Table 1. A comparison of funduscopy findings between Group R1 and Group R2 is shown in Table 2, demonstrating that malarial retinopathy was more severe in R2.

4. Discussion

Previous studies have demonstrated that the eye findings in CM are predictive of outcome and that papilloedema is independently associated with a poor prognosis (Beare et al., 2004; Lewallen et al., 1993). Our current analysis, which includes the largest number of patients reported, categorizes children with clinically defined CM into three funduscopically-defined groups; these groups also differ markedly in terms of case-fatality rates and a number of laboratory features and clinical signs. We suggest that these may be three pathophysiologically distinct subsets of children, all of whom are currently diagnosed as having CM.

Group N children, with normal ocular fundi, have the lowest case-fatality rate. Group N may represent two different types of patients: those with severe non-malarial illnesses, and those with less severe malaria and coma. The mortality is low in this group, and we have previously reported that the two children in this group who died and underwent autopsy had non-malarial causes of death with no evidence of parasitized red cells sequestered in the cerebral microvasculature (Taylor et al., 2004). The current analysis demonstrates that the survivors in Group N have a significantly shorter mean coma resolution time than survivors in either Group R or Group P. This suggests additional potential etiologies for the symptom complex in the Group N patients: a prolonged post-ictal state, sub-threshold convulsions, or simply less severe CM.

The patients in Group R, identified by the presence of retinal whitening, haemorrhages or abnormal vessels (malarial retinopathy) had significantly lower haematocrits and platelet counts and higher blood lactate concentrations than those in Group N or Group P; the parasite density was higher than in Group N. This group could be considered to have 'true' CM. Hyperlactataemia in Group R may be partly the result of impaired blood flow (due to sequestration of parasitized erythrocytes, increased rigidity of red cells and other factors) in tissues with high metabolic demands, e.g. retina and brain. Tissue hypoxia would be exacerbated by anaemia, a prominent feature in many patients in Group R. Sequestration is not uniform within tissues; the patchy retinal whitening of CM is an indication of localized

retinal tissue hypoxia and cellular swelling (oncosis) (Beare et al., 2008). The distribution of retinal whitening suggests microvascular obstruction caused by sequestration. Similar hypoxia and subsequent cellular swelling in the brain could produce the cerebral oedema and raised intracranial pressure observed in Group R2. Consistent with this hypothesis, Table 2 shows that the severity of retinal whitening is significantly worse in those with papilloedema (Group R2) than in those without (Group R1). Post-mortem examination of 15 cases in Groups R1 and R2 showed that all had cerebral sequestration and alternative causes of death were absent in this group (Taylor et al., 2004).

The patients in Group P had papilloedema as their sole fundus abnormality, and this most likely represented underlying raised intracranial pressure. Most of these patients were not anaemic or thrombocytopenic; the platelet and haematocrit values in this group were significantly different from those in Group R2 (also with papilloedema). They had the highest case-fatality rate of all the patient groups, and on average the lowest blood pressures, the longest coma resolution times and the highest frequency of positive blood cultures. We hypothesize that this group consists of parasitaemic patients with a variety of other non-malarial illnesses responsible for raised intracranial pressure. We have now conducted two autopsies on patients in Group P; neither demonstrated cerebral sequestration of parasitized red blood cells in any of nine brain sites examined, and both had an alternative explanation for death; one died of hepatic necrosis and the other of *Streptococcus pneumoniae* pneumonia. The peripheral parasitaemia levels were 27 970 parasites/ μ l and 112 162 parasites/ μ l, respectively. Viral infections and toxicity from accidental poisoning or local medicines are among other illnesses that may remain undiagnosed when accompanied by parasitaemia in African children in malarial endemic regions (Reyburn et al., 2004). A higher proportion of patients in Group P had evidence of shock (arterial pressure <80 mmHg), than in Groups N and R, and the frequency of positive blood culture was higher than that seen in a large series of children with severe malaria (Bronzan et al., 2007). These additional differences in disease characteristics strengthen the suggestion that non-malarial illnesses are responsible for the coma, papilloedema and poor prognosis in this group. Our data do not prove that patients in Group P are not suffering principally from malaria, but are suggestive and provide the rationale for a prospective study to address this question further.

A limitation in this study is the fact that not all children had fundus examination. This was due to the fact that patients who died before the ophthalmologist arrived on the ward could not be adequately examined, and is consistent with both the higher case-fatality rate and the earlier time of death in the unexamined than the examined groups.

Our observations should not prevent clinicians from giving full antimalarial treatment to patients with coma and parasitaemia who fall into Groups N or P, but special consideration should be paid to the possibility of other or additional diagnoses in these groups. In research studies of pathogenesis or treatment, a primary analysis restricted to group R patients should be considered.

In summary, we suggest that children with clinically defined CM should be categorized according to their ocular fundus findings and we plan to do this for all future studies (Taylor et al., 2006). Our hypotheses are firstly, that patients in Group N with normal fundi and quick recovery may have a less severe form of CM, often complicated by convulsions, but without cerebral sequestration. The small subset with prolonged coma or fatal outcome may have non-malarial causes of severe illness accompanied by peripheral parasitaemia. Secondly, that patients in Group R with malarial retinopathy have cerebral sequestration of parasitized erythrocytes in the microvasculature of the brain and the retina, leading to areas of local tissue hypoxia. A subgroup, with a significantly higher case-fatality rate, has raised intracranial pressure, manifested as papilloedema, due to brain swelling that could be caused

by more extensive areas of localized hypoxia in the brain. Thirdly, that patients in Group P with papilloedema but no evidence of malarial retinopathy have malaria parasitaemia combined with another life-threatening illness. They have the highest risk of death and will distort case-fatality statistics, as well as other potential predictor and outcome measures, if included in studies of CM.

We believe that it is very important to include fundus findings in future research studies of CM. Hypoglycaemia, raised intracranial pressure, hypoxaemia, hypovolaemia, deep breathing, erythrocyte rosetting, acidosis, low plasma nitric oxide, arginine and phenylalanine concentrations, and elevated plasma TNF concentrations have all been shown to be associated with higher case-fatality rates in children who meet the standard case definition of CM (Anstey et al., 1996; English et al., 1997; Junge et al., 2006; Lopansri et al., 2003; Maitland et al., 2003; Marsh et al., 1995; Rowe et al., 1995; Taylor et al., 1988) but the strength of these associations may depend on the proportion of subjects in Groups N, R and P. Previously tested hypotheses to determine clinical and laboratory features independently associated with death may reveal new findings if distortions introduced by Group P are excluded.

If the specificity of the diagnosis of CM in research studies is improved by ophthalmoscopy, the recognition of important pathogenic mechanisms ought to increase. To reduce mortality in CM, new treatments must act within the first few hours after presentation, when most deaths occur. The bedside characterization of CM syndromes on the basis of malarial retinopathy can identify which patients with clinically defined CM require further diagnostic investigation, and which would benefit from intensive supportive interventions above and beyond treatment with antimalarial drugs.

Acknowledgments

We thank all the volunteer ophthalmologists who contributed to this study.

Funding: The work was supported by the US National Institutes of Health (AI 34969, T.E. Taylor) and The Wellcome Trust, UK (074125/Z/04/Z, N.A. Beare; 074124, M.E. Molyneux).

References

- Anstey NM, Weinberg JB, Hassanali MY, Mwaikambo ED, Manyenga D, Misukonis MA, Arnelle DR, Hollis D, McDonald MI, Granger DL. Nitric oxide in Tanzanian children with malaria: inverse relationship between malaria severity and nitric oxide production/nitric oxide synthase type 2 expression. *J. Exp. Med.* 1996; 184:557–567. [PubMed: 8760809]
- Beare NA, Southern C, Chalira C, Taylor TE, Molyneux ME, Harding SP. Prognostic significance and course of retinopathy in children with severe malaria. *Arch. Ophthalmol.* 2004; 122:1141–1147. [PubMed: 15302654]
- Beare NAV, Harding SP, Taylor TE, Lewallen S, Molyneux ME. Perfusion abnormalities in children with cerebral malaria and malarial retinopathy. *J. Infect. Dis.* 2008 (in press).
- Bronzan RN, Taylor TE, Mwenechanya J, Tembo M, Kayira K, Bwanaisa L, Njobvu A, Kondowe W, Chalira C, Walsh AL, Phiri A, Wilson LK, Molyneux ME, Graham SM. Bacteremia in Malawian children with severe malaria: prevalence, etiology, HIV coinfection, and outcome. *J. Infect. Dis.* 2007; 195:895–904. [PubMed: 17299721]
- Carter JA, Mung'ala-Odera V, Neville BG, Murira G, Mturi N, Musumba C, Newton CR. Persistent neurocognitive impairments associated with severe falciparum malaria in Kenyan children. *J. Neurol. Neurosurg. Psychiatry.* 2005; 76:476–481. [PubMed: 15774431]
- English M, Sauerwein R, Waruiru C, Mosobo M, Obiero J, Lowe B, Marsh K. Acidosis in severe childhood malaria. *QJM.* 1997; 90:263–270. [PubMed: 9307760]

- Harding SP, Lewallen S, Beare NA, Smith A, Taylor TE, Molyneux ME. Classifying and grading retinal signs in severe malaria. *Trop. Doct.* 2006; 36(Suppl. 1):1–13. [PubMed: 16600082]
- Junge S, Palmer A, Greenwood BM, Kim ME, Weber MW. The spectrum of hypoxaemia in children admitted to hospital in The Gambia, West Africa. *Trop. Med. Int. Health.* 2006; 11:367–372. [PubMed: 16553917]
- Lewallen S, Taylor TE, Molyneux ME, Wills BA, Courtright P. Ocular fundus findings in Malawian children with cerebral malaria. *Ophthalmology.* 1993; 100:857–861. [PubMed: 8510897]
- Lewallen S, Bakker H, Taylor TE, Wills BA, Courtright P, Molyneux ME. Retinal findings predictive of outcome in cerebral malaria. *Trans. R. Soc. Trop. Med. Hyg.* 1996; 90:144–146. [PubMed: 8761574]
- Lewallen S, Harding SP, Ajewole J, Schulenburg WE, Molyneux ME, Marsh K, Usen S, White NJ, Taylor TE. A review of the spectrum of clinical ocular fundus findings in *P. falciparum* malaria in African children with a proposed classification and grading system. *Trans. R. Soc. Trop. Med. Hyg.* 1999; 93:619–622. [PubMed: 10717749]
- Lewallen S, White VA, Whitten RO, Gardiner J, Hoar B, Lindley J, Lochhead J, McCormick A, Wade K, Tembo M, Mwenechanyana J, Molyneux ME, Taylor TE. Clinical-histopathological correlation of the abnormal retinal vessels in cerebral malaria. *Arch. Ophthalmol.* 2000; 118:924–928. [PubMed: 10900105]
- Lopansri BK, Anstey NM, Weinberg JB, Stoddard GJ, Hobbs MR, Levesque MC, Mwaikambo ED, Granger DL. Low plasma arginine concentrations in children with cerebral malaria and decreased nitric oxide production. *Lancet.* 2003; 361:676–678. [PubMed: 12606182]
- Maitland K, Levin M, English M, Mithwani S, Peshu N, Marsh K, Newton CR. Severe *P. falciparum* malaria in Kenyan children: evidence for hypovolaemia. *QJM.* 2003; 96:427–434. [PubMed: 12788961]
- Marsh K, Forster D, Waruiru C, Mwangi I, Winstanley M, Marsh V, Newton C, Winstanley P, Warn P, Peshu N. Indicators of life-threatening malaria in African children. *N. Engl. J. Med.* 1995; 332:1399–1404. [PubMed: 7723795]
- Newton CR, Taylor TE, Whitten RO. Pathophysiology of fatal falciparum malaria in African children. *Am. J. Trop. Med. Hyg.* 1998; 58:673–683. [PubMed: 9598460]
- Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O, Saganda K, Shao J, Kitua A, Olomi R, Greenwood BM, Whitty CJ. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *Br. Med. J.* 2004; 329:1212. [PubMed: 15542534]
- Rowe A, Obeiro J, Newbold CI, Marsh K. *Plasmodium falciparum* rosetting is associated with malaria severity in Kenya. *Infect. Immun.* 1995; 63:2323–2326. [PubMed: 7768616]
- Taylor TE, Molyneux ME, Wirima JJ, Fletcher KA, Morris K. Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. *N. Engl. J. Med.* 1988; 319:1040–1047. [PubMed: 3050516]
- Taylor TE, Fu WJ, Carr RA, Whitten RO, Mueller JS, Fosiko NG, Lewallen S, Liomba NG, Molyneux ME. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. *Nat. Med.* 2004; 10:143–145. [PubMed: 14745442]
- Taylor T, Olola C, Valim C, Agbenyega T, Kremsner P, Krishna S, Kwiatkowski D, Newton C, Missinou M, Pinder M, Wypij D. Standardized data collection for multi-center clinical studies of severe malaria in African children: establishing the SMAC network. *Trans. R. Soc. Trop. Med. Hyg.* 2006; 100:615–622. [PubMed: 16551469]
- White VA, Lewallen S, Beare N, Kayira K, Carr RA, Taylor TE. Correlation of retinal haemorrhages with brain haemorrhages in children dying of cerebral malaria in Malawi. *Trans. R. Soc. Trop. Med. Hyg.* 2001; 95:618–621. [PubMed: 11816433]
- WHO. Severe falciparum malaria. *Trans. R. Soc. Trop. Med. Hyg.* 2000; 94(Suppl. 1)

Table 1

Clinical and laboratory features in groups categorized by eye findings

	Group N (n = 327)	Group R (n = 525)	Group R1 (n = 427)	Group R2 (n = 98)	Group P (n = 27)	P-value ^a	Post-hoc pairwise comparisons
Female (%) (95% CI)	49.2 (41.5–56.9) n = 327	47.2 (41.0–53.4) n = 525	48.3 (41.5–55.1) n = 426	42.4 (37.5–57.3) n = 98	48.1 (21.0–75.2) n = 27	0.69	
Mean age (months) (SD)	42.6 (29.6) n = 327	40.6 (26.9) n = 524	39.3 (25.6) n = 426	46.0 (31.4) n = 98	39.4 (23.3) n = 27	0.54	
Case fatality rate (%) (95% CI)	7.1 (4.2–9.8) n = 327	18.9 (15.7–22.4) n = 525	15.0 (11.6–18.4) n = 427	36.4 (26.9–46.4) n = 98	44.4 (25.3–63.1) n = 27	<0.001	N vs. R < 0.001
Survivors with neurological sequelae (%) (95% CI)	11.6 (8.3–14.8) n = 303	10.3 (7.4–13.2) n = 426	10.7 (7.6–13.9) n = 363	7.9 (1.26–14.6) n = 63	20.0 (0–40.2) n = 15	0.95	N vs. P < 0.001 R vs. P = 0.005
Median hours to BCS 5 (range)	24.0 (4–168) n = 280	32 (4–200) n = 388	30 (4–200) n = 332	44 (6–146) n = 56	48 (8–202) n = 14	<0.001	N vs. R < 0.001
Mean blood pressure (mmHg) (SD)	110 (17) n = 315	107 (18) n = 506	108 (18) n = 416	109 (18) n = 90	97 (22) n = 25	0.002	N vs. P = 0.008 R vs. P = 0.19 N vs. R = 0.23
BP <80mmHg (%) (95% CI)	2.2 (0.6–3.8) n = 315	2.0 (0.8–3.2) n = 506	2.4 (0.9–3.9) n = 416	0 n = 90	20 (0–55.1) n = 25	0.025	N vs. P = 0.001 R vs. P = 0.004 N vs. R = 0.80 N vs. P = 0.001 R vs. P < 0.001
Mean opening CSF pressure (mm water) (SD)	150 (79) n = 221	180 (78) n = 325	178 (80) n = 282	191 (72) n = 43	217 (70) n = 19	<0.001	N vs. R < 0.001 N vs. P < 0.001 R vs. P = 0.05
Deep breathing (%) (95% CI)	25.2 (20.8–29.9) n = 327	32.2 (28.2–36.2) n = 525	32.4 (28.0–36.8) n = 424	31.2 (22.1–40.3) n = 98	38.5 (19.8–57.2) n = 27	0.02	N vs. R = 0.04 N vs. P = 0.16 R vs. P = 0.52
Geometric mean parasite density/μl (95% CI)	32 226 (24 415–42 539) n = 311	45 804 (36 784–57 041) n = 505	48 139 (37 695–61 485) n = 409	37 060 (22 434–61 214) n = 96	63 929 (26 346–155 089) n = 27	0.04	N vs. R = 0.05 N vs. P = 0.17

	Group N (<i>n</i> = 327)	Group R (<i>n</i> = 525)	Group R1 (<i>n</i> = 427)	Group R2 (<i>n</i> = 98)	Group P (<i>n</i> = 27)	<i>P</i> -value ^a	Post-hoc pairwise comparisons
Mean haematocrit (%) (SD)	28.2 (7.3) <i>n</i> = 327	20.4 (7.2) <i>n</i> = 521	20.4 (7.2) <i>n</i> = 425	20.5 (7.0) <i>n</i> = 96	31.2 (7.0) <i>n</i> = 27	<0.001	R vs. <i>P</i> = 0.46 N vs. <i>R</i> < 0.001 N vs. <i>P</i> = 0.04 R vs. <i>P</i> < 0.001
Severe malarial anaemia ^b (%) (95% CI)	12.2 (6.8–17.6) <i>n</i> = 327	52.0 (47.7–56.3) <i>n</i> = 521	51.4 (46.7–56.1) <i>n</i> = 425	54.6 (44.8–64.4) <i>n</i> = 96	3.7 (0–10.8) <i>n</i> = 27	<0.001	N vs. <i>R</i> < 0.001 N vs. <i>P</i> = 0.24 R vs. <i>P</i> < 0.001
Mean lactate (mmol/l) (SD)	7.5 (4.7) <i>n</i> = 69	8.87 (5.1) <i>n</i> = 26	9.3 (5.2) <i>n</i> = 03	6.8 (4.4) <i>n</i> = 23	5.9 (3.4) <i>n</i> = 7	0.08	
Median glucose (mmol/l) (range)	6.1 (0.3–26.6) <i>n</i> = 327	5.4 (0–32.6) <i>n</i> = 515	5.4 (0–32.6) <i>n</i> = 421	5.4 (0.6–20.9) <i>n</i> = 94	5.3 (0–14.0) <i>n</i> = 27	0.03	N vs. <i>R</i> = 0.009 N vs. <i>P</i> = 0.22 R vs. <i>P</i> = 0.53
Hypoglycaemia (%) (95% CI)	6.4 (3.76–9.04) <i>n</i> = 327	8.8 (6.37–11.21) <i>n</i> = 515	8.4 (6.1–10.75) <i>n</i> = 421	10.3 (4.17–16.03) <i>n</i> = 94	3.7 (0–10.82) <i>n</i> = 27	0.53	
Median platelet count (×10 ³ /μl) (range)	150 000 (9000–698 000) <i>n</i> = 252	62 000 (5000–902 000) <i>n</i> = 387	61 000 (5000–563 000) <i>n</i> = 320	73 000 (12 000–902 000) <i>n</i> = 67	127 000 (2500–772 000) <i>n</i> = 25	<0.001	N vs. <i>R</i> < 0.001 N vs. <i>P</i> = 0.89 R vs. <i>P</i> < 0.001
Median white blood count (cells/μl)	10 300 <i>n</i> = 295	10 800 <i>n</i> = 473	10 900 <i>n</i> = 387	10 550 <i>n</i> = 86	13 500 <i>n</i> = 27	0.22	
Positive blood culture (%) (95% CI)	2.2 (0.6–3.8) <i>n</i> = 318	3.2 (1.7–4.7) <i>n</i> = 504	3.2 (1.5–4.9) <i>n</i> = 411	4.3 (0.1–8.4) <i>n</i> = 93	7.7 (0–17.9) <i>n</i> = 26	0.24	

Data were missing for some variables; *n* is shown for every parameter in each group.

BCS: Blantyre Coma Scale; CSF: cerebrospinal fluid; Group N: normal fundus; Group R: malarial retinopathy; Group R1: malarial retinopathy with no papilloedema; Group R2 malarial retinopathy plus papilloedema; Group P: papilloedema only.

^a*P*-value for differences among groups N, R and P.

^bSevere malarial anaemia defined by packed red cell volume 5 mg/dl or patient required a transfusion based on clinical grounds, e.g. respiratory distress.

Table 2

Differences in severity of ocular fundus signs between Groups R1 and R2

Mean severity score ^a of fundus sign	Group R1 (<i>n</i> = 427)	Group R2 (<i>n</i> = 99)	<i>P</i> -value ^b
Haemorrhages	1.07	1.54	<0.001
Macular whitening	1.25	1.71	<0.001
Peripheral whitening	0.96	1.10	0.46
Abnormal vessels	0.91	1.19	0.035

Group R1: malarial retinopathy with no papilloedema; Group R2: malarial retinopathy plus papilloedema.

^aMacular and peripheral whitening were graded on a scale of 0—3; haemorrhages on a scale of 0—4 (Harding et al., 2006).

^bMann-Whitney *U* test.