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Effect of corticosteroids on haemoglobinuria resolution among children with blackwater fever at Soroti regional referral hospital, Uganda: a retrospective cohort study

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Abstract

Background Corticosteroids are sometimes used in clinical practice in the treatment of blackwater fever (BWF), a complication of severe malaria, despite limited evidence of benefit. This study aimed to compare the time to haemoglobinuria resolution between children with BWF who received corticosteroids and those who did not, and determine if corticosteroid use significantly influences this outcome.

Methods This was a retrospective cohort study carried out at Soroti Regional Referral Hospital in Soroti, Uganda, among children diagnosed with blackwater fever (BWF), between 1st January 2023 to 31st December 2024. Participants included in the study were 889. Time to haemoglobinuria resolution was determined using the Kaplan–Meier survival function and compared using log rank test. Predictors of time to haemoglobinuria resolution were determined using an extended cox proportional hazard model, with results expressed as adjusted hazard ratios (aHR) and 95% confidence intervals (CI).

Results The median time to haemoglobinuria resolution was 3 days in both the corticosteroid and non-corticosteroid groups. Corticosteroid use was not significantly associated with time to haemoglobinuria resolution (aHR: 0.90; 95% CI 0.75–1.07, $p = 0.239$). The predictors of time to haemoglobinuria resolution were: antibiotic use (aHR: 0.68; 95% CI 0.58–0.81, $p < 0.001$), blood transfusion (specifically for those who received transfusions twice [aHR: 0.78; 95% CI 0.62–0.97, $p = 0.024$], three times [aHR: 0.59; 95% CI 0.40–0.88, $p = 0.010$], and four times [aHR: 0.36; 95% CI 0.24–0.53, $p < 0.001$]), presence of jaundice (aHR: 1.49; 95% CI 1.14–1.94, $p = 0.003$), and administration of normal saline (aHR: 0.57, 95% CI 0.45–0.74, $p < 0.001$).

Conclusion Corticosteroid use did not accelerate haemoglobinuria resolution in children with blackwater fever, supporting current WHO guidance against their use. These findings suggest limited benefit of corticosteroids in BWF management.

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Background

Blackwater fever (BWF) is a severe complication of *Plasmodium falciparum* malaria characterized by massive intravascular haemolysis leading to haemoglobinuria (typically seen as intermittent tea-coloured urine), anaemia, and potentially acute kidney injury. It primarily affects children and non-immune individuals in malaria-endemic regions [1–3]. The prevalence of BWF was reported to be 12.4% in a multicentre trial conducted in East Africa [4]. In eastern Uganda, the prevalence rates were higher, with 14.5% reported among sick children at Mbale Regional Referral Hospital and 21.8% at Soroti Regional Referral Hospital (SRRH) [4]. BWF is associated with adverse outcomes such as death and frequent admissions as observed in Uganda where up to 46% of children who had BWF and severe anaemia were readmitted atleast once during a 6 month follow up period [5]. It is documented to cause substantial morbidity among children in sub-Saharan Africa SSA [6, 7]. A scoping review involving 100 studies reported 18.1% mortality from BWF, highlighting its clinical severity and public health importance [8].

Effective management of BWF involves prompt initiation of antimalarial therapy, typically with intravenous artesunate followed by a full course of oral artemisinin-based combination therapy (ACT), alongside supportive care to mitigate the effects of intravascular haemolysis [9–11]. Intravenous fluids are administered to maintain renal perfusion and prevent or manage acute kidney injury, while folic acid supplementation supports erythropoiesis during recovery. Blood transfusion is often necessary to correct severe anaemia and stabilize haemodynamics [9, 11].

Corticosteroids have been empirically used as adjunctive therapy for haemoglobinuria associated with BWF, based on the hypothesis that their anti-inflammatory effects might mitigate immune-mediated haemolysis and reduce renal inflammation [1, 12]. However, their use remains controversial. Although some clinicians continue to administer corticosteroids in clinical practice, current evidence supporting their effectiveness is limited, and the World Health Organization (WHO) does not recommend their use in the management of BWF, neither is it recommended by the Uganda clinical guidelines [9, 11].

Despite this, corticosteroids are still used in routine practice at SRRH and other hospitals in Uganda, reflecting ongoing uncertainty among clinicians. To date, no systematic study has evaluated whether corticosteroids influence recovery in children with BWF, particularly with respect to haemoglobinuria resolution, a key clinical marker of improvement. Addressing this gap is especially important in eastern Uganda, where BWF prevalence and associated morbidity remain high. This study, therefore, aimed to compare the time to haemoglobinuria resolution between children with BWF who received corticosteroids and those who did not. By addressing this gap, the study seeks to generate evidence that can inform clinical decision-making, rationalize the use (or non-use) of corticosteroids, and potentially guide updates to treatment protocols in malaria-endemic, resource-limited settings.

Methods

Study design and setting

This retrospective cohort study was conducted at Soroti Regional Referral Hospital (SRRH) in Soroti District, approximately 294 kms northeast of Kampala, Uganda's capital city. SRRH is one of the country's 13 regional referral hospitals and serves the Teso sub-region, which encompasses 10 districts with a combined catchment population of approximately 2.5 million people [13]. The hospital plays a central role in the diagnosis and management of severe malaria and its complications, including blackwater fever (BWF), particularly among children.

Laboratory services at SRRH include malaria diagnosis by malaria rapid diagnostic tests (RDTs) and microscopy of Giemsa-stained blood smears, haematological testing using an automated haematology analyzer, and biochemical assays for renal and liver function using automated chemistry analyzers. Haemoglobinuria is documented based on visual inspection of urine colour and, when available, urinalysis is done using urine dipstick testing. All laboratory tests were conducted following standard operating procedures used routinely at SRRH. The inpatient pediatric ward has a bed capacity of 46. On average, SRRH admits 264 children with severe malaria each month, of whom approximately 16.7% (44 cases) present with BWF. Paediatric cases of BWF are managed by qualified medical officers and paediatricians following standard clinical protocols.

Study population and eligibility criteria

The study included children aged 0–<18 years who were admitted to SRRH between 1st January 2023 and 31st December 2024 with a diagnosis of severe malaria and clinical features suggestive of BWF. BWF was defined clinically as a history of passing tea-colored urine reported by the caregiver and/or directly observed during admission, in the setting of a confirmed *P. falciparum* infection. Severe malaria was defined as *P. falciparum* infection confirmed by either a positive malaria RDT or thick blood smear with at least one clinical or laboratory marker of severity (e.g., impaired consciousness, multiple convulsions, severe anaemia [haemoglobin < 5 g/dL], respiratory distress, hypoglycaemia, jaundice, shock, renal impairment, or hyperparasitaemia). Children with known chronic haemolytic anaemias (e.g., sickle cell disease), other non-malarial causes of haemoglobinuria, or incomplete or missing key clinical data were excluded.

Study variables

The dependent variable was time to haemoglobinuria resolution, defined as the number of days from hospital admission to the documented clearance of tea-colored urine. The main independent variable was corticosteroid use. Other independent variables included sociodemographic factors (age, sex, and weight); clinical factors at admission (presence of fever, vomiting, pallor, splenomegaly, jaundice, duration of symptoms, level of consciousness, and history of previous BWF episodes); baseline laboratory characteristics (haemoglobin level, serum creatinine, and urinalysis results); and treatment-related factors (antibiotic use, blood transfusion, and administration of normal saline and folic acid). Acute kidney injury (AKI) was defined according to the Risk, Injury, Failure, Loss of kidney function and End-Stage kidney disease (RIFLE) criteria as an increase in serum creatinine ≥ 1.5 times baseline or urine output < 0.5 mL/kg/h for at least 6 h.

Data collection procedures

Data was collected using a structured and pretested data-abstraction tool customized based on the SRRH medical records. Data was extracted from chart review by trained research assistaints (RAs) who were medical students in their 4th year of training.

Data quality control and assurance

The data abstraction tool was developed after reviewing different validated questionnaires from previously published literature. The tool was pretested before data collection. Training was given for data collectors. Checking of the completed forms was done at the end of each day of data extraction for consistency, completeness, clarity, and accuracy. Data were double-entered into EpiData version 4.6.

Data analysis

The data was cleaned and then exported to STATA 17 software™ for analysis. The median and interquartile range were used to summarize numerical independent variables. Categorical independent variables were summarized as counts and percentages. The median time to haemoglobinuria resolution was estimated using a Kaplan–Meier survival function. Differences in survival time between children who received corticosteroids and those who did not were compared using the log-rank test.

The scaled Schoenfeld residual test and extended Cox model were used to check the proportional-hazard assumption. An extended Cox proportional hazards model was used to determine the effect of corticosteroid use on the time to haemoglobinuria resolution, adjusting for other independent variables. Any independent variable in bivariate analysis with a p-value less than 0.20 was included in the multivariable regression analysis. Hazard ratio (HR) with 95% confidence intervals (CI) and p-value was reported to assess the strength and significance of the association. A variable with a p-value less than 0.05 in the final model was considered statistically significant. Goodness-of-fit was evaluated by plotting Nelson-Aalen cumulative hazard estimates against Cox-Snell residuals. The chi-square test was used to compare categorical outcomes between the groups.

Ethical considerations

Ethical approval for this study was obtained from the Mbale Regional Referral Hospital Research Ethics Committee, approval number; MRRH-2024-437. As the study involved retrospective data abstraction from medical records with no direct contact with participants, a waiver of informed consent was requested and granted by the REC. The study adhered to the ethical guidelines enshired in the Declaration of Helsinki. Administrative clearance was also granted from the Senior Executive Consultant of Soroti Regional Referral Hopsital. To ensure privacy and confidentiality, all personal identifiers, including names and contact information, were removed, and each participant was assigned a unique study code.

Results

Study profile

Out of 960 medical records of children diagnosed with severe malaria with symptoms suggestive of BWF at SRRH between 1st January 2023 and 31st December 2024, 71 records were excluded. The final analysis included 889 participants. Of these, 711 (80%) received corticosteroids, while 178 (20.0%) did not (Fig. 1).

Study participant characteristics

The median age of children who received corticosteroids was 7 years (IQR: 5–10), compared to 6 years (IQR: 3–8) for those who did not receive corticosteroids. Common clinical features at admission included fever (79.3% vs. 81.5%), vomiting (44.0% vs. 49.4%), and pallor (36.6% vs. 39.3%) in the corticosteroid and non-corticosteroid groups, respectively. Jaundice was present in 29.4% of the corticosteroid group and 30.9% of the non-corticosteroid group. Over half of the children in both groups had no prior history of BWF episodes. Table 1 shows the demographic and baseline clinical characteristics of the participants.

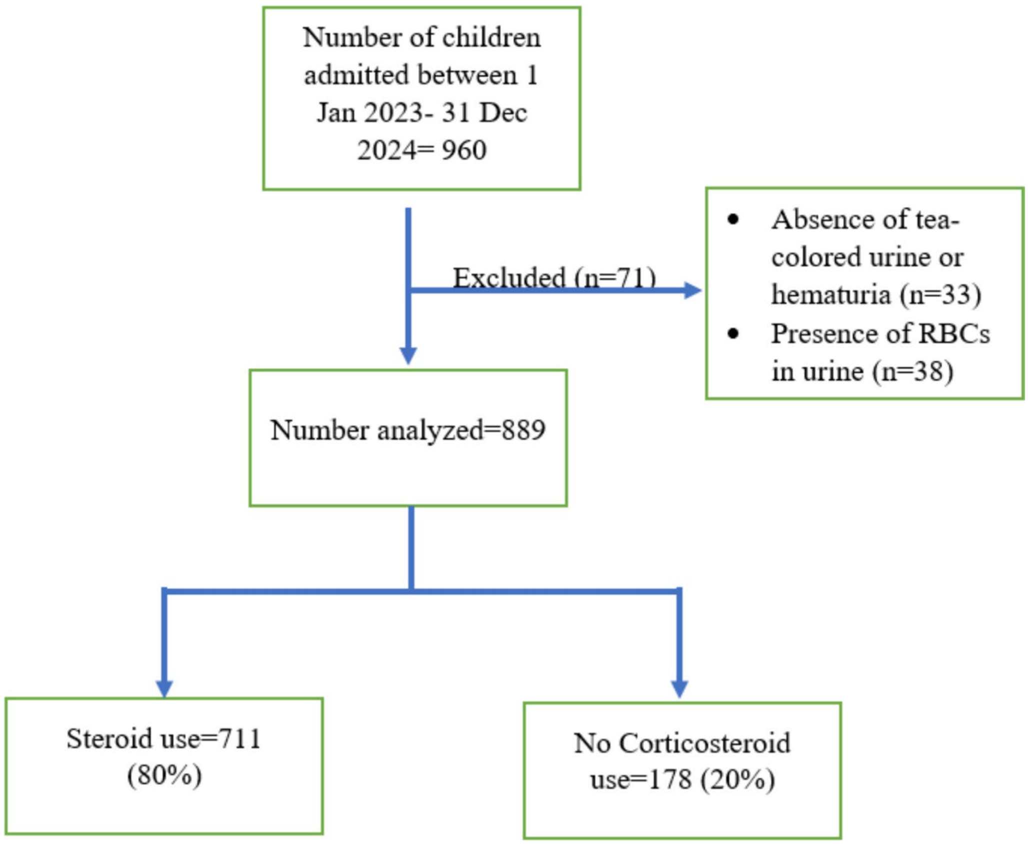

Fig. 1 Study recruitment flowchart

Baseline laboratory and treatment related characteristics of the study participants

A considerable proportion of the participants in both the corticosteroid group and non-corticosteroid group were missing data on haemoglobin level (40.8% vs. 43.8%) and serum creatinine (90.0% vs. 91.0%). However, the median haemoglobin level was 5.4 g/dL (IQR: 4.2–7.4) among children who received corticosteroids compared to 5.1 g/dL (IQR: 4.0–6.1) in those who did not. Antibiotics were commonly administered across both groups, with slightly higher use among children who received corticosteroids (78.9% vs. 75.3%). Blood transfusion was also frequent, with a comparable proportion of children in both groups receiving at least one transfusion. Normal saline was administered to over half of the children in each group. Table 2 presents the baseline laboratory and treatment-related characteristics of the participants.

Time to haemoglobinuria resolution

The median time to haemoglobinuria resolution was 3 days in both groups, with a 95% CI of 2–3 days in the corticosteroid group and 3–3 days in the non-corticosteroid group. The difference in survival curves between the two groups, assessed using the log-rank test, was not statistically significant ($p = 0.078$) (Fig. 2).

Bivariate analysis of factors associated with time to haemoglobinuria resolution

The variables with a p-value less than 0.2 were: vomiting (cHR 1.16, $p = 0.034$), jaundice (cHR 1.30, $p = 0.043$), and previous BWF episodes (cHR 0.80, $p = 0.061$ for those who have a third episode within the last 12 months), haemoglobin (cHR 1.02, $p = 0.101$), serum creatinine (cHR 1.01, $p = 0.052$), corticosteroid use (cHR 0.88, $p = 0.143$), antibiotic use (cHR 0.64, $p < 0.001$), blood transfusion (specifically for those who received transfusions twice [cHR 0.62, $p = 0.029$], three times [cHR 0.22, $p = 0.001$], or four times [cHR 0.14, $p < 0.001$]), normal saline (cHR 0.62, $p < 0.001$), and folic acid (cHR 0.66, $p = 0.010$). The detailed results of the bivariate analysis are shown in Table 3.

Multivariable analysis of factors associated with time to haemoglobinuria resolution

In the multivariable extended Cox regression model, corticosteroid use was not significantly associated with time to haemoglobinuria resolution (aHR: 0.90; 95%

Table 1 Demographic and baseline clinical characteristics of study participants

Variables	Categories	Corticosteroid use N (%)	No Corticosteroid use N (%)	P-value[a]
Median age (IQR)		7 years (5–10)	6 years (3–8)	< 0.001
Median weight (IQR)		21 kg (17–26)	18 kg (13–25)	< 0.001
Sex	Female	300 (42.5%)	78 (43.8%)	0.747
	Male	406 (57.5%)	100 (56.2%)	
Fever	No	147 (20.7%)	33 (18.5%)	0.529
	Yes	564 (79.3%)	145 (81.5%)	
Vomiting	No	398 (56.0%)	90 (50.6%)	0.194
	Yes	313 (44.0%)	88 (9.4%)	
Pallor	No	451 (63.4%)	108 (60.7%)	0.496
	Yes	260 (36.6%)	70 (39.3%)	
Jaundice	No	502 (70.6%)	123 (69.1%)	0.644
	Yes	209 (29.4%)	55 (30.9%)	
Splenomegaly	No	480 (67.5%)	125 (70.2%)	0.127
	Yes	185 (26.0%)	35 (19.7%)	
	Missing	46 (6.5%)	18 (10.1%)	
AVPU score	Alert	643 (90.4%)	149 (83.7%)	0.380
	Verbal	6 (0.8%)	0 (0.0%)	
	Pain	1 (0.2%)	1 (0.6%)	
	Unresponsive	2 (0.3%)	1 (0.6%)	
	Missing	59 (8.3%)	27 (15.1%)	
Previous blackwater fever episodes	None	371 (52.2%)	95 (53.4%)	0.656
	2 episodes in 3 months	106 (4.9%)	28 (15.7%)	
	3 episodes in 6 months	35 (4.9%)	5 (2.8%)	
	3 episodes in 12 months	77 (10.8%)	21 (11.8%)	
	Missing	122 (17.2%)	29 (16.3%)	

[a] P-values obtained from t-tests for continuous variables and chi square test or fisher's exact tests for categorical variables

CI 0.75–1.07, p = 0.239). Factors which were significantly associated with time to haemoglobinuria resolution were; antibiotic use (aHR: 0.68; 95% CI 0.58–0.81, p < 0.001), blood transfusion (specifically for those who received transfusions twice [aHR: 0.78; 95% CI 0.62–0.97, p = 0.024], three times [aHR: 0.59; 95% CI 0.40–0.88, p = 0.010], and four times [aHR: 0.36; 95% CI 0.24–0.53, p < 0.001]), presence of jaundice (aHR: 1.49; 95% CI 1.14–1.94, p = 0.003), and administration of normal saline (aHR: 0.57, 95% CI 0.45–0.74, p < 0.001). There was no interaction between corticosteroid use and the significant variables. Additionally, there were no potential confounders for the relationship between corticosteroid use and time to haemoglobinuria resolution. The result of the multivariable analysis is shown in Table 4 below.

Comparison of the complications of BWF in corticosteroid vs non-corticosteroid groups

The overall prevalence of acute kindly injury was 11.7% (n = 103), with a slight difference between those who received corticosteroids and those who did not, 12.1% vs 10.2% respectively (P = 0.485). In-hospital mortality rate on the other hand was low, at 1.5% (n = 13), with no significant difference between children who received corticosteroids and those who did not receive, 1.4% vs 1.7% (P = 0.782).

Discussion

This study aimed to compare the time to haemoglobinuria resolution between children with BWF who received corticosteroids and those who did not, and determine if corticosteroid use significantly influences this outcome.The study found that the median time to haemoglobinuria resolution was similar in both the corticosteroid and non-corticosteroid groups (3 days), and survival curves did not differ significantly. Additionally, corticosteroid use was not significantly associated with a faster resolution of haemoglobinuria. These findings suggest that corticosteroid administration may not offer an advantage in accelerating clinical recovery from haemoglobinuria in BWF. Corticosteroids may increase the risk of infections, hyperglycaemia, and

Table 2 Baseline laboratory and treatment-related characteristics of study participants

Variables	Categories	Corticosteroid use N (%)	No Corticosteroid use N (%)	P-value[a]
Median haemoglobin (g/dL)		5.4 (4.2–7.4)	5.1 (4.0–6.1)	0.088
Median serum creatinine (mg/dL)		2.0 (0.8–6.1)	4.6 (3.1–9.5)	0.074
Haematuria	No	19 (2.7%)	5 (2.8%)	0.417
	Yes	48 (6.8%)	20 (11.2%)	
	Missing	644 (90.5%)	153 (86.0%)	
Bilirubinuria	No	66 (9.3%)	25 (14.0%)	0.539
	Yes	1 (0.1%)	0 (0.0%)	
	Missing	644 (90.6%)	153 (86.0%)	
Proteinuria	No	62 (8.7%)	25 (14.0%)	0.160
	Yes	5 (0.7%)	0 (0.0%)	
	Missing	644 (90.6%)	153 (86.0%)	
Antimalarial drug used	Artesunate	711 (100.0%)	177 (99.9%)	0.077
	Quinine	0 (0.0%)	1 (0.1%)	
Antibiotic use**	No	151 (21.2%)	47 (26.4%)	0.305
	Yes	560 (78.9%)	131 (73.6%)	
Blood transfusion	None	321 (45.2%)	79 (44.4%)	0.312
	Once	237 (33.3%)	70 (39.3%)	
	Twice	98 (13.8%)	22 (12.4%)	
	Three times	27 (3.8%)	4 (2.2%)	
	Four times	28 (3.9%)	3 (1.7%)	
Normal saline given	No	326 (45.9%)	80 (44.9%)	0.945
	Yes	385 (54.1%)	98 (55.1%)	
Folic acid given	No	41 (5.8%)	20 (11.2%)	0.005
	Yes	670 (94.2%)	158 (88.8%)	

[a] P-values obtained from t-tests for continuous variables and chi square test or fisher's exact tests for categorical variables. **Antibiotics prescribed include ceftriaxone, ciprofloxacin, gentamicin, metronidazole, penicillin G, ampicillin, ampicillin/cloxacillin, and nitrofurantoin

other complications without clear benefit in accelerating haemoglobinuria resolution, supporting guidelines against their routine use in BWF [14]. Corticosteroids may not directly impact the primary drivers of haemoglobinuria in BWF [15]. While corticosteroids are known for modulating inflammatory responses, they may have limited effect on the rate of red blood cell destruction or clearance of free haemoglobin from the circulation and kidneys [8].

The results in this study contrast with earlier reports from Italy and Burundi which documented apparent rapid clearance of coloured urine after corticosteroid administration [1, 12]. These discrepancies may be attributed to differences in study design, patient populations, corticosteroid dosing, and outcome definitions.

Patients who received antibiotics had a 32% lower hazard of achieving haemoglobinuria resolution compared to those who did not, suggesting that antibiotic use was associated with delayed resolution. In this context, antibiotics may have been initiated as preventive therapy or for presumed secondary bacterial infection, which is not uncommon in severe malaria, including BWF. Thus, antibiotic use in our study likely reflects illness severity rather than a direct causal role in prolonging haemoglobinuria.

Patients who received one, two, three, or four blood transfusions had a 14%, 22%, 41%, and 64% lower hazard, respectively, of achieving haemoglobinuria resolution compared to those who were not transfused. This apparent dose–response pattern likely reflects underlying disease severity rather than a direct effect of transfusion on recovery. Children who required multiple transfusions probably had more extensive intravascular haemolysis and more profound anaemia at presentation, placing them at higher risk for prolonged illness and complications. In this context, blood transfusion serves as a clinical marker of severity, consistent with previous reports linking severe anaemia and BWF to poor clinical outcomes [1, 4, 5, 8, 16].

The hazard of haemoglobinuria resolution among subjects with jaundice was 1.5 times that of subjects without jaundice. This means that the presence of jaundice was associated with faster resolution of haemoglobinuria. This finding may seem counterintuitive, given

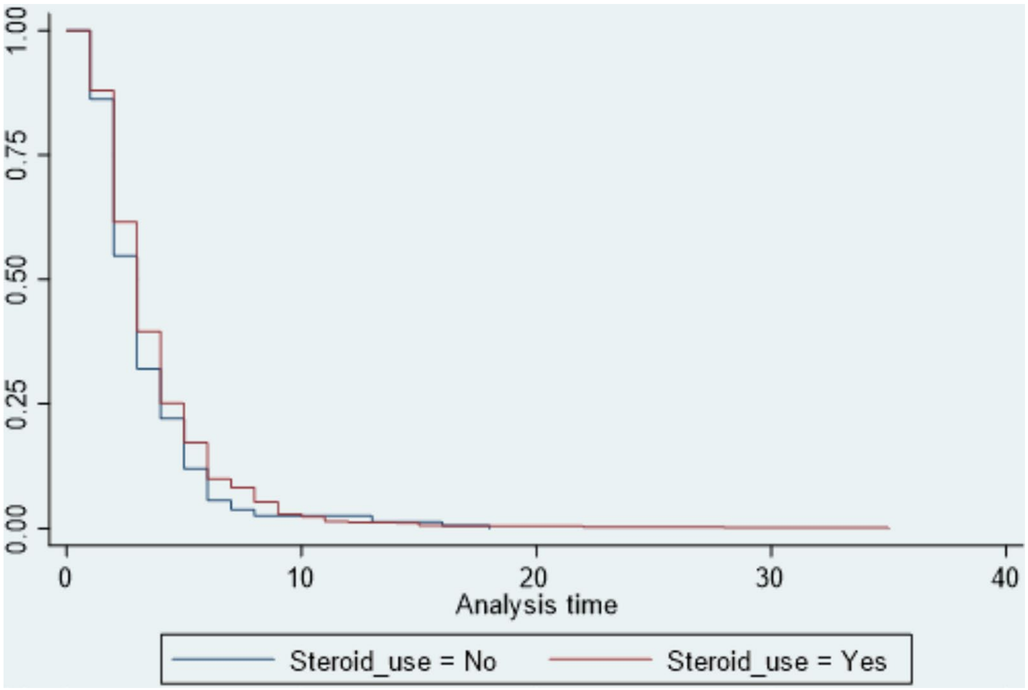

Fig. 2 Kaplan–Meier curve comparing time to hemoglobinuria resolution between corticosteroid and non-corticosteroid groups

that jaundice is often a marker of haemolysis severity[17]. However, it is possible that the presence of jaundice prompted earlier recognition of illness, more aggressive supportive management, or closer clinical monitoring, which may have contributed to faster recovery.

Subjects who received normal saline had a 43% lower hazard of achieving haemoglobinuria resolution compared to those who did not, indicating a slower recovery following normal saline administration. This association may be explained by confounding by indication, where children who were more critically ill, particularly those with suspected or evolving acute kidney injury, were more likely to receive intravenous fluid resuscitation.

In such cases, normal saline administration reflects the severity of illness rather than being a direct cause of delayed recovery. This pattern has been observed in other studies of severe malaria, where aggressive fluid management is commonly reserved for children presenting with shock, reduced urine output, or or impaired consciousness, all of which are linked to poorer otcomes[17–19].

This study found low rates of In-hospital mortality, which were comparable among children who received corticosteroids and those who did not and administration of corticosteroids did not provide additional protection from mortality among the admitted children with BWF. Earlier studies in Northern and Eastern Uganda demonstrated low rates of In-hospital mortality among children with severe malaria in the absence of kidney injury [20, 21].

This study had several limitations. First, some variables, such as previous BWF and urinalysis results, had > 15% missing data. However, participants with missing data were generally similar to those with complete data regarding key characteristics. Second, key laboratory markers, including quantitative bilirubin levels, renal function tests, and markers of haemolysis such as lactate dehydrogenase and haptoglobin, were not routinely available, limiting the depth of clinical characterization. Third, the outcome definition of haemoglobinuria resolution relied on subjective clinical documentation of tea-colored urine clearance, which may vary by clinician or timing of assessment. Lastly, because the study was conducted at a single referral hospital, the findings may not be generalizable to other settings with different patient populations or case management practices.

Conclusion

Corticosteroid use did not accelerate haemoglobinuria resolution in children with blackwater fever, supporting current WHO guidance against their use. Delayed recovery was observed in children who received antibiotics, blood transfusions, or normal saline; however, this likely reflects underlying disease severity rather than a direct effect of these interventions. The presence of jaundice was associated with faster resolution,

Table 3 Bivariate analysis of the factors associated with time to haemoglobinuria resolution

Variables	Categories	CHR (95% CI)	p-values
Age		1.00 (0.98–1.02)	0.783
Sex	Female	Reference	Reference
	Male	1.07 (0.93–1.23)	0.344
Fever	No	Reference	Reference
	Yes	0.95 (0.80–1.13)	0.562
Vomiting	No	Reference	Reference
	Yes	1.16 (1.01–1.33)	0.034[a]
Pallor	No	Reference	Reference
	Yes	1.09 (0.94–1.26)	0.260
Splenomegaly	No	Reference	Reference
	Yes	0.94 (0.80–1.10)	0.437
Jaundice**	No	Reference	Reference
	Yes	1.30 (1.01–1.68)	0.043[a]
Previous blackwater fever episodes	None	Reference	Reference
	2 episodes in 3 months	0.96 (0.78–1.17)	0.669
	3 episodes in 6 months	1.01 (0.73–1.40)	0.959
	3 episodes in 12 months	0.80 (0.64–1.01)	0.061[a]
Jaundice**	No	Reference	Reference
	Yes	1.30 (1.01–1.68)	0.043[a]
Previous blackwater fever episodes	None	Reference	Reference
	2 episodes in 3 months	0.96 (0.78–1.17)	0.669
	3 episodes in 6 months	1.01 (0.73–1.40)	0.959
	3 episodes in 12 months	0.80 (0.64–1.01)	0.061[a]
Haemoglobin in g/dL		1.02 (1.00–1.05)	0.101[a]
Serum creatinine		1.01 (1.00–1.03)	0.052[a]
Haematuria	No	Reference	Reference
	Yes	1.25 (0.75–2.08)	0.397
Bilirubinuria	No	Reference	Reference
	Yes	0.42 (0.06–3.01)	0.387
Proteinuria	No	Reference	Reference
	Yes	0.94 (0.38–2.32)	0.891
Corticosteroid use	No	Reference	Reference
	Yes	0.88 (0.74–1.05)	0.143
Antibiotic use	No	Reference	Reference
	Yes	0.64 (0.54–0.75)	< 0.001[a]
Blood transfusion	None	Reference	Reference
	Once	0.96 (0.71–1.29)	0.782
	Twice	0.62 (0.41–0.95)	0.029[a]
	Three times	0.22 (0.09–0.53)	0.001[a]
	Four times	0.14 (0.06–0.33)	< 0.001[a]
Normal saline given **	No	Reference	Reference
	Yes	0.62 (0.48–0.79)	< 0.001[a]
Folic acid given	No	Reference	Reference
	Yes	0.66 (0.49–0.91)	0.010[a]

[a] p-value < 0.20, **Time-varying covariate

highlighting its potential role as an early clinical indicator. These findings emphasize the need for careful clinical evaluation and tailored supportive care, and further

Table 4 Multivariable analysis of the factors associated with time to haemoglobinuria resolution

Variables	Categories	aHR (95% CI)	p-values
Corticosteroid use	No	Reference	Reference
	Yes	0.90 (0.75–1.07)	0.239
Antibiotic use	No	Reference	Reference
	Yes	0.68 (0.58–0.81)	< 0.001*
Blood transfusion	None	Reference	Reference
	Once	0.86 (0.73–1.00)	0.055
	Twice	0.78 (0.62–0.97)	0.024*
	Three times	0.59 (0.40–0.88)	0.010*
	Four times	0.36 (0.24–0.53)	< 0.001*
Jaundice**	No	Reference	Reference
	Yes	1.488 (1.143–1.937)	0.003*
Normal saline given**	No	Reference	Reference
	Yes	0.57 (0.45–0.74)	< 0.001*

*P-value<0.05, **Time varying covariate

studies are needed to optimize management of this severe malaria complication.

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Author contributions
Conceptualization: AO, IE and RO. **Data curation and analysis:** PL. **Methodology**: PL, RO and MO. **Validation and Visualization**; RO, PL, MO, IE and AO. **Writing—original draft**. PL, MO. **Writing—review & editing:** **RO, AO, MO.**

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Data availability
Data used for this study are included in this Manuscript.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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