Original Article

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Paediatrics Section

Bedside Prognostic Indicators of Fatal Outcome among Children with Cerebral Malaria at a Tertiary Nigerian Hospital

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ABSTRACT

Introduction: Cerebral Malaria (CM) is a severe manifestation of malaria and commonly causes poor outcomes. It affects upto one million people per year worldwide predominantly sub-Saharan African children. It is clinically expedient that, children with CM are identified promptly and easily to halt fatal outcomes.

Aim: To evaluate bedside prognostic indicators of poor outcome among children with CM.

Materials and Methods: A prospective, observational study was conducted at LAUTECH Teaching Hospital Ogbomoso, Oyo State, Nigeria among children diagnosed with CM from February 2018 to September 2018. Fifty children with age range of six months to 12 years were included in the study. Outcome indicators were full recovery, alive with neurological sequelae and death. Nine of the identified clinical factors demonstrable on bedside were assigned score of 1 each and each score summated to form Bedside Prognostic Index (BPI). The median BPI Score ≥4 indicated fatal outcome. Receiver Operating Characteristic (ROC) curve validated the predictive ability of the BPI score on clinical outcomes. Chi-square test and Student's t-test were used for statistical analysis.

Results: Out of total 50 children, 30 (60%) recovered fully, 11 (22%) participants had neurological deficit(s) and 9 (18%) participants died. The median BPI score among completely recovered, survived with neurological deficit(s) and died was 8, 6 and 4, respectively. BPI score ≥4 was an independent predictor of fatal outcome {Odd's Ratio (OR)=7.875, p-value=0.013, Confidence Interval (CI)=1.547-40.091} with sensitivity and specificity of 80% and 76.67%, respectively. The ROC of the predictive ability of BPI on clinical outcomes was 80.2%.

Conclusion: Poor outcome was significantly associated with BPI of ≥4 in children with CM. The use of this scoring index should be encouraged to promptly manage children with CM at risk of poor outcome.

Keywords: Clinical predictive scores, Neurological sequelae determinants, Paediatric mortality trend

INTRODUCTION

World Health Organisation (WHO) reported approximately 3.3 billion of the world population are at risk of the malaria infection. In year 2020, the estimated number of cases worldwide was 241 million and the WHO African region had about 228 million cases in 2020, accounted for about 95% of cases [1]. Severe malaria is one of the most serious infectious disease emergencies in children mostly related to *Plasmodium falciparum* [2,3]. It may be lethal and can lead to cerebral malaria which can rapidly progress to severe illness and lead to fatal outcome especially in children [2–4]. Cerebral malaria affects upto 1 million people per year worldwide, the vast majority being under 5-year-old children living in Sub-Saharan African (SSA) and these groups accounted for highest morbidity and mortality rates [5-7]. According to reports, cerebral malaria ranked next to severe malarial anaemia as a common complication of *Plasmodium falciparum* malaria in many hospitalised children [8,9]. According to previous studies, despite optimal treatment 15-22% of children accounts for deaths [8-10]. Prevalence of CM may depend on the geographic area of the study, season of the year, type of health Institution and the study design [10-12].

Studies across regions in Africa, one to two decades ago had reported major differences in the clinical manifestations and outcomes of CM in children at different ages and under different levels of malaria endemicity and patterns of transmission [10-13]. However, more emphasis needs to be placed on identifying bedside clinical and laboratory factors that could promptly and reliably detect cerebral malaria children with poor clinical outcome. Identification of bedside prognostic factors at early stage may help to reduce mortality and morbidity associated with CM. Some studies have reported different prognostic factors, but the present study formulated a bedside prognostic index score that would involve combination of different factors together so as to strongly predict poor outcome. The bedside prognostic index for CM when determined, will give a better estimate of prognosis than is possible using any single clinical or laboratory feature. These bedside indicators will be highly useful in many low-resource environments where access to optimal healthcare remains a huge task and with challenge of limitations or poor access to high technology facilities. The result of the present study is expected to aid paediatricians and all other healthcare providers to quickly recognise children with CM at risk of death or neurological sequelae so as to promptly initiate the appropriate management. Therefore, the present study aimed to formulate a bedside prognostic index score to predict poor outcome among children with cerebral malaria, especially in a low-resource community.

MATERIALS AND METHODS

This was a prospective, observational study conducted in the Children's Emergency Unit (CEU) at Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital Ogbomoso, Oyo State Nigeria, from February 2018 to September 2018. Informed consent was sought and only those that gave their written consent were included in the study. Ethical clearance was obtained from Ethics and Review Committee (Protocol number: LTH/OGB/EC/2017/145).

Inclusion criteria: Children between the age of six months to 12 years with unarousable coma lasting more than 30 minutes in the presence of demonstrable peripheral asexual *Plasmodium falciparum* parasitaemia and who developed deterioration in their level of consciousness after admission were included in the study. Consecutive children with cerebral malaria, who met the WHO criteria of a patient, who could not localise a painful stimulus, who

had peripheral asexual *Plasmodium falciparum* parasitaemia and had no other identified causes of an encephalopathy (such as meningitis, hypoglycaemia, encephalitis etc.) were included in the study [14].

Exclusion criteria: Children with positive Cerebrospinal Fluid (CSF) biochemical result (elevated CSF protein, low CSF Glucose) and/or CSF microbiological result (positive gram stain/elevated white blood cells and positive CSF culture) were excluded from the study. Those with a previous neurological deficit, who have demonstrable evidence of intracranial infections and whose caregiver declined granting consent for their participation in the study were excluded from the study.

Sample size calculation: The sample size for the study was calculated from the following formulae [15].

NF=N/[1+{(N–1)/Pop}]

NF=Desired minimum sample size for finite population

N=Desired sample size when the population is more than 10,000

Pop=Estimate of the population size (The annual population of children with cerebral malaria in LAUTECH Teaching Hospital Ogbomoso was 70)

$$\text{However, } N=\frac{Z^2pq}{d^2}$$

Z=Standard normal deviate usually set at 1.96, which corresponds to the 95% confidence level

p=Proportion in the target population estimated to have a particular characteristic, prevalence of 5.5% was used [16].

d=Degree of accuracy desired, set at the 0.05 level with standard error of 5%

q=1.0-p

$$\text{Therefore, } N=\frac{(1.96\times1.96)\times0.055\ (1\text{-}0.055)=79.8=80}{(0.05\times0.05)}$$

Applying the formula for the finite population, NF=N/[1+{(N–1)/Pop}]

NF=N/[1+{(N–1)/Pop}]; 80/[1+{(80-1)/70}]; NF=80/[1+{(79)/70}]; 80/{1+(1.2857)}=80/(2.12857)=37.58

With a 10% attrition rate, the minimum sample was 41. The sample size was rounded upto 50 children.

Study Procedure

Information was obtained on proforma which include details of CM such as bio data, the nature and duration of symptoms, pretreatment history followed by detailed clinical examination including general and neurological examinations [17].

Patients were classified using the presence or absence of selected clinical and laboratory parameters. Such clinical features included fever, loss of consciousness, convulsion, difficulty breathing, paleness of body, jaundice, dark brown urine, reduction in urine output. General physical signs such as pallor, icteric, respiratory distress and degree of dehydration. Others include neurological assessment such as depth of coma, corneal and pupillary reflexes, papilloedema/retinal haemorrhage, posture, tone and deep tendon reflexes. Tone is defined as muscle resistance to passive movement at rest [17].

The selected laboratory factors included Packed Cell Volume (PCV) level, white blood cell count, differential platelet count and parasite density. These were cross-tabulated against patient outcome to determine possibilities of association. Hyperparasitaemia is defined as parasite density >250,000/μL [18] and leucocytosis as level of white blood cell count greater than 12,000 cells/cumm^3 as defined by Oluwayemi O et al., [16].

Patients were also grouped based on the possible outcome as [19]:

(i) Patients who completely recovered

(ii) Patients survived with neurological deficit(s)

(iii) Patients who died during the treatment.

Level of consciousness was assessed using Blantyre's Coma Scale (BCS) [18]. Only children with an abnormal score (4 or less) were included in the study. Deep coma was defined as Blantyre coma score of 0-2.

At presentation blood was taken from each patient for full blood count, thin and thick film for malaria parasite to detect malaria parasite. The blood films for malaria parasite were examined for the type of species. Parasite density was then estimated as follows [20].

$$\text{Parasites/μL blood}=\frac{\text{Number of parasites counted X white blood cells count/μL}}{\text{Number of white blood cells counted on the smear}}$$

Blood film for malaria parasites was monitored daily while other investigations were carried out as the patients' clinical condition dictated. CSF was also obtained for chemistry and microbiology laboratory examination to exclude intracranial infections.

Based on WHO treatment guidelines of malaria, all patients were treated with intravenous artesunate [21]. Associated complications such as seizures, anaemia and raised intracranial pressure were treated appropriately [4,21]. The required supportive therapy was adequately provided such as airway management, oxygen administration, fluid therapy, input and output monitoring and adequate nutrition. Level of consciousness and vital signs were strictly monitored as condition of each patient dictated and patients were discharged from the hospital, when they had improved clinically and were able to continue their treatment orally at home. The outcome of each patient was assessed as either alive without neurological sequelae, alive but with neurological sequelae or died.

Bedside Prognostic Index (BPI): BPI was defined based on the prognostic factors that can be easily determined by the bedside of children with CM [13]. There are nine clinical/neurological factors that were found to be easily assessed and demonstrable clinically at the bedside. Each of these clinical findings were assigned score of 1 each. This forms the basis for formulation of BPI score as shown in [Table/Fig-1]. BPI was determined and the box plot for the BPI in relation to outcome was then done. The score range of 4-9 was assessed as bad/poor and scores <4 as good.

Variables	Scoring system
Convulsion	A score of 1 and 0 are assigned to the presence and absence of each parameter at bedside. Sum of the parameters was obtained for each child. Median BPI score was obtained across treatment outcome
Difficulty breathing	
Blantyre's coma score of 0-2	
Coma recovery time >26 hours	
Poor pupillary light reflexes	
Absent cornea reflexes	
Papilloedema/haemorrhage	
Abnormal posturing (decorticate and decerebrate)	
Abnormal deep tendon reflexes (hyporeflexia and hyper-reflexia)	

[Table/Fig-1]: Scoring technique for bedside prognostic index. This shows the detail of scoring of the nine items used in formulating the bedside prognostic score.

STATISTICAL ANALYSIS

Statistical analysis was done using IBM Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc, Chicago, USA). Chi-square test was used for test of association between variables. Student's t-test was used to compare means of normally distributed continuous variables. Logistic regression analysis was employed to determine the prognostic significance of various clinical parameters among those who had association at bivariate level. The sensitivity, specificity and the predictive testing of model that was used to predict the outcome were also carried out. The level of significance p-value was set at <0.05.

RESULTS

A total of 25 boys and 25 girls with cerebral malaria were recruited constituting 50 (5.6%) of 892 children admitted into CEU during the study period. Their ages ranged between six months and

12 years with 60% aged less than five years. The mean age was 4.86±3.16 years and mean weight 18.30±11.57 kgs. The mean *Plasmodium falciparum* parasites density per µL of blood, was 324,006 with 70% of the children recruited having parasite density >250,000/µL (hyperparasitaemia).

All the 50 (100%) patients presented with fever and altered sensorium. Convulsion was observed in 39 (78%) children, 6 (12%) of the children presented with history of paleness of the body and 31 (62%) of them were actually pale, 14 (28%) complained of jaundice but 9 (18%) were found to be icteric upon physical examination. Difficulty in breathing were reported only among 12 (24%) and 24 (48%) were found to be in respiratory distress. Twenty (51.3%) of 39 children with convulsion recovered fully as against 19 (48.7%) of them with poor outcome (neurological sequelae and death). Of the 12 children with difficulty in breathing at presentation, only 3 (25%) had a good outcome while 9 (75%) had poor outcome of either died or had a sequelae. In all participants, convulsion (χ=4.08; p=0.043) and difficulty in breathing (χ=6.25; p-value=0.012) were the presenting complaints significantly associated with poor outcome [Table/Fig-2].

Presenting complaints	n	Clinical outcomes (A) Full recovery n (%)	(B) Alive with sequelae n (%)	(C) Death n (%)	χ^2/ χ^2+	A* (B+C) p-value
Fever	50	30 (60)	11 (22)	9 (18)	NA	NA
Loss of consciousness	50	30 (60)	11 (22)	9 (18)	NA	NA
Convulsion	39	20 (51.3)	11 (28.2)	8 (20.5)	4 84	0.043*
Difficulty breathing	12	3 (25)	2 (16.7)	7 (58.3)	6.255	0.012*
Paleness of body	6	3 (50)	0 (0)	3 (50)	0 07	0.929
Jaundice	14	9 (64.3)	2 (14.3)	3 (21.4)	0 77	0.780
Dark brown urine	6	2 (33.3)	1 (16.7)	3 (50)	0.955	0.328
Reduction in urine output	16	8 (50)	1 (6.2)	7 (43.8)	0.980	0.322
General physical signs						
Temperature <38.5°C	23	15 (65.2)	3 (13)	5 (21.7)	0.483	0.487
Temperature ≥38.5°C	27	15 (55.6)	8 (29.6)	4 (14.8)	-	-
Pallor	31	16 (51.6)	8 (25.8)	7 (22.6)	2.391	0.112
Icteric	9	6 (66.7)	0 (0)	3 (33.3)	0.203	0.652
Respiratory distress	24	11 (45.8)	4 (16.7)	9 (37.5)	3.860	0.050
Degree of dehydration						
Severe	7	2 (28.6)	1(14.3)	4 (57.1)	3.350	0.067
Non severe	43	28 (65.1)	10 (23.3)	5 (11.6)	-	-

[Table/Fig-2]: Clinical outcome based on the presenting complaint and general physical signs shows association between the clinical findings and the outcome among the study population.
χ^2+: Chi-square with Yates's correction, NA: Not Applicable. *p-value <0.05 was considered statistically significant

Neurological examination findings at presentation in relation to the clinical outcome showed that deep coma (Blantyre's coma score 0-2), prolonged coma recovery time (>26 hours), absent corneal reflex, absent pupillary reflex, papilloedema/retinal haemorrhage, abnormal posturing, hyporeflexia and hyper-reflexia were significantly associated with poor outcome (p-value <0.05). Full details on the association are shown in [Table/Fig-3]. The mean Coma Recovery Time (CRT) was significantly lower in children who recovered fully (26.77±13.81 hours) compared to children, who recovered with neurological sequelae (41.91±28.25 hours) and this was statistically significant, (t-value=2.308, p-value=0.026) [Table/Fig-3].

[Table/Fig-4] shows that the mean leucocyte count is significantly associated with mortality and neurological sequelae, (t-value=-2.769;

Neurological parameters	Clinical outcome (A) Full recovery n (%)	(B) Alive with sequelae n (%)	(C) Death n (%)	RR	χ^2	A* (B+C) p-value
Coma recovery time (Hours)	26.77±13.81 (Mean±SD)	41.9±28.25 (Mean±SD)	-	-	-	0.026
Posturing						
*Abnormal	3 (23.1)	4 (30.8)	6 (46.2)	-	-	-
Normal	27 (73)	7 (18.9)	3 (8.1)	2.85 (1.55-5.22)	9.979	0.002*
Blantyre's coma score						
0-2	8 (40)	3 (15)	9 (45)	-	-	-
3-4	22 (73.3)	8 (73.3)	0	2.25 (1.1-4.5)	5.362	0.021*
Cornea reflexes						
Absent	3 (27.3)	3 (27.3)	5 (45.5)	-	-	-
Present	27 (69.2)	8 (20.5)	4 (10.3)	2.36 (1.31-4.28)	6.294	0.012*
Pupillary light reflexes						
Sluggish/no reaction	16 (48.5)	8 (24.2)	9 (27.3)	2.92 (1.1-8.59)	5.362	0.021*
Normal reaction	14 (82.4)	3 (17.6)	0	-	-	-
Fundoscopy						
Papilloedema/ Haemorrhage	3 (21.4)	4 (28.6)	7 (50)	-	-	-
Normal	27 (75)	7 (19.4)	2 (5.6)	3.14 (1.68-5.89)	12 54	0.001*
Tone						
Normal	7 (87.5)	0	1 (12.5)	-	-	-
Hypotonia	17 (58.6)	5 (17.2)	7 (24.1)	3.31 (0.50-21.78)	2.295	0.129
Hypertonia	6 (46.2)	6 (46.2)	1 (7.7)	4.31 (0.64-28.84)	3.590	0 58
Tendon reflexes						
Normal	13 (86.7)	2 (13.3)	0	-	-	-
Depressed	12 (52.2)	3 (13)	8 (34.8)	3.59 (0.92-13.96)	4.799	0.028*
Hyper-reflexia	5 (41.7)	6 (50)	1 (8.3)	4.38 (1.11-17.32	6 75	0.014*

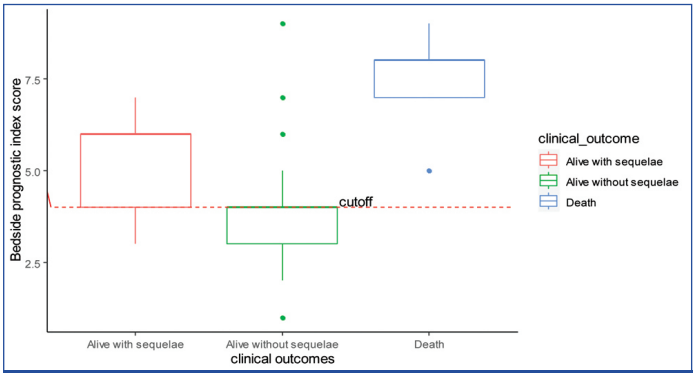
[Table/Fig-3]: Neurological examination in relation to the clinical outcome. This explains the relationship between the neurological examination findings at presentation in relation to the clinical outcome of full recovery, alive with sequelae and death.
RR: Relative risk of death or recovery with neurological sequelae, *Abnormal posturing includes decorticate/decerebrate posture.
*p-value <0.05 was considered statistically significant

p-value=0.008). Subjects who died or had neurological sequelae also had a higher mean parasite density, in relation to those who recovered without sequelae and this was statistically significant with the clinical outcome (t-value=-2.614, p-value=0.001). In fully recovered children, parasite count was 12.42±0.606=246,175 per µL, in alive children with neurological sequelae parasite count was 12.78±0.582=353,557 per µL and in dead children parasite count was 12.93±0.417=410,692 per µL. Mean packed cell volume (PCV) was lower among children who died (20±9.41%) as compared to those who recovered fully (24.37±8.34%), but no statistical significant association between PCV level and clinical outcome was recorded.

At bivariable level, association between clinical findings and clinical outcome using Chi-square was determined. Those clinical parameters that showed significant association at this level and which can be assessed at bedside were used for formulation of BPI score. Of total, 16 (32%) children had good score of less than 4 while 34 (68%) children had poor score. The median bedside prognostic index score was higher in children who died (median=8), followed by a median score of 6 among those who survived with neurological deficit and score of 4 among children, who survived without neurological deficit [Table/Fig-5].

Laboratory parameters	Clinical outcomes (A) Full recovery Mean±SD	(B) Alive with sequelae Mean±SD	(C) Death Mean±SD	t-value	A vs (B+C) p-value
Packed cell volume (%)	24.37±8.34	24.64±5.52	20.00±9.41	0.220	0.982
WBC count (cells/mm^3)	11.07±5.23	18.75±8.52	20.39±8.99	-2.769	0.008*
Platelet count (cells/mm^3)	186.7±50.57	186.54±23.3	145.11±36.4	1.433	0.158
Log (Parasite density)	12.42±0.606	12.78±0.582	12.93±0.417	-2.614	0.001*
			-	-	

[Table/Fig-4]: Mean of laboratory parameters and duration on admission across the clinical outcome in the study population. It explain the association between the mean white blood cell count, packed cell volume, platelets counts and parasite density and the clinical outcome among the 50 children with cerebral malaria.
WBC: White blood cells; *p-value <0.05 was considered statistically significant



[Table/Fig-5]: Bedside prognostic index score in children with cerebral malaria. It is the box plots showing relationship between bedside prognostic scores and the clinical outcome of children with cerebral malaria. With the cut-off median score of 4 for poor outcome, poor outcome of death and neurological sequelae had score 4 or more, while score below 4 indicates full recovery.

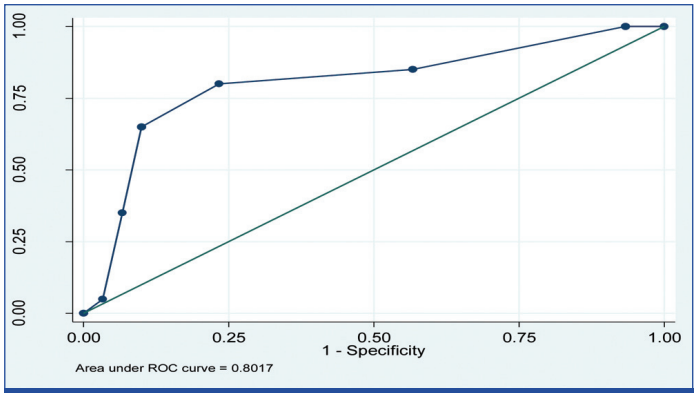
The sensitivity, specificity and predictive value of the bedside prognostic index score was also determined for each of the score. The Receiver Operating Characteristic (ROC) curve validated the predictive ability of bedside prognostic index score on clinical outcomes.

Sensitivity, specificity and predictive value of bedside prognostic index: The best sensitivity and specificity were obtained for a cut-off greater than or equal to 4 with a sensitivity of 80% and specificity of 76.67% [Table/Fig-6]. The ROC of the predictive ability of bedside prognostic index on clinical outcomes is as shown in [Table/Fig-7]. The Area Under the Curve (AUC) was 80.2% which indicates that the bedside prognostic index was able to distinguish between children of different outcome.

Cut-off point	Sensitivity	Specificity	Correctly classified
≥1	100	0	40
≥2	100	6.67	44
≥3	85	43.33	60
≥4	80	76.67	78
≥5	65	90.00	80
≥6	35	93.33	70
≥7	5	96.67	60
8	0	100	60

[Table/Fig-6]: Sensitivity and specificity for different cut-offs of bedside prognostic index. Shows sensitivity and specificity for different cut-offs of bedside prognostic index score and the best sensitivity and specificity were obtained for a cut-off greater than or equal to 4 with a sensitivity of 80% and specificity of 76.67%, respectively.
Area under the curve: 80.2% 95% CI: 66.7-93.7

Clinical outcome was significantly associated with bedside prognostic index. Children with prognostic score less than 4 were about eight times more likely to survive compared to children with a score of 4 or more. Thus bedside prognostic index of 4 or more, was found to be a significant predictor of poor outcome [Table/Fig-8].



[Table/Fig-7]: Receiver Operating Characteristic curve of bedside prognostic index. Shows the receiver operating characteristic curve (ROC) to determine the predictive ability of bedside prognostic index on clinical outcomes using different cut-off points of sensitivity and specificity. The area under the curve is 0.802 (80.2% which indicates and supports that the bedside prognostic index was able to distinguish significantly between children of different outcome.

Variables	Coefficient (B)	Odds ratio	95% CI for Odds ratio		p-value
Constant	-1.946	0.143	-	-	-
BPI score ≥4	2.064	7.875	1.547	40.091	0.013*

[Table/Fig-8]: Relationship between clinical outcome and bedside prognostic index. It shows the level of association between the bedside prognostic score and the poor clinical outcome among the 50 children with cerebral malaria.
*p-value <0.05 indicates significance

DISCUSSION

The present study evaluated bedside prognostic index of poor outcome of children with cerebral malaria. Fever, altered sensorium and convulsions were found to be the most prevailing symptoms and these findings were similar to clinical features documented in other studies but the prevalence varied across different studies [19,16,22]. Fever was present in all the children recruited for the present study, this is similar to reports by Oluwayemi O et al., and Lesi FE et al., [16,22]. In similar to presence of fever, loss of consciousness/altered sensorium was present in 100% of children with CM in the present study, this is in consonance with reports by many authors [13,16,23,24]. Out of total, 79% patients in this study had convulsion at presentation. It was similar to 82% and 79.6% found in studies in Malawi and Nigeria, respectively but lower than 89.3% and 95% found in studies in Oluwayemi O et al., and Oninla S et al., Nigeria, respectively [13,12,16,19]. [Table/Fig-9] is showing the comparison of prognostic features of CM in various studies with the present study [16,22,24,25].

Parameters	Author, year and place of the study: Current study 2022	Olumese PE et al., [25] 1999 Ibadan	Lesi FE et al., [22] 2005 Lagos	Jiya MN et al., [24] 2006 Sokoto	Oluwayemi O et al., [16] 2013 Ado-Ekiti
Sample size	50	103	107	78	66
Prognostic features	Outcome				
Age	-	++	-	++	++
Prolonged coma	++	++	_	++	_
Intractable convulsion	-	++	_	++	_
Decerebration	++	++	++	++	_
Difficulty in breathing	++	_	_	++	++
Absent corneal reflexes	++	++	_	_	++
Dilated pupils	_	_	_	++	_
Papilloaedema	++	_	_	++	_
Retinal haemorrhages	++	_	_	++	++
Hypoglycemia	-	_	_	++	++

Severe anaemia	_	_	_	_	_
Low bicarbonate	_	_	_	_	_
Hyperparasitaemia	++	_	_	_	_
Leucocytosis	++	_	_	_	++

[Table/Fig-9]: Selected extracts from the profile of published reports on the prognostic features of cerebral malaria in children [16,22,24,25].
Note: ++=significant-=not significant

The findings of short duration of fever and unconsciousness among children with CM prior presentation suggest that an uncomplicated malaria can progress rapidly to cerebral malaria, this supported the findings reported by Jiya MN et al., and Molyneux ME et al., [24,13]. Thus, a strong need arises for clinicians to be very observant in monitoring the patients and prompt in the management of uncomplicated malaria to prevent rapid progression to CM. Despite the prevailing incidence of children with fever in CM, children with CM had also been documented to present with subnormal to normal temperature but this was not found in the present study as all children studied had varying degree of fever [16,24].

Respiratory distress was a less prevalent clinical findings in this study with regard to fever, loss of consciousness and convulsion. It was recorded in about half of the subjects (48%) in this study. This doubles reports of 22.7% and 20% from studies by Oluwayemi O et al., and Oninla S et al., respectively [16,12]. This difference may be partly due to the heterogeneous populations of different studies and different definition used for respiratory distress across children with cerebral malaria. Other important clinical signs in this study were pallor, jaundice and dark brown urine as observed in 62%, 28% and 12%, respectively and they were found not to be associated with poor outcome. The report of pallor and jaundice in this were in contrast with study by Lesi FE et al., who reported 70.1% and 50.4%, respectively for pallor and jaundice [22]. However, the finding of 12% for dark brown urine is very similar to 10% reported in a retrospective study by Oninla S et al., [12]. The notable variance in prevalence of jaundice, pallor and passage of dark brown urine in the present study and others may be a pointer to other undetected underlying causes of haemolysis (such G6PD deficiency and other enzymopathy, haemoglobinopathy etc.) which may be a co-morbid [26].

Cerebral malaria has been reported to present with non specific features of diffuse, symmetrical, neurological and some specific neurological features that were associated with poor prognosis [25]. Neurological findings of poor pupillary reflex, absent corneal reflex, papilloedema and retinal haemorrhage in the present study were generally similar to, but in varying rate of occurrences as some previous studies [12,16,24]. A total of 22% patients had absent cornea reflexes in this study which was higher than 14% in study by Olumese PE et al., [25] and doubles findings of 10% documented by Oluwayemi O et al., [16]. Papilloedema/retinal haemorrhage has been reported to be predictors of poor outcome across studies [13,16,27,28]. It was found in 28% of children with CM in the current study and it form part of bedside prognostic index score. A total of 40% of children in the present study were deeply comatose (Blantyre's score 0-2), this is higher than 12% reported by Genton B et al., [23], but lower than 68.2% documented by Oluwayemi O et al., [16]. Furthermore, deep coma (Blantyre's score 0-2) was also found to be poor predictors of poor outcome of CM in the present study, similar to previous reports [13,16,22,23,29]. A total of 70% of children with CM in the present study had abnormal deep tendon reflex and 84% presented with abnormal tone, this is comparable to report of abnormal tone of 70% and abnormal deep tendon reflexes of 74% from other study [25]. The variation in the pattern of neurological findings and the prognostic ability may generally be explained by different age range of the patient across studies, severity of the symptoms, associated co-morbidities as well as management modalities [12-15,22].

The mean PCV in the present study was found to be similar among those who recovered fully and survivors with sequelae (24%), but marginally lower (20%) among those that died. The mean PCV is within the range of 23.9% reported by Oninla et al., however, the report from Oninla et al., did not compare among different outcome parameter of CM [12]. The mean PCV level showed no association with poor outcome as similar to other studies [13,16]. However leucocytosis was found to be an indicator of poor outcome in the present study. This was also reported by researchers across Africa [13,16,23]. In the present study, the children had a high mean parasite counts as demonstrated amongst 70% of them. These far outweighed what was reported from many studies in Nigeria [16,19,24]. The explanation for this was not clearly understood. The malaria parasites count in the blood films could vary based on timing of the sample collection in respect to the peak of fever, which may positively affect the yield [12,30]. There could also be deep tissue sequestrations, leaving the peripheral blood of few or no malaria parasite thus affecting the parasite count [12]. In general, demonstrable bedside signs such as convulsion, difficulty in breathing, deep and prolonged coma, absent corneal and pupillary reflexes, papilloedema/retina haemorrhage, abnormal deep tendon reflex and abnormal posturing were found in the present study to be predictors of poor outcome. These findings are consistent with previous studies in Nigeria [16,19,24] and across Africa [10,13,23].

The bedside prognostic index score formulated in the present study was more accurately predictive of outcome than any single clinical feature among children with CM. The children with CM who had BPI score of 4 or more have about eight times risk of dying or developing neurological sequelae as those with BPI score of less than 4 and this is similar to report by Molyneux ME et al., [13]. The reported prognostic index score by Molyneux ME et al., have different components as in the present study [13]. No other study to the best of authors' knowledge had reported prospective study on bedside prognostic index score for cerebral malaria in children as in this study. Furthermore, in the present study, the bedside prognostic index score has a sensitivity of 80% and specificity of 76.67%, this sensitivity is higher than 66% recorded in a previous study but specificity was not reported in that study [13]. Furthermore, bedside prognostic index of score ≥4 was found to be an independent predictor of poor outcome of death and development of neurological sequelae. The presence of these independent predictors of poor outcome in children with CM calls for a strict monitoring among them to prevent poor outcome. Identifying easily accessible prognostic factors that may predict bad outcome will go a long way to stem down the mortality and sequelae from cerebral malaria in developing countries like Nigeria and other Sub-Saharan Africans. The presence of any or all of the clinical parameters findings that form the bedside prognostic index score may assist clinicians in quick assessment and prompt management of CM in children to prevent poor outcome. A combined prognostic index of this kind could provide a measure of the severity of the presenting illness similar to report from other study [13]. Furthermore, bedside assessment score will be relevant in regions where malaria is endemic; and resources, in terms of qualified healthcare providers, appropriate medication, prompt testing, and monitoring equipment, are often not sufficient to meet all the needs. Identification of bedside risk factors also help to set up priorities right in such treatment centres.

Limitation(s)

Some of the limitations of the present study included the inability to exhaustively study all factors, that may serve as predictors in the outcome of the disease. The influence of all possible concomitant diseases, could not be fully investigated and this may impact negatively on the outcome.

CONCLUSION(S)

The bedside prognostic index scoring is a good predictor of outcome in the children with BPI score ≥4, as an independent predictor of poor outcome (death and development of neurological symptoms). Children with CM with BPI score less than 4 had eight times chance of survival than those with poor outcome. The aggregation of signs summed to form BPI score will likely be useful for prediction of outcome in children with CM, than any single clinical or laboratory factors. This is to promptly predict outcome of CM with the aim of initiating early appropriate treatment with potential to improving outcomes in those with potentially poor outcome. Utilisation of this bedside scoring index should be encouraged for children with CM among health workers, especially in low resource countries.

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