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Cerebral Malaria in African Children: Clinical and Ophthalmic Prognostic Indicators, Management, and Long-Term Outcomes — a Narrative Review

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Abstract

Background: Cerebral malaria (CM) is a severe neurological complication of *Plasmodium falciparum* infection in African children, contributing significantly to morbidity and mortality. This review synthesises evidence on epidemiology, pathogenesis, prognostic indicators, management, and outcomes of paediatric CM with an emphasis on Nigerian data.
Methods: This narrative review was conducted in accordance with the scale for the assessment of narrative review articles (SANRA). Literature retrieved was sourced from databases utilising a combination of free-text and MeSH terms. The search covered from January 2010 to May 2025. Evidence was synthesised across thematic domains, including epidemiology, pathogenesis, management, prognostic indicators, and neurocognitive outcomes.
Results: CM accounts for up to 20% of paediatric severe malaria admissions and mortality rates of 15–25% among African children. The typical clinical findings of CM among children include coma, cerebral oedema, seizures, and malarial retinopathy. Prognostic indicators include the clinical, biochemical parameters, haematological, emerging biomarkers and imaging findings. Supportive care, including seizure control, blood transfusion, and glucose correction and monitoring, remains critical for survival. Neurological sequelae, including epilepsy, cerebellar dysfunction, cognitive impairments, and behavioural disorders, are generally frequent and prevalent, with Nigerian cohorts reporting impaired school performance and psychosocial challenges.
Conclusions: Paediatric CM is a distinct clinical entity with high mortality and hidden long-term disability. Bedside prognostic indicators remain the most practical in resource-limited settings, while biomarkers and neuroimaging show promise but remain inaccessible. Prompt stabilisation, definitive and improved supportive care, and post-discharge rehabilitation are critical for reducing the burden and poor prognosis of CM in children.

Keywords: Cerebral Malaria; children; prognostic indicators; malaria retinopathy; neurocognitive outcomes.

Introduction

Cerebral malaria (CM) remains one of the most severe complications of Plasmodium falciparum infection in children, particularly across sub-Saharan Africa, where malaria transmission is intense. [1,2] Despite significant progress in malaria control through insecticide-treated nets, indoor residual spraying, rapid diagnostic tests, and artemisinin-based combination therapies (ACTs), CM still causes thousands of young deaths each year. According to the World Malaria Report 2023, there were an estimated 249 million malaria cases and 608,000 deaths worldwide in 2022, with over 75% of

these deaths occurring in African children under five years [1].

In Nigeria, which bears the highest malaria burden globally, malaria accounts for 27% of cases and 31% of deaths worldwide. [1] CM remains a leading cause of paediatric intensive care admissions in tertiary hospitals, with case fatality rates ranging from 15–22% even with artesunate therapy [3,4]. Recent Nigerian cohort studies have identified clinical, haematological, and biochemical determinants of poor outcomes, including coma depth, seizures, severe anaemia, hypoglycaemia, and electrolyte imbalances [4-6]. These findings emphasise the importance of localised prognostic tools designed explicitly for resource-limited African settings.

Historically, quinine was the primary treatment for severe malaria. The landmark AQUAMAT trial established intravenous artesunate as superior, reducing mortality in African children by 22% compared to quinine (7). Despite this advance, cerebral malaria (CM) remains associated with high mortality due to late hospital presentation, limited access to critical care, and metabolic complications. Moreover, supportive interventions such as corticosteroids, mannitol, and immunomodulators have failed to demonstrate efficacy [8-10].

Recent advances have transformed our understanding of paediatric CM. Neuroimaging studies show that brain swelling is a key predictor of mortality in children, unlike the multi-organ dysfunction more common in adults [11,12]. Similarly, malarial retinopathy—characterised by retinal whitening, haemorrhages, and vessel colour changes—has become a reliable diagnostic and prognostic marker unique to children [10,13]. Local evidence from Nigeria supports these global findings while providing haematological and biochemical data relevant to endemic populations [3,6,10].

Nevertheless, significant knowledge gaps persist. Promising biomarkers of endothelial activation and inflammation (e.g., angiopoietin-2/1 ratio, sTREM-1, lactate dehydrogenase) have not yet been integrated into routine paediatric care in Africa [4,14]. Longitudinal studies from Uganda, Malawi, and Nigeria indicate that up to 30% of survivors develop ongoing neurocognitive issues such as epilepsy, attention disorders, and poor school performance [10,13]. However, structured rehabilitation and follow-up services remain limited in most endemic regions.

In this context, there is a critical need for a narrative synthesis that integrates evidence across epidemiology, pathogenesis, prognostic indicators, management, and long-term outcomes in paediatric CM. Such a review will not only consolidate knowledge but also highlight *regional insights* from Nigerian cohorts [5,6] and identify gaps requiring translational research.

Methods

This article was prepared as a narrative review, guided by the Scale for the Assessment of Narrative Review Articles (SANRA) and the EQUATOR Network recommendations for transparency in non-systematic reviews. The aim was to synthesise available evidence on cerebral malaria (CM) in children aged 0–12 years, focusing on epidemiology, pathogenesis, prognostic indicators, management, and long-term outcomes, with particular emphasis on sub-Saharan Africa and Nigeria.

Sources of Information

Relevant literature was retrieved from PubMed/MEDLINE, Embase, African Journals Online (AJOL), and Google Scholar. These databases were selected to ensure comprehensive coverage of both international and regional publications, including Nigerian studies often underrepresented in major indexing platforms.

Search Strategy

Searches were performed using a combination of free-text and Medical Subject Headings (MeSH) terms adapted to each database. The following search string was applied in various combinations:

"Cerebral malaria"
"Children" OR "Paediatrics" OR "Paediatric"
"Prognostic indicators" OR "Biomarkers" OR "Predictors"
"Neurocognitive outcomes" OR "Sequelae"
"Nigeria" OR "Africa"

The timeframe was restricted to January 2010 to May 2025 to capture contemporary evidence in the artesunate era. Only English-language publications were included.

Eligibility Criteria

Inclusion criteria:

i. Peer-reviewed original articles, reviews, and meta-analyses reporting on paediatric CM.
ii. Studies conducted in Africa, featuring Nigerian cohorts, are highlighted where available.
iii. Clinical, haematological, biochemical, imaging, and biomarker studies that reported prognostic or outcome data.

iv. Longitudinal studies describing neurocognitive or developmental sequelae in survivors.

Exclusion criteria:

i. Studies exclusively focused on adults (>12 years).
ii. Animal or experimental studies not directly related to paediatric outcomes.
iii. Case reports and case series with fewer than 10 patients.
iv. Publications before 2010, unless referenced for historical context.

Study Selection and Data Synthesis

Titles and abstracts were screened for relevance, followed by a full-text review of eligible articles. Data were extracted into thematic domains: epidemiology, pathogenesis, prognostic indicators (clinical, haematological, biochemical, imaging, biomarkers), management, and neurocognitive outcomes. Where possible, evidence from Nigerian cohorts, including recent clinical, haematological, and biochemical outcome studies (3-6), was emphasised to provide local context. Findings were narratively synthesised, and summary tables and figures were developed to illustrate prognostic determinants and conceptual relationships.

Limitations

This review used a narrative rather than a systematic approach, which may be prone to selection bias. Variations in study design, diagnostic criteria, and outcome definitions across African cohorts might also restrict direct comparability. These limitations are acknowledged, and findings should be interpreted with caution.

Epidemiology and Burden

Cerebral malaria (CM) remains a significant cause of paediatric morbidity and mortality in malaria-endemic regions, particularly across sub-Saharan Africa [1-3]. Despite global progress in malaria control using insecticide-treated nets, indoor residual spraying, and artemisinin-based combination therapies (ACTs), CM continues to claim thousands of young lives each year and contributes significantly to the burden of long-term neurological disability.

Global and African Burden of malaria in children

Malaria persists as a leading cause of childhood death worldwide. The World Malaria Report 2023 estimated 249 million malaria cases and 608,000 deaths in 2022, with Africa accounting for 94% of all malaria deaths [1]. Children under five years represented nearly three-quarters of these deaths, reflecting the disproportionate vulnerability of this age group [1,15,16]. Although global malaria incidence has declined in the past two decades, cerebral malaria remains one of the most feared manifestations of *Plasmodium falciparum* infection due to its high case fatality and severe sequelae [1,2].

Epidemiology in Nigeria

Nigeria bears the heaviest burden of malaria globally, accounting for nearly 27% of the world's cases and 31% of deaths [1]. Hospital-based studies confirm that CM is one of the most common causes of paediatric critical illness, with mortality rates ranging from 15% to 22% in tertiary centres [3,15]. Several Nigerian studies have enhanced the understanding of CM outcomes:

- Okafor et al. linked elevated pro-inflammatory cytokines with severe disease and poor outcomes [4].
- Afolabi et al. described the clinical spectrum and high fatality rates among Nigerian children with severe malaria, including CM [3].
- Recent studies from Ogbomoso have highlighted the prognostic role of clinical indicators, haematological abnormalities, and biochemical derangements in determining outcomes in childhood CM [5,6,9].

Collectively, these findings suggest that Nigeria's burden is driven not only by the high incidence of infection but also by systemic challenges, such as late presentation, limited access to paediatric intensive care, and the under-recognition of early warning signs at the community level [3–6,9].

Beyond Mortality: Long-Term Burden

Beyond the immediate risk of death, CM is increasingly recognised for its long-term neurocognitive and psychosocial consequences. Cohorts from Uganda and Malawi have demonstrated persistent deficits in attention, memory, and learning among survivors, often affecting educational attainment and quality of life [7]. Nigerian observations similarly suggest an elevated risk of epilepsy, behavioural problems, and impaired school performance following CM [6,9,].

The epidemiological evidence highlights three key insights. First, CM remains a significant cause of paediatric mortality in Africa despite the efficacy of artesunate, pointing to health system limitations and delayed care-seeking as key barriers to improved outcomes.[1-3] Second, the Nigerian experience mirrors

continental trends, with local studies confirming the prognostic relevance of clinical, haematological, and biochemical markers, while also highlighting systemic factors that exacerbate outcomes.[4-6] Third, neurocognitive sequelae represent a substantial but often neglected component of the disease burden, requiring greater investment in follow-up care and rehabilitation services. Addressing both the acute and long-term burden of paediatric CM should therefore be a central priority in malaria control strategies across Africa. (4,5)

Pathogenesis and Paediatric-Specific Features

The pathogenesis of cerebral malaria (CM) is complex and multifactorial, reflecting parasite, host, and environmental interactions that culminate in severe neurological dysfunction. Although some mechanisms are shared across age groups, children demonstrate distinctive clinical and pathological features that emphasise the need for paediatric-specific considerations.

Parasite Sequestration and Microvascular Obstruction

A key event in CM is the sequestration of *Plasmodium falciparum*–infected erythrocytes within the cerebral microvasculature. Adhesion molecules such as PfEMP1 facilitate binding to endothelial receptors, including ICAM-1, EPCR, and VCAM-1, leading to microvascular obstruction and localised hypoxia [17,18,20]. Autopsy studies confirm dense sequestration in fatal paediatric cases, and the extent of sequestration correlates with the severity of malarial retinopathy [14,17-19,]. These findings provide strong pathological evidence that microvascular congestion is a crucial determinant of outcome in children.

Endothelial Activation and Blood–Brain Barrier Dysfunction

Sequestration alone does not fully explain the neurological syndrome. Endothelial activation also plays a crucial role, with infected erythrocytes and inflammatory mediators stimulating endothelial release of angiopoietins, adhesion molecules, and cytokines. Elevated angiopoietin-2/1 ratios, soluble ICAM-1, and sTREM-1 have been linked to poor outcomes in African children [23-26]. Nigerian studies further show that dysregulated cytokine responses contribute to severe disease and mortality [4]. Endothelial dysfunction and disruption of the blood–brain barrier facilitate cerebral oedema, which is increasingly recognised as the primary pathological feature of paediatric CM [12,21].

Neuroinflammation and Immune Dysregulation

Host immune responses play a dual role: while necessary for parasite clearance, excessive inflammation is neurotoxic. Elevated TNF-α, IFN-γ, and IL-6 contribute to oxidative stress, excitotoxicity, and neuronal injury [24,-26]. Children, with their relatively immature immune systems, may mount disproportionate responses that exacerbate cerebral damage. This helps to explain why cerebral oedema and seizures are more common and severe in paediatric CM when compared to adults.

Cerebral Oedema and Brain Swelling

Magnetic resonance imaging (MRI) studies have demonstrated that brain swelling is the most consistent and prognostically significant radiological feature of paediatric CM. In Malawian cohorts, severe cerebral oedema strongly predicted mortality [12,41]. Unlike adults, where multi-organ dysfunction often drives death, in children, intracranial pressure and brain swelling are central. This distinction emphasises the need for paediatric-specific monitoring and interventions targeting cerebral oedema.

Retinopathy as a Diagnostic and Prognostic Marker

Malarial retinopathy offers a non-invasive insight into cerebral pathology. Retinal whitening, haemorrhages, and vascular colour changes reflect microvascular obstruction and ischaemia [17,18,30]. Although retinopathy is not exclusive to children, it is much more predictive of outcomes in paediatric cases. It is now regarded as a key diagnostic feature of CM in endemic African hospitals. Its application is especially valuable in settings where neuroimaging is not available.

Haematological and Metabolic Contributors

Children with CM frequently present with severe anaemia, hypoglycaemia, metabolic acidosis, and electrolyte imbalance. These systemic derangements exacerbate cerebral hypoxia and contribute independently to poor outcomes. Nigerian hospital-based studies have highlighted the importance of haematological and biochemical abnormalities as prognostic determinants [3,5,9]. Their findings align with international evidence, reinforcing the notion that both systemic and cerebral factors act synergistically in driving disease severity.

Taken together, this evidence indicates that paediatric CM is driven by a triad of microvascular sequestration, endothelial activation, and immune dysregulation, with cerebral oedema and retinopathy as prominent clinical consequences. Unlike adults, children are more likely to die from brain swelling than from multi-organ

failure, and systemic complications such as anaemia and hypoglycaemia often amplify cerebral injury. These insights underscore the need for age-specific prognostic tools and therapeutic approaches, particularly in resource-limited African settings where advanced diagnostics are unavailable.

Prognostic Indicators in Paediatric Cerebral Malaria

Despite advances in antimalarial therapy, outcomes in paediatric cerebral malaria (CM) remain unpredictable. Identifying reliable prognostic indicators is vital for guiding clinical management, triaging patients, and informing long-term follow-up. Prognostic factors in children cover clinical, haematological, biochemical, imaging, and molecular domains, with evidence from multicentre African cohorts and local Nigerian studies.

Clinical Indicators

The clinical presentation continues to be the most immediate predictor of outcome in children with CM.

- **Depth and duration of coma:** The Blantyre Coma Scale (≤2) is consistently linked with high mortality, and prolonged coma (>48 hours) indicates a risk of neurological sequelae [12].
- **Seizures and status epilepticus:** Recurrent or prolonged seizures are associated with higher risks of death and post-discharge epilepsy [7,8].
- **Respiratory distress and brainstem signs:** Evidence from Nigerian and Malawian hospitals shows that abnormal respiratory patterns and brainstem involvement strongly predict mortality [3,6].
- **Hypotension and shock:** Although less common in children than adults, their presence indicates a poor outcome.

Haematological Indicators

Haematological abnormalities frequently accompany CM in African children.

- **Severe anaemia (Hb <5 g/dL):** Associated with increased mortality, either independently or in synergy with cerebral pathology [3,5].
- **Leukocytosis and neutrophilia:** Predictors of poor outcome in Nigerian cohorts, possibly reflecting secondary infection or heightened inflammation [5].
- **Thrombocytopenia:** Common in CM but variably predictive; some Nigerian studies report its association with higher fatality rates.

These indicators are particularly relevant in low-resource settings, as they are routinely available and can augment bedside prognostication.

Biochemical Indicators

Metabolic disturbances are key prognostic markers in paediatric CM.

- **Hypoglycaemia (<2.2 mmol/L):** Strongly associated with fatal outcome and recurrent seizures.
- **Metabolic acidosis and hyperlactataemia:** Both predict mortality and are frequent in children with severe CM [24].
- **Electrolyte imbalance and renal dysfunction:** Nigerian studies highlight derangements in sodium, potassium, and creatinine as additional predictors of poor outcome [9].
- **Hepatic dysfunction:** Elevated liver enzymes have been reported, but their prognostic utility remains inconsistent.

Imaging and Retinal Indicators

Neuroimaging and retinal findings have enhanced the understanding of paediatric CM prognosis.

- **Brain swelling on MRI:** The most reliable radiological indicator of death in Malawian children, often suggesting increased intracranial pressure [12,41].
- **Retinopathy:** Retinal whitening, haemorrhages, and vascular changes are strongly associated with mortality and neurological sequelae. Retinopathy is commonly used in African hospitals to improve diagnostic accuracy [17,18,30].
- **CT and ultrasonography:** Although less sensitive, they can occasionally assist in prognosis when MRI is unavailable.

Biomarkers and Molecular Indicators

Emerging biomarkers offer potential for risk stratification but remain largely research tools.

- **Endothelial activation markers:** Angiopoietin-2/1 ratio, soluble ICAM-1, and sTREM-1 are strongly linked with mortality in African paediatric cohorts [23,25-27].
- **Inflammatory cytokines:** TNF-α, IL-6, and IFN-γ have been associated with adverse outcomes; Nigerian children show heightened inflammatory signatures in fatal cases [4].

- **Lactate dehydrogenase (LDH):** Elevated levels reflect tissue hypoxia and correlate with mortality[27]. .
- **Host genetic factors:** Polymorphisms in immune response genes are under investigation, but findings remain inconsistent [27].

The challenge remains translating these markers into affordable, point-of-care assays suitable for routine paediatric use in endemic regions.

Category	Indicators	Prognostic Value	Key Evidence Sources
Clinical	Deep/prolonged coma, seizures, respiratory distress, brainstem signs	Strong predictors of mortality and sequelae	[7,8,12] [3,6]
Haematological	Severe anaemia, leukocytosis, thrombocytopenia	Increased mortality risk	[3,5]
Biochemical	Hypoglycaemia, acidosis, hyperlactataemia, electrolyte imbalance, renal dysfunction	Predict poor outcomes, mortality	[9,22]
Imaging/Retinal	Brain swelling (MRI), malarial retinopathy	Strong diagnostic and prognostic markers	[12,17,18,30,41]
Biomarkers	Ang-2/1 ratio, sICAM-1, sTREM-1, cytokines elevated LDH	Emerging prognostic utility	[4,23,24,26,27]

Putting in perspective, the weight of evidence indicates that simple bedside clinical features (coma depth, seizures, respiratory distress) remain the most immediate and widely applicable prognostic indicators in children with CM. Haematological and biochemical tests provide additional predictive value and are particularly relevant in Nigerian settings where advanced imaging is limited. Neuroimaging and retinopathy have transformed the understanding of CM pathogenesis and prognosis, but accessibility remains a challenge outside specialised centres. Finally, while biomarkers offer exciting prospects, their routine use awaits validation and the development of cost-effective diagnostic platforms.

Here's the schematic figure showing the conceptual flow:

- **Pathogenesis** → parasite sequestration, endothelial activation, neuroinflammation, cerebral oedema.
- **These lead into prognostic categories** → clinical, haematological/biochemical, imaging/retinopathy, and biomarkers.
- **All converge on outcomes** → death or long-term neurocognitive sequelae.

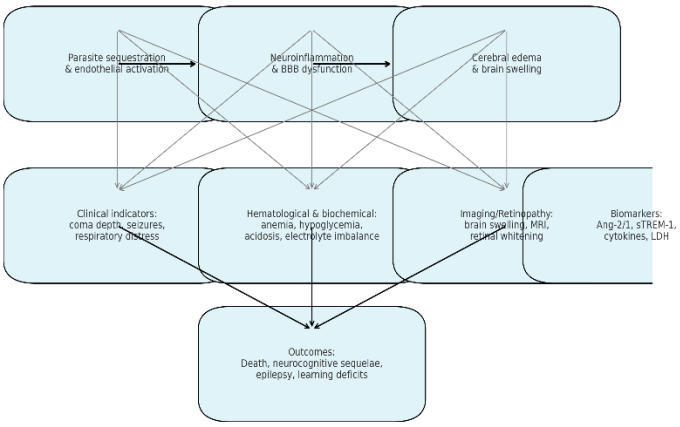

Figure 1. Conceptual framework linking pathogenesis, prognostic indicators, and outcomes in paediatric cerebral malaria

Management and Therapeutic Approaches

The management of paediatric cerebral malaria (CM) is centred on rapid administration of effective antimalarial therapy, correction of life-threatening metabolic derangements, and supportive care. Despite advances, treatment remains challenging in resource-

Antimalarial Therapy

The most significant advance in CM management has been the replacement of quinine with intravenous artesunate. The landmark AQUAMAT trial showed a 22% relative reduction in mortality with artesunate compared to quinine in African children with severe malaria [10]. On this basis, artesunate has become the global standard of care, recommended by the World Health Organisation. Transition from quinine to artesunate has been achieved in many Nigerian hospitals, although stockouts and delays in administration remain common [4]. After stabilisation, children are transitioned to oral artemisinin-based combination therapy (ACT) to complete treatment, and

ensuring full adherence is crucial to prevent recrudescence and resistance [1,4,11].

Supportive Care

Supportive management addresses complications that strongly influence outcome:

- Hypoglycemia should be corrected promptly with intravenous dextrose, as recurrent episodes are strongly linked to mortality [5].
- Seizure control is critical; benzodiazepines or phenobarbital are frequently used. Refractory seizures have been associated with post-discharge epilepsy and poor prognosis [2].
- Severe anaemia requires early blood transfusion, which reduces mortality risk in African children [4].
- Fluid management is complex: while over-hydration of children with cerebral malaria who have dehydration can precipitate cerebral oedema, cautious replacement prevents hypovolemia and shock [2,4].
- Monitoring of electrolytes and renal function is recommended but is inconsistently available in Nigerian hospitals. A recent tertiary-hospital cohort demonstrated that electrolyte imbalance and renal dysfunction were independently associated with poor prognosis [5].

Although these principles are well established, resource constraints in Nigeria and other endemic regions frequently limit implementation. Inadequate monitoring of glucose, electrolytes, and intracranial pressure contributes significantly to avoidable deaths [3–5].

Adjunctive and Experimental Therapies

Numerous adjunctive therapies have been evaluated, but none have consistently improved outcomes in paediatric CM.

- Corticosteroids, mannitol, and osmotic agents have not shown clinical benefit and may worsen outcomes [2].
- Immunomodulatory agents, such as anti-TNF therapies, remain experimental and unproven in children [2].
- Neuroprotective agents, including erythropoietin, statins, and sodium valproate, show promise in preclinical and pilot studies, but paediatric trial data remain limited [2].
- Adjunctive anticonvulsant prophylaxis is controversial: while high-dose phenobarbital reduced seizure recurrence in earlier studies, it was associated with increased mortality due to respiratory depression [2].

Health System and Implementation Challenges

Beyond drug efficacy, outcomes are shaped by health system capacity. Delayed presentation is common in Nigeria, with many children presenting after >24 hours of coma, which reduces survival odds [4]. Stockouts of artesunate and ACTs compromise continuity of treatment [4]. In addition, the absence of paediatric intensive care units, limited access to neuroimaging and retinopathy screening, and referral delays from peripheral health facilities exacerbate mortality [3–5]. Overall, the management of paediatric CM requires a multifaceted approach: rapid artesunate administration, correction of metabolic derangements, seizure control, and supportive care. While artesunate has reduced mortality [1], survival gains are constrained by weak health systems, limited monitoring capacity, and lack of paediatric critical care infrastructure [3–5]. Experimental adjunctive therapies hold promise but require validation in multicentre paediatric trials. Bridging the implementation gap in endemic countries like Nigeria is essential to improve outcomes further.

Neurocognitive and Long-Term Outcomes

While the acute mortality of paediatric cerebral malaria (CM) remains a significant challenge, increasing attention has been directed towards the long-term consequences among survivors, up to one-third of children who survive CM experience persistent neurological, cognitive, and behavioural impairments that significantly affect quality of life, schooling, and social functioning.

Neurological Sequelae

Common post-CM neurological sequelae include epilepsy, motor deficits, visual impairment, and speech disorders. Epilepsy occurs in approximately 10–15% of survivors, with a higher risk among those who experienced prolonged seizures or status epilepticus during the acute illness [1,2]. Hemiplegia and cranial nerve palsies have also been documented, though less frequently. These outcomes often manifest within the first year after discharge and may persist for life.

Cognitive Impairments

Cognitive sequelae represent the most significant long-term burden. Studies in Malawi and Uganda have shown deficits in working memory, attention, language, and executive function persisting months to years after the initial illness [2,3]. Longitudinal follow-up revealed that some impairments improve with time,

but others—particularly attention and memory deficits—remain long-standing [3]. Nigerian cohorts similarly report impaired school performance and reduced cognitive scores in children with a history of CM [4,5]. These deficits contribute to poor educational attainment and limit future socioeconomic opportunities.

Behavioural and Mental Health Disorders

Behavioural sequelae, including hyperactivity, aggression, and mood disorders, are increasingly recognised in CM survivors. A Ugandan cohort demonstrated that children post-CM are more likely to meet criteria for attention deficit hyperactivity disorder (ADHD) and conduct disorder than community controls [2]. Nigerian hospital-based reports have described increased rates of behavioural problems, poor concentration, and irritability in post-CM children [4]. These findings emphasise the importance of integrating psychosocial support and school-based interventions into malaria control programmes.

Predictors of Long-Term Sequelae

Prognostic factors for long-term impairment overlap with those for acute mortality. Deep coma, prolonged seizures, hypoglycaemia, and cerebral oedema are strongly predictive of subsequent neurological and cognitive complications [1,3,5]. Importantly, evidence suggests that survivors with subtle cognitive impairment often go unrecognised in clinical practice, particularly in resource-limited African settings. This underlines the importance of systematic follow-up and screening after hospital discharge.

Implications for Care

Despite the increasing recognition of post-CM sequelae, rehabilitation services remain extremely limited in most endemic regions. Neurocognitive and behavioural impairments are rarely evaluated during routine paediatric follow-up, and access to speech therapy, occupational therapy, or psychological support is scarce. Interventional studies, such as caregiver training programmes and school-based cognitive rehabilitation in Uganda, have demonstrated promising results in reducing some deficits [3]. Expanding such approaches across Nigeria and sub-Saharan Africa could significantly lessen the hidden burden of CM.

The long-term effects of paediatric CM go far beyond just survival. Neurological complications, cognitive difficulties, and behavioural issues are common and often last a long time, creating serious challenges for children, families, and healthcare systems. Indicators of initial severity, such as the depth of coma, seizures, hypoglycaemia, and cerebral oedema, also help predict long-term outcomes, highlighting the importance of both improving initial treatment and implementing structured follow-up. Rehabilitation services, although currently limited in regions where the disease is common, are a vital area for enhancing the quality of life for survivors.

Discussion

Cerebral malaria (CM) remains one of the most severe complications of *Plasmodium falciparum* infection in children, with high mortality and long-term disability despite advances in therapy. This review highlights the persistent burden in Africa, particularly in Nigeria, and underscores the need to contextualise management and prognostication to paediatric populations.

Persistent Mortality Despite Effective Therapy

The introduction of artesunate has significantly reduced mortality in severe malaria, yet paediatric CM continues to claim thousands of lives annually [1]. Nigerian tertiary hospitals still report case fatality rates of 15–22% [4,6], reflecting the reality that drug efficacy alone is insufficient when children present late, monitoring is limited, and critical care resources are scarce. Strengthening health system capacity—including early referral pathways, reliable supply chains, and basic critical care infrastructure—remains essential to improve survival [4,6].

Distinctive Paediatric Pathophysiology

Children with CM exhibit pathophysiological features distinct from adults. In paediatric cases, cerebral oedema and raised intracranial pressure are the dominant causes of death [2], while adults more often die from multi-organ failure. Retinopathy, a reliable diagnostic and prognostic marker, is also more specific to children [9]. These differences argue strongly for age-specific prognostic and therapeutic frameworks, rather than applying adult-derived models to children. [16,18].

Prognostic Indicators: Clinical Utility and Gaps

Clinical features such as coma depth, seizures, and brainstem signs remain the most widely used prognostic indicators at the bedside [2,4]. Haematological and biochemical derangements—such as anaemia, hypoglycemia, and electrolyte imbalance—provide additional predictive value, especially in Nigerian and other African settings where advanced technologies are lacking [4–6]. Neuroimaging and retinal findings represent strong predictors [2,9] but remain inaccessible in most

endemic hospitals. Molecular biomarkers, including angiopoietin-2/1 ratios and sTREM-1, show strong associations with mortality [3], yet translation into affordable, point-of-care assays is still unrealised.

Management: Implementation Challenges

Artesunate has become the global standard of care [1], but health system challenges often undermine its benefits. Delayed presentation, drug stockouts, and weak monitoring capacity compromise outcomes in Nigerian hospitals [4–6]. Supportive care measures—such as glucose correction, seizure control, transfusion for anaemia, and cautious fluid replacement—are lifesaving but inconsistently applied due to limited resources. Adjunctive therapies (e.g., corticosteroids, mannitol, immunomodulators) have not improved outcomes [2], while promising neuroprotective strategies remain experimental. Thus, the implementation gap between guideline-recommended care and real-world practice represents the most pressing challenge.

Long-Term Outcomes: The Hidden Burden

Beyond acute survival, CM imposes a substantial burden of neurocognitive and behavioural sequelae. Survivors frequently suffer epilepsy, learning difficulties, attention deficits, and psychosocial disorders [7,8]. Nigerian reports echo these findings, highlighting impaired school performance and behavioural challenges [4,6]. Yet, rehabilitation services are largely absent in endemic regions. The long-term burden remains under-recognised in policy frameworks, reflecting a need to extend malaria care beyond survival to recovery and quality of life.

Practice and Research Implications

Several priorities emerge from this synthesis:

- Clinical practice: Bedside prognostic indicators (coma depth, seizures, anaemia, hypoglycemia) should be systematically integrated into triage tools. Retinopathy screening offers a low-cost diagnostic adjunct where feasible. Regular monitoring of glucose and electrolytes, even with basic tools, should be emphasised in Nigerian hospitals.
- Health systems: Improving referral efficiency, ensuring consistent artesunate supply, and expanding paediatric intensive care services are critical to reducing case fatality.

Research priorities:

1. Development and validation of integrated prognostic scores tailored to African children.
2. Translation of biomarkers into affordable, rapid diagnostic tests.
3. Clinical trials focused on therapies targeting cerebral oedema, the key driver of paediatric mortality.
4. Longitudinal studies in Nigeria and Africa to characterise neurocognitive outcomes and test low-cost rehabilitation strategies.
5. Health systems research to close the gap between evidence-based care and real-world practice.

Cerebral malaria in children is a distinct clinical syndrome marked by high mortality, unique pathophysiology, and significant long-term consequences. Prognostic indicators across clinical, haematological, biochemical, imaging, and biomarker areas offer valuable predictive insights, but their usefulness is limited by restricted access to diagnostics and monitoring in endemic regions. Addressing these gaps requires both strengthening health systems and conducting innovative research that focuses on paediatric populations. Ultimately, improving outcomes will depend not only on effective medications but also on comprehensive strategies that encompass acute care, rehabilitation, and long-term child development.

Conclusion

Cerebral malaria in children continues to be a significant cause of illness and death in sub-Saharan Africa, especially in Nigeria. Although artesunate has proven to improve survival, case fatality rates remain unacceptably high due to late presentation, poor monitoring, and limited access to paediatric intensive care. Distinctive pathophysiological features—such as cerebral oedema and malarial retinopathy—set paediatric CM apart from adult disease and require age-specific management strategies. Reliable prognostic indicators are available across clinical, haematological, biochemical, imaging, and biomarker domains. However, the routine use for biochemical , imaging and biomarkers parameter is limited by availability and cost. Simple bedside indicators—like coma severity,

seizures, hypoglycaemia, and anaemia—are still the most practical tools for triage in resource-limited settings. Imaging and molecular biomarkers show promise but need to be adapted into affordable, point-of-care formats. Beyond immediate survival, the often-overlooked burden of long-term neurocognitive and behavioural effects is increasingly recognised but remains under-addressed in policy and practice. This highlights the urgent need to incorporate rehabilitation and long-term follow-up into malaria control efforts. Future priorities include creating validated paediatric prognostic scores, developing affordable biomarker-based diagnostics, targeted approaches for cerebral oedema, and conducting longitudinal studies on neurocognitive outcomes in African children. Strengthening health systems to bridge the gap between evidence and implementation is equally important. Ultimately, reducing the burden of paediatric CM will require a comprehensive approach that extends beyond antimalarial medication to include timely diagnosis, effective supportive care, strengthening of the health system, and post-discharge rehabilitation. Only then can we improve the whole trajectory of survival and recovery for African children affected by this devastating disease.

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