Malaria Journal

RESEARCH

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Epidemiology, clinical spectrum, and outcomes of severe malaria in Eastern Uganda: a prospective study

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Abstract

Background In sub-Saharan Africa, malaria remains a public health problem despite some reports of declining incidence in the period 2000–2018. Since 2019, there have been some reports of disease epidemics and resurgences in areas that had registered steep declines and unusual clinical presentations. This study aimed to describe the epidemiology, clinical spectrum, and outcomes of severe malaria in children among malaria-endemic Eastern Uganda, a region that has recently experienced disease epidemics.

Methods This prospective study was conducted at Mbale Regional Referral Hospital, Uganda, from 08th May 2019 to August 15, 2023, as part of the Malaria Epidemiological, Pathophysiological and Intervention studies in Highly Endemic Eastern Uganda (EDCTP–TMA2016SF-1514-MEPIE Study). Children aged 60 days to 12 years who at admission tested positive for malaria and fulfilled the clinical World Health Organization criteria for surveillance of severe malaria were enrolled into the study following appropriate informed consent. Data were collected using a customized proforma on social demographic characteristics, clinical presentation, treatment, and outcomes. Laboratory analyses included complete blood counts, lactate, glucose, blood gases, electrolytes, metabolites, and coagulation markers. In addition, urinalysis using dipsticks was done. Data were analysed using STATA V15. The study had ethical and regulatory approval before data collection commenced.

Results A total of 1,379 participants were recruited. The median age was 4 years (2 months–12 years). Most children 757/1379 (54.9%) were under 5 years, and 825/1379 (59.8%) were males. The common symptoms were fever 1368 (99.2%), poor appetite 1095 (79.5%), inability to sit upright 1051 (76.2%), vomiting 944 (68.4%) and yellow eyes 833 (60.4%). The common signs included prostration, haemoglobinuria and jaundice. Prolonged hospitalization was found in 284/1339 (21.2%) and was associated with impaired consciousness 116/166 (30.1%), $P=0.003$; haemoglobinuria 514/705 (27.1%), $P<0.001$ and jaundice 505/690 (26.8%) $P<0.001$. The overall mortality was 40/1347 (3.0%). Children who had > 1 severity feature were at a higher risk of mortality.

Conclusion In this prospective study of children with severe malaria in Eastern Uganda, the overall mortality was 3.0% and the more the disease clinical syndromes the higher the risk of death.

Keywords Clinical spectrum, Severe malaria, Child, Prolonged hospitalisation, Mortality

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Background

Malaria remains a significant public health challenge in sub-Saharan Africa (SSA) despite earlier reports of declines in incidence [1, 2]. The global number of malaria cases increased from 232 million in 2019 to 247 million in 2021, showing a continued rise over these years [3, 4]. The SSA contributes to approximately 80% of global disease burden [5]. Endemic countries and regions continue to report high transmission rates [6], and there has been a resurgence of malaria cases in areas that had previously seen significant declines [7].

Additionally, malaria epidemics are emerging in traditionally endemic areas, highlighting the dynamic and unpredictable nature of malaria transmission in SSA [2]. Severe malaria is particularly concerning due to its impact on multiple organ systems and its diverse clinical spectrum [8–10]. Previous research has shown that the clinical presentations and outcomes of severe malaria vary based on factors such as age, geographical location, and transmission intensity [11–14]. Children are especially vulnerable to malaria, often experiencing more severe manifestations and higher mortality rates compared to adults [15]. These trends underscore the need for ongoing surveillance and intervention to effectively manage and control the disease. Understanding the clinical presentation of severe malaria remains essential for effective treatment [16, 17], enhancing early diagnosis, and intervention strategies [18, 19] and resource allocation [17, 19], especially in light of recent shifts in malaria epidemiology in East Africa. Increasing drug resistance, particularly partial artemisinin resistance, has emerged across Uganda, raising concerns about treatment efficacy and possible changes in how severe malaria manifests clinically [20]. In addition, after years of intensive vector control, a significant malaria resurgence has been observed in Eastern Uganda, suggesting a loss of acquired immunity and heightened vulnerability to severe cases [21]. Recent studies have also noted a shift in severe malaria cases toward older children in Eastern Uganda, as documented by Namayanja and others signalling a possible alteration in immunity patterns across age groups [22]. This study was conducted to provide a comprehensive analysis of the epidemiology, clinical spectrum, and outcomes of severe malaria in children in malaria-endemic Eastern Uganda. This region recently reported malaria epidemic outbreaks associated with unusual clinical presentation of the disease [22]. Improving understanding of the disease in these aspects remains crucial for informing actions for surveillance and improved case management [22, 23].

Methods

Study setting

This was part of the studies on the Malaria Epidemiological, Pathophysiological and Intervention studies in Highly Endemic Eastern Uganda (EDCTP: TMA 2016SF-1514-MEPIE Study, https://mepiestudy.org) conducted at Mbale Regional Referral Hospital (Mbale RRH). This study was conducted at the Paediatric Acute Care Unit (PACU). The hospital, equipped with 470 beds, including 95 paediatric beds, receives an average of 17,000 paediatric admissions annually. The PACU attends to all children aged 2 months to 12 years with acute illnesses reporting to the hospital. Those not discharged within the first 2 days after stabilisation are subsequently transferred to recuperate in Children's Ward 3 [24]. The disease was surveyed using the World Health Organization (WHO) clinical criteria [25]. Briefly, the criteria included severe anaemia (Hb less than 5 g/dl), prostration (generalized weakness so that the person is unable to sit, stand or walk without assistance), shock (compensated shock was capillary refill time ≥ 3 s or temperature gradient and no hypotension. Decompensation shock was defined as systolic blood pressure < 70 mmHg in children with evidence of impaired perfusion (cool peripheries or prolonged capillary refill), spontaneous haemorrhage (recurrent or prolonged bleeding from nose gums or venipuncture sites; haematemesis or melaena), recurrent convulsions (2 or more convulsions in 24 h), impaired consciousness (Blantyre coma score < 3), jaundice (plasma bilirubin > 50 umol/L (> 3 mg/dl)), pulmonary oedema/respiratory distress (Kussmaul's breathing manifesting as deep breathing with signs of increased work of breathing) and (haemoglobinuria), hyperparasitaemia (greater than 10% in highly endemic areas), acidosis (venous plasma lactate > 5 mmol/L), hypoglycaemia (< 2.2 mmol/L or < 40 mg/dL), lactic acidosis (lactate > 5 mol/L), renal failure (serum creatinine > 3 mg/dL/BUN > 20 mmol/L).

Patient eligibility

All children presenting for admission at the acute care unit (ACU) of Mbale RRH were screened for malaria using malaria rapid diagnostic test (RDT). This study targeted patients aged 2 months to 12 years admitted with features of severe *Plasmodium falciparum* malaria. Children with positive RDT and with any one feature of severe/complicated malaria [26], were further tested using a 10% Giemsa-stained blood slide to confirm the diagnosis of asexual *P. falciparum* parasitaemia. Those with a positive blood slide for *P. falciparum* were invited to participate in the study among the patients who

reported for care from 8:00 am to 5:00 pm from Monday to Friday.

Study procedures

The study was conducted in the ACU ward of Mbale RRH and the laboratory procedures at Mbale Clinical Research Institute (MCRI). At the ward, some of the study bedside procedures included screening for malaria using RDT (SD-Bio line malaria –AG-Pf/Pan manufactured by Standard Diagnostics), random blood sugar assays (RBS) using glucometer Xpress (mmol/L) model manufactured by Nova BIOMEDICAL cooperation USA, lactate lactometer Xpress (mmol/L) model manufactured by Nova BIOMEDICAL cooperation USA) and urine dipstick. In addition, i-STAT CHEM8 + was used to measure blood sodium, potassium, chloride, total carbon dioxide, anion gap, ionised calcium, glucose, urea nitrogen, creatinine, lactate, haematocrit, and haemoglobin. Qualified and certified staff carried out CBC using Beckman coulter model DxH-500 haematology analyser among, biochemistry using cobas111 and blood slide at MCRI laboratory. Malaria blood smears were performed following standard procedures. Two independent, trained microscopists examined each smear to ensure accuracy. Discrepancies were resolved by a third reader. Haemoglobin was obtained using Hemocue Hb-301 manufactured by Hemocue AB, Angelholm Sweden. Lastly, urine dipstick results were obtained using the Siemens multistix10SG reagent strips.

Quality control

Dedicated research teams were trained in data collection methods. All data from this study were cleaned and analysed using STATA version 15 (STATA Corporation, College Station, TX). The database was designed according to the outline and sections of the questionnaire for easy data entry and resolution of data queries. Data were captured and entered using redcap V12.2.1 by GCP-trained data assistants.

Data management

The collected data were downloaded into Excel as a comma separated variables (CSV) file and stored in a database available at the MCRI data office under a lock and key data system. This was later exported to STATA 15 for cleaning and analysis.

Statistics and data analysis

Statistical analyses were conducted using STATA version 15. Descriptive statistics were employed to summarize the demographic and clinical characteristics of participants. Continuous variables were analysed for normality, with results presented as means with standard deviations (SD) for normally distributed data or medians with interquartile ranges (IQR) for skewed data. Categorical variables were summarized using frequencies and percentages.

Bivariate analyses were performed to evaluate the association between severe malaria phenotypes and clinical outcomes such as prolonged hospitalization and mortality. Chi-square or Fisher's exact tests were applied to compare categorical variables, and independent t-tests or Mann–Whitney U tests were used for continuous variables as appropriate.

Multivariate logistic regression was employed to identify independent predictors of prolonged hospitalization and in-hospital mortality. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were calculated, with a significance level set at $P < 0.05$ for all analyses.

Patient care

The standardized management of severe malaria in children, as outlined in the Uganda Clinical Guidelines 2016 was followed by attending clinicians. These included initial assessment and resuscitation, IV artesunate treatment, supportive care (e.g., blood transfusions, anticonvulsants), continuous monitoring, management of comorbidities, and follow-up care [27].

Results

A total of 1379 eligible participants aged 2 months to 12 years were enrolled from May 8, 2019, to August 15, 2023.

Social demographic characteristics

The median age in this study was 4 years (IQR: 2–4 years). Of the 1379 participants recruited, 757 (54.9%) were under the age of 5, and 622 (45.1%) were 5 years or older. Furthermore, the majority of participants, 824 (59.8%), were males. A significant portion of the participants came from the districts in Eastern Uganda where the malaria epidemic had been reported by the Uganda Ministry of Health [28]. Specifically, the distribution was as follows: Mbale (398 participants, 28.9%), Budaka (288, 20.9%), Kibuku (100, 7.3%), Bukedea (87, 6.3%), Butebo (87, 6.3%), Butaleja (77, 5.6%), Sironko (77, 5.6%), Namutumba (70, 5.1%), Manafwa (48, 3.5%), and Pallisa (37, 2.7%) (see Fig. 1).

Clinical spectrum of severe malaria

Prostration was the most observed presentation in 801/1379 (58.1%), of whom 425/801 (53.1%) had severe anaemia and 374/801(46.7%) had previously received a blood transfusion.

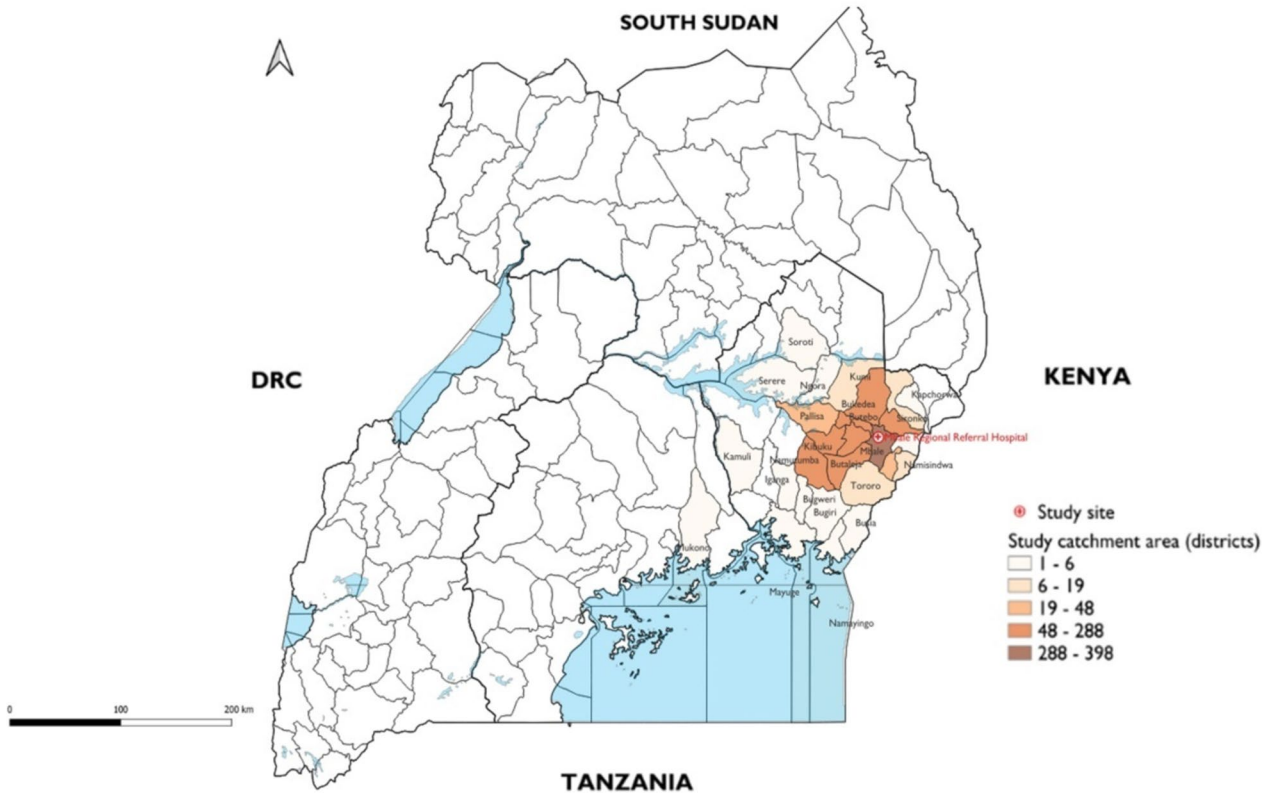

Fig. 1 A sketch Map showing the distribution of study participants by district of origin

Haemoglobinuria was observed in 728/1379 (52.8%) participants, of whom 351/728 (48.2%) also had severe anaemia. Among the participants with haemoglobinuria, 232/351 (66.1%) had previously received a blood transfusion. Additionally, 653/728 (89.7%) reported abdominal pain, and 208/728 (28.6%) reported vomiting. More than half (417/728, 57.3%) had two or more admissions in the previous year. Other findings in this cohort included jaundice in 528/728 (72.8%), severe/profound anaemia in 347/728 (47.7%), and elevated LDH in 343/728 (47.1%).

In the group with severe malaria anaemia (625/1379, 45.3%), 305/625 (48.8%) reported abdominal pain, 452/625 (72.3%) had vomiting, and 351/625 (56.2%) reported passing blood or Coca-Cola-coloured urine. Additionally, tachycardia was present in 465/625 (74.4%), 56/625 (9%) had respiratory distress, and 133/625 (21.3%) had a weak pulse. LDH was elevated in 265/625 (42.4%) participants, and other findings included leucocytosis in 49/572 (8.6%), thrombocytopenia in 55/572 (9.6%), and elevated bilirubin in 106/549 (19.3%).

Recurrent convulsions were observed in 255/1379 (18.5%) participants in whom a majority 212/255 (83.1%) were less than 5 years old and 43/255 (16.9%) were 5 years or more. 150/255 (58.8%) were male and 105/255 (41.2%) were female. About one half 132/255 (51.8%) were febrile ($T^0 = \text{or} > 37.5$ ℃) and 67/255 (26.3%) had impaired consciousness, while 20/255 (7.8%) had respiratory distress. LDH was elevated in 48/255 (18.8%) of the participants, and 17/255 (6.7%) (7.7%) had hypoglycaemia.

Impaired consciousness was present in 168/1,379 (12.2%) participants. Of those, a majority, 121/168 (72%), reported experiencing vomiting, and 42/168 (25%) had a history of febrile convulsions. Participants with impaired consciousness also exhibited the following additional laboratory features: leucocytosis 9/67 (13.4%), Hyperparasitaemia 68/168 (40.5%), hyperglycaemia 43/168 (25.6%), and hyperpyrexia was in 5/168 (3.0%).

Acidosis (lactic acidosis) was observed in 125/1379 (9.1%) participants, the majority 103/125 (82.4%) had severe anaemia and 95/125 (76%) had jaundice. Leucocytosis was observed in 2/48 (4.2%) and 71/125 (56.8%) had elevated lactic dehydrogenase (LDH). Hyperparasitaemia was observed in 422/1379 (30.6%) participants, 248/422 (58.8%) were below 5 years of age.

Respiratory distress was found in 88/1379 (6.4%) participants. Of these 43/88 (48.9%) had impaired consciousness. Only one patient had pneumonia as a comorbidity. Cerebral malaria was recorded in 54/1379 (3.9%) participants. 31/54 (57.4%) of participants with cerebral malaria

Table 1 The proportion of children under each classification of Severe Malaria

Variables	Freq (N = 1379)	Percent (%)
Prostration	801	58.1
Haemoglobinuria	728	52.8
Jaundice	710	51.5
Severe malaria anaemia (SMA)	625	45.3
Hyperparasitaemia	422	30.6
Renal failure	179	13.0
Impaired consciousness	168	12.2
Acidosis	125	9.1
Recurrent convulsions	255	18.5
Respiratory distress	88	6.4
Hypoglycaemia	80	5.8
Cerebral malaria	54	3.9
Hypovolaemic shock	19	1.4
Spontaneous bleeding (DIC)	14	1.0

were below 5 years. 37/54 (68.5%) had recurrent convulsions and 15/54 (27.8%) had jaundice. Only 3/54 (5.6%) were hypoglycaemic.

Impaired renal function (elevated BUN > 20 mg/dL and raised creatinine levels), was observed in 179/1379 (13.9%) participants, of whom 33/101 (32.7%) had blackwater fever. Among the study participants with renal impairment, a triad of blackwater fever, jaundice and severe anaemia was present in 49/169 (29.2%) of these participants. One study participant progressed to acute kidney failure with anuria and electrolyte derangement.

The clinical features that were not observed frequently included hypoglycaemia (random blood sugar < 2.2 mmol/L) which was observed in 80/1379 (5.8%) and hypovolemic shock in 19/1379 (3.9%) participants. Spontaneous bleeding (DIC) was recorded in 14/1379 (1.0%). These 3 clinical features were the least commonly reported in this study. The proportions of these features are summarised in Table 1.

Figure 2 presents the number of cases with various combinations of severe malaria classifications identified in this study. Of the 15 classifications used in this study, the majority of participants had a combination of 2–3 features, followed by those with one and 4 features. Some had up to all the 11 features as shown in Fig. 2.

Outcomes

The outcomes were determined in 1347/1379 (97.7%) study participants with complete outcomes data. Mortality was 40/1347 (3.0%), 59/1347 (4.4%) had self-discharge status (runaways) and the majority 1248 (92.7%) were discharged alive.

Association of severe malaria phenotypes with prolonged hospital stay (Lasting in the hospital above 5 days)

Table 2 presents the bivariate results for the association between severe malaria phenotypes and prolonged hospitalization. Among 252 children with recurrent convulsions, 16.7% had hospital stays of 5 days or more, ($P = 0.05$). Haemoglobinuria observed in 705 children, was associated with longer hospital stays in 27.1% of cases ($P < 0.001$). Of the 607 children with SMA, 23.7% were hospitalized for 5 days or more ($P = 0.040$). Jaundice was present in 690 children, with 26.8% staying for 5 days or longer, a significant correlation. Among 771 children with prostration, 25.8% had extended hospital stays, ($P < 0.001$). Lastly, impaired consciousness was reported in 166 children, 30.1% of cases with prolonged hospital stay ($P = 0.003$).

Table 3 presents the multivariate results for the association between severe malaria phenotypes and prolonged hospital stay. The association between severe malaria phenotypes and prolonged hospital stay, showed significantly associated with extended hospitalization: haemoglobinuria, impaired consciousness, and prostration. Haemoglobinuria was associated with a 1.9-times likelihood of keeping the child at the hospital for 5 or more days (AOR = 1.9, 95% CI 1.4–2.6, $P < 0.001$). Impaired consciousness was also linked to a 1.6-times higher likelihood of staying in the hospital for more than 5 days (AOR = 1.6, 95% CI 1.1–2.3, $P < 0.022$). Similarly, prostration was associated with a 1.6-times increased likelihood of keeping the child in the hospital for 5 or more days (AOR = 1.6, 95% CI 1.2–2.2, $P < 0.002$). See Table 3.

Association of severe malaria phenotypes with hospital mortality

Table 4 presents the bivariate results for the association between severe malaria phenotypes and hospital mortality. Among the various phenotypes studied, several showed significant associations with hospital mortality. Cerebral malaria was present in 54 children, with a mortality rate of 20.4%, indicating a significant association with hospital mortality ($P < 0.001$). Hypovolemic shock was observed in 19 children, with a 26.3% mortality rate, also showing a significant association ($P < 0.001$). Severe malaria anaemia (SMA) affected 625 children, with a mortality rate of 4.6%, demonstrating a significant correlation ($P < 0.001$). Hypoglycaemia was reported in 80 children, with a 16.7% mortality rate, indicating a significant relationship ($P < 0.001$). Respiratory distress affected 88 children, with an 18.2% mortality rate, showing a significant association ($P < 0.001$). Acidosis was present in 125 children, with a mortality rate of 13%, also demonstrating a significant correlation ($P < 0.001$). Renal failure was observed in 179 children, with an 8.1% mortality rate,

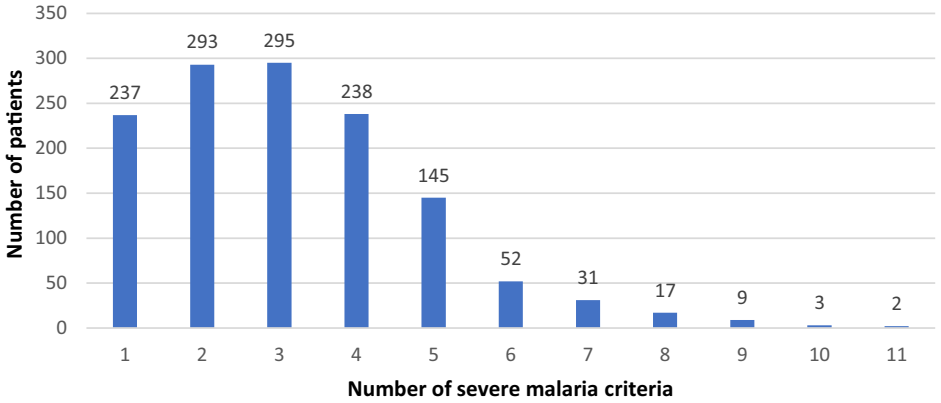

Fig. 2 Proportion of participants exhibiting one or more criteria

indicating a significant association ($P<0.001$). Jaundice affected 710 children, with a mortality rate of 3.9%, showing a significant correlation ($P<0.039$). Prostration was reported in 801 children, with a mortality rate of 3.9%, indicating a significant relationship ($P<0.024$). Impaired consciousness was present in 168 children, with a mortality rate of 14.5%, showing a significant association with hospital mortality ($P<0.001$). See Table 4.

Among all the severe malaria phenotypes we investigated, only three phenotypes predicted mortality during a prolonged hospital stay: cerebral malaria, impaired consciousness, and hypoglycaemia. Children with cerebral malaria had a 6.9 times higher likelihood of mortality (AOR = 6.9, 95% CI 2.3–20.9, $P<0.001$). Hypoglycaemia was associated with a 3.9 times increased chance of death (AOR = 3.9, 95% CI 1.5–9.8, $P<0.005$). Additionally, impaired consciousness was linked to a 3.2 times higher likelihood of mortality from severe malaria (AOR = 3.2, 95% CI 1.2–8.3, $P<0.001$). See Table 5.

Discussion

This was the longest prospective epidemiological study on malaria in Eastern Uganda where a recent malaria epidemic with unusual clinical presentations from October 1, 2021, to September 7, 2022, were reported [22]. The study enrolled patients from 8:00 a.m. to 5:00 p.m., Monday to Friday, which ensured consistency of the surveillance data quality. Eligibility required *P. falciparum* confirmation by blood smear. In this study, the epidemiology, clinical spectrum, and outcomes of severe malaria in children presenting severe malaria. It started on May 8, 2019, and ended on August 15, 2023. The study enrolled 1,379 children (median age 4 years). The three common severe malaria phenotypes included prostration (58.1%), haemoglobinuria (52.8%), and severe malaria anaemia (45.3%). Prolonged hospital stays were linked to haemoglobinuria, impaired consciousness, and prostration. Mortality was 3%, with cerebral malaria, hypoglycaemia, and impaired consciousness significantly predicting in-hospital death.

The participants for this study came from 11 of the 16 districts served by Mbale RRH in Eastern Uganda (Fig. 1). The median age reported in this study (4 years) is much higher than the 18 months reported from the same settings in a study reporting severe malaria data May 5, 2011–April 30, 2012 [24] and the median of 30 months by Mpimbaza and colleagues elsewhere in Uganda [29]. In addition, the proportion of children under 5 years of age was low (54.9%) compared to 91.1% in 2011–2012 data from the same settings [24], or over 70% of the under 5 s in the 2017–2018 data reported elsewhere in Uganda [29]. This trend of increasing age in children with malaria has previously been observed [22]. The shift towards older children in severe malaria cases, with a reduced proportion among those under 5 years, may be influenced by better malaria prevention [30], with emphasis on the use of malaria protection measures in these age groups. The trend of the current spectrum may point towards variability in immunity levels across different age groups. While children under five typically have higher exposure to malaria, which leads to some level of acquired immunity, it is also possible that older children (over five) could have experienced a reduction in immunity due to recent malaria control efforts that may have limited their exposure over the past years.

Earlier studies have documented that this changing trend in the clinical spectrum of the disease is very likely modified by age [22, 24, 31]. Data reporting an increase in age with the severity of malaria [22, 24, 30, 31], however, do not fully explain the roles of changing transmission patterns, evolving parasite strains, or variations in

healthcare access and behaviour. The consistent predominance of Mbale (28.9%) and Budaka (20.9%) which also are epidemic prone districts [22, 24, 31] may indicate that these areas are emerging hotspots for malaria, but needs serialized geospatial-temporal data to confirm. Regarding the gender difference, this study also found variation in gender, with severe malaria in males accounting for 59.8%. This is not surprising, as previous studies done on malaria in the country have established the burden and severity of malaria in male children [32]. This finding is also consistent with similar studies by Abossie and colleagues in Ethiopia [33], and a recent study in Tanzania by Mandai and colleagues [34]. Previous malaria studies in Eastern Uganda have shown only a slightly higher proportion of males [22, 24, 31]. Identifying a pronounced gender difference is crucial for targeted interventions, resource allocation, further research, comparative analyses, and informing policy development.

On the clinical spectrum of severity in this setting, several common symptoms among children with severe malaria were noted. Fever was the most prevalent symptom. While fever is commonly used as an indicator of malaria infection, in this study, it was not an exclusive criterion for malaria diagnosis, as all cases were confirmed with blood smear microscopy, the gold standard for malaria diagnosis, to avoid reliance on fever alone.

In patients who had received recent antipyretics or anti-malarial treatment or in those presenting with shock, fever was masked or absent, but this was only in < 1% of the cases. The study did not set a specific threshold of parasitaemia (e.g., > 5000 parasites/μL) for defining malaria; rather, it aimed to capture the full clinical spectrum of severe malaria presentations in this setting. This approach aligns with real-world clinical practice where severe malaria may present variably, especially in regions with high malaria endemicity where immunity can modulate typical symptoms. In addition, symptoms

Table 2 Bivariate results of association of severe malaria phenotypes with prolonged hospitalization

Variable	Overall (n)	Hospital stay		*P-value*
		< 5 days n(%)	> 5 days n(%)	
Cerebral malaria	53	38 (71.7)	15 (28.3)	0.197
Recurrent convulsions	252	210 (83.3)	42 (16.7)	0.050
Haemoglobinuria	705	514 (72.9)	191 (27.1)	< 0.001
Hypovolaemic shock	19	16 (84.2)	3 (15.8)	0.560
Severe malaria anaemia (SMA)	607	463 (76.3)	144 (23.7)	0.040
Hypoglycaemia	77	65 (84.4)	12 (15.6)	0.214
Respiratory distress	86	70 (81.4)	16 (18.6)	0.541
Acidosis	121	97 (80.2)	24 (19.8)	0.698
Renal failure	173	128 (74)	45 (26)	0.098
Jaundice	690	505 (73.2)	185 (26.8)	< 0.001
Prostration	771	572 (74.2)	199 (25.8)	< 0.001
Impaired consciousness	166	116 (69.9)	50 (30.1)	0.003
Spontaneous bleeding (DIC)	14	9 (64.3)	5 (35.7)	0.182
Hyperparasitaemia	412	321 (77.9)	91 (22.1)	0.601

Table 3 Multivariate results of association of severe malaria phenotypes with prolonged hospitalization

Variable	COR (95%CI)	*P-value*	AOR (95%CI)	*P-value*
Recurrent convulsions	0.4 (0.2,0.8)	0.006	0.9 (0.4,1.8)	0.673
Haemoglobinuria	2.2 (1.6,2.9)	0.001	1.9 (1.4,2.6)	0.001
Impaired consciousness	1.7 (1.2,2.5)	0.003	1.6 (1.1,2.3)	0.022
Severe Malaria Anaemia (SMA)	1.3 (1.0,1.7)	0.041	1.0 (0.8,1.4)	0.799
Jaundice	2.0 (1.6,2.7)	0.001	1.4 (1.0,1.9)	0.055
Prostration	2.0 (1.5,2.6)	0.001	1.6 (1.2,2.2)	0.002

Table 4 Bivariate results of association of severe malaria phenotypes with hospital mortality

Variable	Overall	Hospital Mortality		*P-value*
		Alive n (%)	Dead n (%)	
Cerebral malaria	54	43 (79.6)	11 (20.4)	< 0.001
Recurrent convulsions	253	243 (96)	10 (4)	0.542
Haemoglobinuria	728	685(96.6)	24 (3.4)	0.344
Hypovolaemic Shock	19	14(73.7)	5 (26.3)	< 0.001
Severe Malaria Anaemia (SMA)	625	583 (95.4)	28 (4.6)	< 0.001
Hypoglycaemia	80	65 (83.3)	13 (16.7)	< 0.001
Respiratory distress	88	72 (82.8)	16 (18.2)	< 0.001
Acidosis	125	107 (87)	16 (13)	< 0.001
Renal failure	179	159 (91.9)	14 (8.1)	< 0.001
Jaundice	710	666(96.1)	27 (3.9)	0.039
Prostration	801	746 (96.1)	30 (3.9)	0.024
Impaired consciousness	168	142(85.5)	24 (14.5)	< 0.001
Spontaneous bleeding (DIC)	14	13 (92.9)	1 (7.1)	0.355
Hyperparasitaemia	422	399 (96.4)	15 (3.6)	0.347

like poor appetite, inability to sit upright (prostration), and yellow eyes (jaundice) characterizing most of the study participants. These symptoms are largely due to the pathophysiology of malaria and how it affects the body. These findings are similar to a previous study in the same setting on the unusual spectrum of malaria in eastern Uganda during a malaria epidemic [22], notably, diverse clinical manifestations of severe malaria in these settings. Elevated lactate dehydrogenase (LDH) levels were found in 33.9% of the study participants, signalling significant haemolysis and tissue damage, which are hallmark features of severe malaria. Leucocytosis was present in 5.6% of participants, reflecting the body's inflammatory response to infection. Thrombocytopenia was observed in 10.9% of participants, which increases the risk of bleeding and suggests impaired platelet production or increased destruction, which are very common in severe infections. Elevated bilirubin levels were detected in 21.3% of participants, indicating haemolysis and potential liver dysfunction. The laboratory markers found in this study were very indicative of the pathophysiology of severe malaria in these settings and demonstrated the need for comprehensive diagnostics and therapeutic approaches to mitigate these severe complications to prevent mortality in children. This is similar to the findings by Mathias and colleagues on the laboratory markers of malaria infection [35].

This study advances understanding into the clinical manifestations and complications associated with severe malaria, highlighting the prevalence and impact of various phenotypes such as prostration, haemoglobinuria, and renal impairment. These findings underscore the complexity and severity of malaria in affected populations, particularly in children, who are the most vulnerable to these complications.

Prostration was the most frequently observed clinical presentation, affecting 58.1% of the participants. Among these, more than half had severe anaemia, and a significant proportion had received a blood transfusion prior to the study. This association between prostration and severe anaemia underscores the severity of malaria's impact on the body's ability to transport oxygen, necessitating interventions such as blood transfusions.

Haemoglobinuria, characterized by the presence of haemoglobin in the urine, was observed in 52.8% of the participants. This condition was more common in males and in children aged 5 years or older. Haemoglobinuria is often a sign of intravascular haemolysis, where red blood cells are destroyed within the blood vessels, leading to the release of haemoglobin into the bloodstream and subsequently into the urine [36]. This process can cause severe

Table 5 Multivariate results for the association of severe malaria phenotypes with in-hospital mortality

Variable	COR (95% CI)	*P-value*	AOR (95% CI)	*P-value*
Cerebral malaria	11 (5.2, 23.8)	0.001	6.9 (2.3, 20.9)	0.001
Hypovolaemic shock	13.2 (4.5, 38.7)	0.001	1.7 (0.4, 7.8)	0.465
Severe Malaria Anaemia (SMA)	2.9 (1.5, 5.7)	0.002	2.1 (1.0, 4.8)	0.065
Hypoglycaemia	9.2 (4.5, 18.6)	0.001	3.9 (1.5, 9.8)	0.005
Respiratory distress	9.2 (4.7, 18.4)	0.001	2.1 (0.8, 5.4)	0.112
Acidosis	7.5 (3.9, 14.5)	0.001	1.5 (0.6, 3.9)	0.383
Renal failure	3.9 (2.0, 7.6)	0.001	1.9 (0.8, 4.5)	0.142
Jaundice	2.0 (1.0, 3.9)	0.043	1.2 (0.6, 3.0)	0.540
Prostration	2.3 (1.1, 4.7)	0.028	0.9 (0.4, 2.2)	0.813
Impaired consciousness	12.3 (6.4, 23.7)	0.001	3.2 (1.2, 8.3)	0.001

anaemia and is often associated with blackwater fever, a complication of malaria characterized by dark urine, jaundice, and renal impairment [36]. The study found that nearly half of the participants with haemoglobinuria had severe anaemia, with a substantial portion requiring blood transfusions. The presence of abdominal pain and vomiting in a majority of these cases further complicates the clinical picture, as these symptoms can exacerbate dehydration and electrolyte imbalances, increasing the risk of renal impairment. Additionally, 72.8% of participants with haemoglobinuria also had jaundice, a condition often linked to both severe haemolysis and liver dysfunction.

Renal impairment was observed in 13.9% of the study participants, with a significant overlap with haemoglobinuria. Elevated blood urea nitrogen (BUN) and creatinine levels, indicative of impaired kidney function, were prevalent in participants with haemoglobinuria [37]. This condition, characterized by the triad of blackwater fever, jaundice, and severe anaemia, was present in nearly a third of participants with renal impairment [37]. The progression of one participant to acute kidney failure highlights the potential severity of renal complications in severe malaria, where electrolyte disturbances and anuria can lead to life-threatening conditions.

Severe malaria anaemia (SMA), another critical phenotype, was observed in 45.3% of participants, many of whom exhibited symptoms such as abdominal pain, vomiting, and the passage of dark urine. The high prevalence of tachycardia, respiratory distress, and weak pulse in these participants suggests that SMA significantly impacts cardiovascular function, necessitating careful monitoring and management to prevent further complications [38].

The study also sheds light on less common but serious complications such as cerebral malaria, acidosis, and respiratory distress, each contributing to the overall morbidity and mortality associated with severe malaria. The presence of elevated LDH levels across various phenotypes indicates widespread tissue damage and cellular turnover, further complicating the clinical management of these patients [39]. This is also the reason why LDH is a marker of poor prognosis [39].

The outcomes of severe malaria investigated in this study were prolonged hospitalization which reflected morbidity and hospital mortality. A a significant proportion (92.7%) of children admitted to the hospital during the study period with severe malaria were discharged alive. Only 4.4% were classified as runaways. Mortality was reported in 3% of the study participants. The severe malaria clinical phenotypes that predicted mortality or severity among the 3% who died, were phenotypes like cerebral malaria, hypoglycaemia and impaired consciousness. Specifically, deaths due to cerebral malaria are often connected to developing severe neurological complications of malaria that lead to coma, seizures, and profound impairment of brain function [40]. This could explain the deaths in these children due to complications related to brain swelling, increased intracranial pressure, and systemic organ failure. On the other hand, hypoglycaemia can lead to critically low blood glucose levels, which can cause seizures, loss of consciousness, and cardiovascular collapse. This is a medical emergency which can be fatal if not promptly and effectively treated, hence this could explain its association with mortality. Additionally, the presence of impaired consciousness despite its variations from drowsiness to coma, increases the risk of complications related to aspiration pneumonia, reduced ability to maintain airway patency, and other systemic complications.

This study's limitations include potential under-detection of severe malaria cases due to restricted enrolment hours (8:00 a.m. to 5:00 p.m., Monday to Friday), potentially missing after-hours cases. Despite this limitation, this approach helped ensure consistency and reduce bias in data collection, allowing for standardized clinical evaluations and laboratory processing. Although RDTs were used for initial screening to enhance malaria case detection, emerging HRP-2 deletions in *P. falciparum* may have led to missed RDT-negative, smear-positive cases, underscoring the need for updated diagnostic strategies and evaluation of the disease spectrum and outcomes in these cases. The use of blood smears for confirmation, however, is in line with the current severe malaria WHO surveillance criteria, which recommends Giemsa-stained slides as the gold standard, minimizing the potential for misclassification and improving diagnostic accuracy.

Conclusion and recommendations

In conclusion, this study highlights the multifaceted nature of severe malaria, with prostration, haemoglobinuria, and renal impairment emerging as significant clinical challenges. The overlap between these conditions underscores the need for comprehensive clinical management strategies that address the complex interplay between anaemia, haemolysis, and organ dysfunction in severe malaria. The overall mortality was 3%.

Acknowledgements

We do acknowledge all the healthcare professionals from the study health facilities for their various contributions to this work.

Author contributions

P.OO. conceived and supervised the overall study, provided expert guidance, and critically revised the manuscript for important intellectual content. C.N. G.P. and C.B.O. Participated in data collection and contributed to manuscript

writing. Y.A.M.L. J.P.A. and G.P. performed statistical analysis, contributed to the interpretation of the data, offered guidance on study design and critically reviewed the manuscript. D.A. W.O. P.O. G.A. and R.M. contributed to data collection, managed the study logistics, and assisted in the preparation of the manuscript. All authors contributed to editing the paper and approved the final submission.

Funding
This publication was produced by the MEPIE Study which is part of the EDCTP2 programme supported by the European Union (Grant Number (TMA2016SF-1514-MEPIE Study). The views and opinions of the authors expressed herein do not necessarily state or reflect those of EDCTP.

Availability of data and materials
The study data is available by request to the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Mbale Regional Referral Hospital Research & Ethics Committee. Local permission to conduct the study was obtained from the respective hospital heads. The study conformed to the provisions of ethical standards in Uganda.

Consent for publication
The Mbale Clinical Research Institute (MCRI, www.mcri.ac.ug), a research entity affiliated to the Uganda National Health Research Organization, approved the publication of this manuscript.

Competing interests
The authors declare no competing interests.

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Received: 19 September 2024 Accepted: 11 December 2024
Published online: 07 February 2025

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