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Prevalence and associated factors of severe malaria-hemoglobinuria among children below 15 years: A retrospective cross-sectional study at a tertiary regional referral hospital in Uganda.

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Abstract

Background:

The World Health Organization (WHO) report of 2022 showed that Uganda accounted for 5.1% of the global case burden. Severe malaria presenting with hemoglobinuria is characterized by tea coloured urine, jaundice, and anemia. This study aimed to understand the prevalence and associated factors of severe malaria-hemoglobinuria among children below 15 years admitted to a tertiary hospital in Uganda.

Methods:

A retrospective study that involved reviewing patient files of children aged 15 years and below admitted at Kayunga regional referral hospital in Uganda during 2023. Data was extracted using a standardized checklist developed according to the WHO 2015 clinical surveillance criteria for severe malaria. Sociodemographic, clinical, and laboratory data were collected and analyzed using Stata 18. Logistic regression analysis was used to evaluate the factors associated with severe malaria-hemoglobinuria. A p-value <0.05 indicated statistical significance.

Results:

The prevalence of severe malaria-hemoglobinuria was 27.7% with the majority (48.2%) in the age group of 5-9 years. Males were the majority (54.7%). The associated factors of severe malaria-hemoglobinuria were hyperparasitemia (p-value=<0.001), convulsions (p-value=0.051), and anemia (p-value=0.012). The mortality rate among the study participants was 1.4%. The average hospitalization duration for patients was 3 days. There was no difference in mortality and duration of hospital stay among patients who received standard treatment alone versus those who received an adjuvant like steroids.

Conclusions:

The prevalence of severe malaria-hemoglobinuria was 27.7% higher than in earlier studies in central Uganda, with the overall mortality rate of 1.4%. Hyperparasitemia, anemia, and convulsions were the associated factors. The higher prevalence among children aged 5 and above highlights the need for enhanced surveillance and targeted interventions in this age group to improve outcomes in similar settings.

Recommendation:

Further prospective studies are recommended to explore causal relationships and optimize care strategies.

Keywords: *Severe Malaria, Hemoglobinuria, Pediatric, Black-water fever.*
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Background

Malaria remains highly prevalent and endemic in many Sub-Saharan Africa (SSA) countries, accounting for 249 (95% of global cases) million malaria cases globally in 2022, according to the World Health Organization report. [1]. The report showed that only four countries, notably Nigeria

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(26.8%), the Democratic Republic of the Congo (12.3%), Uganda (5.1%), and Mozambique (4.2%), contributed to the global malaria burden in 2021 [1].

The World Health Organization (WHO) clinical criteria for surveillance of severe malaria include hemoglobinuria as a parameter. [2]. Hemoglobinuria is the presence of excess hemoglobin in urine, a molecule in red blood cells that transports oxygen through the body. It's usually due to excessive intravascular hemolysis, in which large numbers of red blood cells (RBCs) are destroyed, releasing free hemoglobin into the plasma. Excessive hemoglobin is filtered by the kidneys, which is excreted in urine, resulting in the passing of dark/tea coloured urine for the patient.

Studies on the prevalence rates of severe Malaria and hemoglobinuria in Uganda have shown regional variances. A study in Eastern Uganda found a prevalence of severe malaria with hemoglobinuria at 52.7% [3]. Another study in Uganda showed that the incidence of severe malaria and hemoglobinuria was approximately 2 times higher in the Eastern region, i.e., Soroti district (severe anemia 43%, backwater fever 22%) than in Mulago (severe malaria 23%, bwf-6%) [4].

Studies from other Sub-Saharan Countries where Malaria is endemic show almost similar trends in prevalence patterns. In Abadan, Nigeria, the incidence of hemoglobinuria was reported to be 19.1% with children below 5 years contributing about 78% of the study population. [5]. A study on the resurgence of blackwater fevers (hemoglobinuria) in sub-Saharan Africa revealed a prevalence of 6-48% among patients with severe malaria. [6].

Several factors are known to be associated with severe malaria-hemoglobinuria. A study from Nigeria showed the median age for children diagnosed with hemoglobinuria was 52.5 months, which was higher than that among patients without hemoglobinuria (35 months), and boys were found to be more affected than girls [5]. Despite the World Health Organization recommending blood transfusion and anti-malarial as standard treatment for severe malaria with hemoglobinuria [2], it is not uncommon to find country-specific variations.

In Uganda, the malaria guidelines recommend that children with hemoglobinuria should be treated with I/V artesunate and blood transfusion if Hb is < 8g/dl. [7] . A study in Burundi started children with hemoglobinuria on a combination of corticosteroids, antimalarials, and blood transfusions on the assumption that the hemoglobinuria may have been immune-mediated; however, it is not clear whether this was beneficial compared to those who did not receive corticosteroids. [8].

Cognizant of this variation, this study aimed to understand the prevalence of severe malaria with hemoglobinuria, associated factors, and treatment outcomes among children below 15 years at a tertiary regional referral hospital in Uganda.

Methods

Study design and Setting

A retrospective cross-sectional study that involved reviewing patient files of children aged 15 years and below admitted at Kayunga regional referral hospital (KRRH) in 2023. The hospital is a regional referral and teaching hospital located in Kayunga district. It has a capacity of about 200 beds and serves the 7 districts of Buikwe, Kamuli, Jinja, Kayunga, Luwero, Mukono, and Nakasongola. About 30% of arable land in the district is used for commercial sugarcane planting, which is conducive to mosquito breeding. The district has a total population of 368,062 people, of which 53.8% (198,057) are children less than 15 years of age. [9]. The hospital provides outpatient, inpatient, and laboratory services. Most of the severe malaria cases and complications are treated in the hospital, except in some cases where patients require specialized services for the disease complications, such as severe renal failure requiring dialysis.

Sampling Technique

This study used stratified time sampling/seasonal sampling (purposive), which included 2 months at the beginning (January and February), middle (June and July), and the end (November and December) of the year, 2023. This aimed to capture seasonal variation in malaria prevalence.

Inclusion and Exclusion criteria

All the patient files from the selected months for children under 15 years admitted with a confirmed diagnosis of malaria were included. Children with no clear diagnosis of malaria or those admitted with other diagnoses other than malaria were excluded from the study.

Data Collection and Management

A customized checklist was used to abstract data on social demographic and clinical characteristics from patients' files. The data collection was carried out between July and August 2025. The study collected clinical features of severe malaria

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according to the WHO 2015 clinical surveillance criteria for severe malaria from patients' files. In addition, outcome data on signs and symptoms resolution, mortality, referrals, and length of hospital stay were collected. Data was coded and entered in Microsoft Excel 2023 for cleaning.

Statistical analysis

Data was analyzed using Stata 18. Descriptive statistics were computed for categorical variables as frequencies and percentages, while continuous variables were summarized using means and standard deviations or medians and interquartile ranges. Group comparisons were conducted using the chi-square test or Fisher's exact test for categorical variables and the independent t-test or Mann-Whitney U test for continuous variables.

Prevalence Ratios (PRs) and corresponding 95% Confidence Intervals (CIs) were estimated using a Modified Poisson Regression Model with robust standard errors, based on complete cases. Variables were included in the adjusted model if they had a p-value < 0.2 in the unadjusted analysis. Multicollinearity was assessed using the Variance Inflation Factor (VIF), and variables with high collinearity were excluded, leading to the removal of weight from the final model. Model selection was performed using backward elimination, sequentially removing non-significant variables to identify the most parsimonious model. Statistical significance was set at $p < 0.05$.

Ethical Considerations

Ethical approval was sought from the institutional review board, Mildmay Uganda. Research Ethics Committee (MUREC) with initial approval granted on 23rd August 2024, under the ethical clearance number, MUREC-2024-460. Amendments were sought, and approval was received on the 10th January 2025, which is valid until 23rd August 2026. Administrative clearance was obtained from the Kayunga Regional Referral Hospital. The National Council of Science and Technology (UNCST) approved the research project on 18th July 2025 with registration number HS6156ES.

Privacy and confidentiality:

All efforts were made to maintain privacy and confidentiality by ensuring that questionnaires were marked by coded numbers, and no individual identifying information was used. Filled questionnaires were kept in a lockable safe, and data were entered in a password-protected computer.

Risks and mitigation:

There were minimal risks related to the study.

Results.

Prevalence of severe malaria and hemoglobinuria among children < 15 years.

In the period of review, a total of 2,230 admissions were made, of which 501 cases of severe malaria and 139 cases of severe malaria-hemoglobinuria were recorded. Therefore, this study recorded a prevalence of severe malaria among children below 15 years of age of 22.5% and the prevalence of severe malaria-hemoglobinuria was 27.7% (Figure 1).

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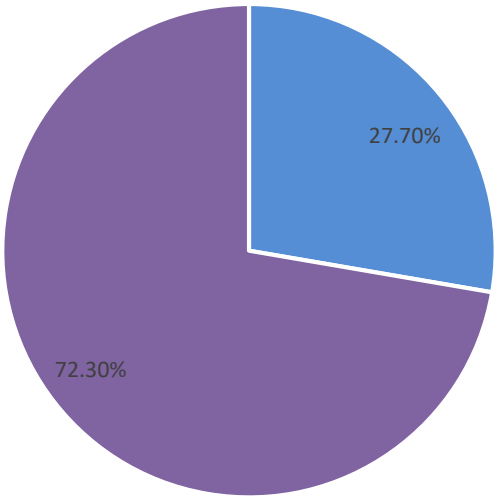
Figure 1:Prevalence of severe malaria-haemoglobinuria



Characteristics of participants diagnosed with severe malaria-hemoglobinuria

The median age of the patients was 5 years (IQR 3.0,7.0), with the majority (48.2%) falling in the age group of 5-9 years. The males were the majority (54.7%). The top three reported associated signs and symptoms were fever (133, 32.0%), pallor (90, 21.6%), and vomiting (75, 18.0%). Only 9 (6.5%) patients were reported to have had sickle cell disease as a listed chronic illness (Table 1a).

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Table 1a: Demographics and clinical features of the study participants

Characteristic	n (%)
All	139
Age Years Median (IQR)	5.0 (3.0, 7.0)
Age categories	
0-4 years	56 (40.3)
5-9 years	67 (48.2)
10-14 years	16 (11.5)
Sex	
Female	60 (43.2)
Male	76 (54.7)
Unknown	3 (2.1)
Weight Kgs Median (IQR)	16 (12, 20)
Past medical history of severe malaria with hemoglobinuria	
No	130 (93.5)
Yes	9 (6.5)
History of previous blood transfusions	
No	119 (85.6)
Yes	20 (14.4)
History of prophylactic antimalarial use	
No	136 (97.8)
Yes	3 (2.2)
Known sickle cell disease	
No	130 (93.5)
Yes	9 (6.5)
Complications	
Convulsion	3 (2.2)
Severe jaundice	2 (1.4)
Respiratory distress	4 (2.9)
Hyperparastaemia	35 (25.2)

n stands for absolute frequencies. **The denominator used to calculate the prevalence rates for the signs and symptoms is 416.

A review of the complete blood count (CBC) test results performed on the patients during hospital stay showed that the majority had their white blood cell count (47.5%), neutrophil count (40.3%), platelet count (46.0%), and lymphocyte count (41.7%). However, severe anemia was reported in 27(19.4%) of the patients, Table 1b.

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Table 1b: Laboratory results of the study participants

Characteristic	n (%)
Complete Blood Count	
White Blood Cell Count	
Leucocytosis	13 (9.3)
Leucopenia	5 (3.6)
Low	0 (0.0)
Normal	66 (47.5)
Not done	55 (39.6)
Neutrophil	
High	25 (18.0)
Low	3 (2.1)
Normal	56 (40.3)
Not done	55 (39.6)
Haemoglobin	
High	7 (5.0)
Mild anemia	7 (5.0)
Moderate anemia	24 (17.4)
Normal	20 (14.4)
Not done	54 (38.8)
Severe anemia	27 (19.4)
Platelets	
High	3 (2.2)
Low	16 (11.5)
Normal	64 (46.0)
Not done	55 (39.6)
Very low	1 (0.7)
Lymphocytes	
High	4 (2.9)
Low	22 (15.8)
Normal	58 (41.7)
Not done	55 (39.6)

n stands for absolute frequencies. **The denominator used to calculate the prevalence rates for the signs and symptoms is 416.

The majority (105, 75.5%) of patients received intravenous (IV) artesunate as the standard treatment for severe malaria. Of the adjuvant medicines received, only 17 (12.2%) were reported to have received a steroid, and 56 (40.3%) had a blood transfusion. Of the patients who received blood transfusions, 19(33.9%) and 13 (23.2%) had severe and moderate anemia, respectively. The majority of patients (107, 77.0%) were discharged, and 10 out of the 11 referred out patients were due to blood transfusion (Table 1c).

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Table 1c: Treatment given, outcomes, and length of hospital stay of the study participants

Characteristic	n (%)
Treatment given	
IV quinine	
No	134 (96.4)
Yes	5 (3.6)
IV artesunate	
No	4 (2.9)
Yes	135 (97.1)
Blood transfusion	
No	83 (59.7)
Yes	56 (40.3)
ACT	
No	34 (24.5)
Yes	105 (75.5)
Steroid use	
No	122 (87.8)
Yes	17 (12.2)
Treatment outcome	
Died	2 (1.4)
Discharged	107 (77.0)
Referred	11 (7.9)
Unknown	19 (13.7)
Length of hospital stay	
≤ 3days	65 (46.8)
> 3days	55 (39.6)
Unknown	19 (13.6)

n stands for absolute frequencies. **The denominator used to calculate the prevalence rates for the signs and symptoms is 416.

Factors associated with severe malaria-hemoglobinuria among children < 15 years

This study's results showed that Children within the age group of 10-14 years were more likely to suffer from severe malaria-hemoglobinuria (p-value <0.001), Table 4. The prevalence rate of mild anemia among children with severe malaria-hemoglobinuria was 2.58 (p-value=0.012), and the majority of these patients' duration of stay in hospital was longer than 3 days (p-value=0.052). Hyperparasitemia (p-value=<0.001) and convulsions (p-value=0.051) were significantly associated with severe malaria-hemoglobinuria.

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Table 2a: Modified Poisson regression for factors associated with severe malaria-hemoglobinuria among children <15 years.

Characteristic	Un-adjusted PR (95% CI)	p-value	Adjusted PR (95% CI)	p-value
Age groups				
0-4 years	Reference		Reference	
5-9 years	2.11(1.56-2.85)	<0.001	2.18(1.22-3.88)	0.008
10-14 years	2.04(1.3-3.2)	<0.001	2.54(1.62-3.98)	<0.001
Sex				
Female	Reference		Reference	
Male	1.22(0.91-1.62)	0.184	0.91(0.62-1.35)	0.649
Weight (kgs)	1.05(1.03-1.06)	<0.001	NA	NA
Past medical history of severe malaria with hemoglobinuria			NA	NA
No	Reference		NA	NA
Yes	3.08(2.25-4.23)	<0.001	NA	NA
History of previous blood transfusions			NA	NA
No	Reference		NA	NA
Yes	2.46(1.80-3.36)	<0.001	NA	NA
History of prophylactic antimalarial use				
No	Reference		Reference	
Yes	3.66(3.17-4.23)	<0.001	1.03(0.45-2.36)	0.95
Sickle cell disease				
No	Reference		NA	NA
Yes	1.51(0.89-2.54)	0.125	NA	NA
Convulsion				
No	Reference		Reference	
Yes	0.18(0.06-0.53)	0.002	0.16(0.03-1.01)	0.051
Severe jaundice				
No	Reference		Reference	
Yes	3.64(3.16-4.2)	<0.001	1.53(0.9-2.6)	0.116
Respiratory distress				
No	Reference		NA	NA
Yes	0.96(0.41-2.25)	0.925	NA	NA

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Table 2b: Modified Poisson regression for laboratory characteristics.

Characteristic	Un-adjusted PR (95% CI)	p-value	Adjusted PR (95% CI)	p-value
Hyperparastaemia				
No	Reference			
Yes	0.23(0.16-0.32)	<0.001	0.27(0.15-0.5)	<0.001
Neutrophil - CBC results				
High	1.21(0.83-1.76)	0.324	NA	NA
Low	1.57(0.68-3.61)	0.286	NA	NA
Normal	Reference		NA	NA
Hemoglobin - CBC results				
High	3.29(1.87-5.78)	<0.001	2.00(0.96-4.15)	0.065
Mild anemia	1.73(0.85-3.51)	0.128	2.58(1.23-5.39)	0.012
Moderate anemia	2.17(1.33-3.53)	0.002	1.71(0.95-3.08)	0.072
Normal	Reference		Reference	
Severe anemia	1.69(1.03-2.77)	0.037	1.31(0.66-2.61)	0.444
Platelet - CBC results				
High	0.76(0.28-2.03)	0.583	NA	NA
Low	0.77(0.48-1.22)	0.261	NA	NA
Normal	Reference		NA	NA
Very Low	2.78(2.29-3.39)	<0.001	NA	NA
Lymphocyte - CBC results				
High	1(0.43-2.33)	0.995	NA	NA
Low	1.59(1.1-2.3)	0.013	NA	NA
Normal	Reference		NA	NA

Table 2c: Modified Poisson regression for Treatment outcomes and length of hospital stay.

Characteristic	Un-adjusted PR (95% CI)	p-value	Adjusted PR (95% CI)	p-value
Treatment outcome				
Discharged	Reference		NA	NA
Referred	2.62(1.78-3.87)	<0.001	NA	NA
Died	0.74(0.21-2.61)	0.637	NA	NA
Length of hospital stay in days				
≤ 3days	Reference		Reference	
> 3days	1.82(1.34-2.46)	<0.001	1.09 (1.00-1.19)	0.052

Prevalence Ratios (PRs) and their corresponding 95% Confidence Intervals (CIs) were estimated using a modified Poisson regression model. Variables with a p-value < 0.1 in the unadjusted analysis were included in the adjusted model. Multicollinearity was assessed using the Variance Inflation Factor (VIF); weight and age were collinear (age was maintained), and history of transfusion was collinear with history of antimalarial use (history of transfusion was dropped). Backward elimination was applied for variable selection.

Outcomes of patients with severe malaria-hemoglobinuria versus treatment received during hospital stay.

The majority of patients with severe malaria-hemoglobinuria who received standard treatment alone, i.e., IV artesunate or IV quinine, were discharged (107, 89.9%), see Table 2 for reference. There was no difference in regards to mortality and duration of hospital stay among patients

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who received standard treatment alone versus those who received an adjuvant, i.e., steroid or blood transfusion (table 3).

Table 3: Outcomes of patients with severe malaria-hemoglobinuria versus treatment received during hospital stay.

Characteristics	Patients who received standard treatment and blood transfusion (n=50)	Patients who received standard treatment and used steroids (n=16)
Treatment Outcomes		
Died	1 (2.0)	1 (7.7)
Discharged	44 (89.8)	9 (69.2)
Referred	4 (8.2)	3 (23.1)
Runaway		
Length of Stay in Hospital		
≤ 3 days	16 (32.0)	6 (50.0)
>3days	34 (68.0)	6 (50.0)

Discussion

This study showed a high prevalence of 27.7% among children below 15 years diagnosed with severe malaria hemoglobinuria at Kayunga regional referral hospital in Uganda. This high rate is consistent with other studies done within the region that showed the occurrence of hemoglobinuria among children with severe malaria to be as high as 33.2% from a cross-sectional study done in Western Uganda and 52.8% from a prospective study done in Eastern Uganda [10,11]. The likely reasons for the high prevalence of severe malaria-hemoglobinuria in these settings are that malaria is endemic in the region. The 2022 Uganda Demographics Health Survey showed a 23% prevalence rate of Malaria among children under 5 years [12]. This picture is on a backdrop of structural barriers to timely diagnosis and treatment of malaria, resulting in these complications [13,14].

There was a significant difference in the age distribution of patients with severe malaria-hemoglobinuria, with children below nine years accounting for a higher proportion (88.5%) compared to those above nine years. This signifies the risk of complications associated with severe malaria among younger children owing to their immature immune system and higher parasite loads. [15]. The proportion of boys (54.7%) in this study was slightly higher than that of girls (43.2%), a finding that is consistent with previous studies done in other settings. [5,16]. The sex distribution of study participants enrolled for this study reflected the general pattern of admissions into the hospital pediatric ward.

This study only collected weight as a nutritional assessment variable of the patients, which limited the integration of nutritional status (z-score) in the analysis. But previous studies also have not shown any significant relationship between the incidence of severe malaria-heamoglobinuria and nutritional status among children. [5,17,18]. However, it is important to note the synergistic relation between malaria and malnutrition in children, in that malaria infection can cause poor nutritional status due to loss of appetite, deranged nutrient absorption issues as a result of diarrhea, and increased nutrient requirements, and at the same time, malnutrition, in turn, can weaken the immune system and increase susceptibility to malaria.

Hyperparasitemia (p-value=<0.001) and convulsions (p-value=0.051) were significantly associated with severe malaria-hemoglobinuria in this study. These findings are consistent with previous studies that showed high incidence rates of hemoglobinuria in areas of high malaria transmission and parasitemia. [19]. Hyperparasitemia is associated with microvascular obstruction, which causes hypoxic and hypoglycemic effects to the brain, thereby leading to convulsions among patients with severe malaria. [20]. However, studies have not shown any direct correlation between hyperparasitemia and hemoglobinuria, with implications related to the body's immune response and the effects of certain anti-malarial drugs. [21,22] Being the cause of the hemoglobinuria (tea coloured urine), an aspect that this paper did not interrogate.

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Despite previous studies showing a significant association between jaundice and hemoglobinuria [23,24], this study did not find any statistically significant association between severe malaria hemoglobinuria and jaundice (p-value=0.116). However, this study showed that anemia, i.e., mild (p-value=0.012) and moderate (p-value=0.072), was significantly associated with hemoglobinuria. This observation can be explained by the increased intravascular breakdown of red blood cells coupled with poor nutritional status common in many Ugandan children, resulting in the anemic state.

Previous studies have linked hemoglobinuria with certain antimalarials, particularly quinine. [23,24]. However, even though our study did not collect the exact anti-malarial medication taken before hospital admission, we did not find any significant association between prophylactic antimalarial use and hemoglobinuria (p-value=0.95). It is also important to note that according to the Uganda clinical guidelines, the use of intravenous (IV) quinine for treating severe malaria is placed as a second-line option. [25] As such, repeated exposure is minimal.

This study showed that the mortality rate from severe malaria-heamoglobinuria was 1.4% and hospital duration stay of longer than three days was significantly related to severe malaria-heamoglobinuria (p-value=0.052). On mortality rate, our study finding is relatively low compared with findings from a prospective study done in Eastern Uganda that showed mortality rates among children with severe malaria-heamoglobinuria at 3.4% [10]. Higher mortality rates of 12.5% were reported in a prospective case-control study carried out in Nigeria. [5]. Our study showed no significant difference in outcomes for patients who received standard treatment alone (IV artesunate or IV quinine) versus those who received standard treatment along with an adjuvant, which was either a blood transfusion or a steroid. These findings are consistent with a scoping review on clinical management of blackwater fever that showed no evidence of literature on the standard of treatment. [26].

The findings of this retrospective study, which reported a prevalence of malaria with hemoglobinuria of 27.7% and identified associated factors in an endemic area, may be generalizable to similar settings with comparable malaria transmission intensity and population dynamics. However, caution is warranted when extrapolating these results to non-endemic areas or populations with different epidemiological characteristics.

Limitations:

The findings of this retrospective study, which identified a prevalence of malaria with hemoglobinuria of 27.7% and identified associated factors in an endemic area, may be generalizable to similar settings with comparable malaria transmission intensity and population demographics. However, caution is warranted when extrapolating these results to non-endemic areas or populations with different epidemiological characteristics.

This study had several limitations, including incomplete patient notes that lacked some important parameters for our study, which could have affected the factors associated with malaria hemoglobinuria.

Conclusions

In conclusion, the prevalence of severe malaria-hemoglobinuria in this study was found to be high at 27.7% The study highlights the multifaceted nature of severe malaria-hemoglobinuria with hyperparasitemia, jaundice, and anemia emerging as significant clinical challenges. Despite the low mortality rates (1.4%), it is critical to appreciate the long hospital stay that was associated with hemoglobinuria. Therefore, such an overlap of the clinical syndrome presents an important need for comprehensive clinical management strategies to address the complex interplay between complications associated with severe malaria-hemoglobinuria, i.e., anemia, hemolysis, and organ dysfunction. The higher prevalence among children aged 5 and above highlights the need for enhanced surveillance and targeted interventions in this age group to improve outcomes in similar settings. Further prospective studies are recommended to explore causal relationships and optimize care strategies.

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List of abbreviations

BWF: Black water fever
CBC: Complete Blood Count
Hb: Haemoglobin
IV: Intravenous
KRRH: Kayunga regional referral hospital
MUREC: Mildmay Uganda Research Ethics Committee
RBC: Red Blood Cells
SSA: Sub-Saharan Africa
UNCST: Uganda National Council for Science and Technology
WBC: White Blood Cell Count
WHO: World Health Organization

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The datasets used are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

SN, ZA, EIEE JN, and RS conceived the idea for the study
ZA, CWC, and EN carried out the data collection
RM carried out the laboratory diagnostics and interpretations
SN, EIEE, and ZA did the data analysis, first drafting of the manuscript, and visuals
SN provided supervisory guidance in writing the manuscript
All authors read and approved the final manuscript for submission

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