Prevalence, Associated Factors, and Prognosis of Acute Kidney Injury in Severe Malaria Among Sub-Saharan Africans

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ABSTRACT

Introduction. Acute kidney injury is one of the most severe complications of severe malaria, with an overall incidence reaching 60% and a mortality rate of up to 45%. We conducted this study to determine the prevalence of acute kidney injury in malaria, acute kidney injury, associated factors and the impact of acute kidney injury on vital prognosis.

Patients and Methods. This was a multicenter, retrospective, descriptive, and analytical study over a 5-year period from January 1, 2019 to December 31, 2023, in the nephrology and infectious diseases departments and intensive care units of Dakar hospitals. We included all admitted patients during this period, regardless of whether they had acute kidney injury or not. Acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes criteria. Severe malaria was defined according to world health organization criteria.

Results. A total of 321 patients were included, 158 of whom had acute kidney injury, with a prevalence of 49.2%. The study population comprised 244 men and 77 women, with a sex ratio of 3.14. The mean age of patients was 36.25 years (12 and 86 years). Anuria was present in 64.3% of cases, oliguria in 26.8%, and edema in 7.14%. Mean blood urea was 1.20 g/L ± 2.60. Mean creatinine was 34.7 mg/L ± 40.1. Rehydration was performed in 96.8% of cases. Hemodialysis was performed in 19 patients, with an average of 1.89 sessions. Death occurred in 41 (12.77%) patients. In multivariate analysis, acute kidney injury-associated factors were herbal medicine (p = 0.045; OR = 1.509; IC95%: [0.513- 4.439]), diabetes (p = 0.044; OR = 3.375; IC95%: [0.850-13.393]), respiratory distress (p = 0.034; OR = 2.758; IC95%: [0.907-8.389]) and anemia (p = 0.002; OR = 0.407; IC95%: [0.232-0.713]). Acute kidney injury was a factor associated with death (p = 0.004; OR = 3.584; IC 95%: [1.467-8.754]).

Conclusion: Acute kidney injury is common during malaria. Acute kidney injury is associated with the severity of malaria, the presence of comorbidities and the use of nephrotoxic products. Acute kidney injury is independently associated with increased risk of death in malaria.

KEYWORDS: Acute kidney injury, malaria, comorbidities, nephrotoxic products

Introduction

Globally, in 2023, the number of malaria cases was estimated at 263 million, with an incidence of 60.4 cases per 1000 population at risk [1]. This is an increase of 11 million cases from the previous year and a rise in incidence from 58.6 cases per 1000 population at risk in 2022 [1]. The world health organization (WHO) African Region continues to carry the heaviest burden of the disease, accounting for an estimated 94% of malaria cases worldwide in 2023. The WHO African Region continues to carry the heaviest burden of mortality, with 95% of estimated malaria deaths worldwide [1]. The severity of malaria is related to its possible visceral complications, particularly acute kidney injury (AKI). AKI is one of the most severe complications of severe malaria, with an overall incidence reaching 60% and a mortality rate of up to 45% [2]. AKI is a frequent life-threatening complication of severe malaria that can increase risk of death and long-term morbidity [3]. The aims of this study were to determine the prevalence of AKI during severe malaria, to describe the factors associated with the occurrence of AKI in patients with severe malaria, and to describe the impact of AKI on vital prognosis during severe malaria.

Patients and methods

This was a retrospective, descriptive, and analytical study conducted over a 5-year period from January 1, 2019 to December 31, 2023. The study was carried out in two nephrology departments (Dalal Jamm, and Ouakam military hospitals), three intensive care units (Dalal Jamm, Pikine, and Idrissa Pouye General hospitals), and an infectious diseases department (Fann hospital). Dalal Jamm, Pikine, Ouakam, Fann, and Idrissa Pouye General hospitals are publicly funded institution affiliated with the faculty of medicine of Cheikh Anta Diop University.

Study population

Patients with severe malaria were included. Patients with known End-Stage Renal Disease (ESRD) prior to the diagnosis of malaria were not included.

Study variables

Severe malaria was defined according to WHO criteria [4]. Severe *falciparum* malaria is defined as one or more of the manifestations described in Table 1, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia. Severe *vivax malaria* is defined as for *falciparum* malaria but with no parasite density thresholds. Severe *Plasmodium knowlesi* malaria is defined according to the criteria used for *Plasmodium falciparum* malaria, with two specific exceptions: (1) *P. knowlesi* hyperparasitaemia defined as a parasite density > 100,000/µL; (2) presence of jaundice associated with a parasite density > 20,000/µL [4]. The diagnosis of AKI was based on the Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria [5]. Serum creatinine was measured in patients upon admission to hospital. For patients with a previous serum creatinine in the 7-365 days prior to admission, the most recent serum creatinine value was considered the baseline creatinine. For patients without a baseline creatinine in the 7-365 days prior to admission, the admission creatinine was imputed on the basis of a Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) of 75 ml/min/1.73m^2 as per the KDIGO AKI guidelines [5]. Peak serum urea and serum creatinine levels were reported. Urine output was collected via Foley catheterization. Anuria and oliguria were defined, respectively, as urine output less than 300 mL/day and 500 mL/day. We used the SOFA excluding renal injury (non-renal SOFA) to assess the severity of the disease.

Criteria	Definition / Threshold
Impaired Consciousness	Glasgow Coma Score < 11 (adults) or Blantyre Coma Score < 3 (children)
Prostration	Generalized weakness: unable to sit, stand, or walk without assistance
Multiple Convulsions	More than 2 episodes within 24 hours
Acidosis	Base deficit > 8 mEq/L OR plasma bicarbonate < 15 mmol/L OR venous plasma lactate ≥ 5 mmol/L; manifests as respiratory distress (rapid, deep, labored breathing)
Hypoglycaemia	Blood/plasma glucose < 2.2 mmol/L (< 40 mg/dL)
Severe Malarial Anaemia	Children < 12 years: Hb ≤ 5 g/dL or hematocrit ≤ 15%; Adults: Hb < 7 g/dL or hematocrit < 20%; plus parasite count > 10,000/µL
Renal Impairment	Plasma/serum creatinine > 265 µmol/L (3 mg/dL) OR blood urea > 20 mmol/L
Jaundice	Plasma/serum bilirubin > 50 µmol/L (3 mg/dL) with parasite count > 100,000/µL
Pulmonary Oedema	Radiologically confirmed OR oxygen saturation < 92% on room air + respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
Significant Bleeding	Recurrent/prolonged bleeding (e.g., nose, gums, venepuncture sites) OR haematemesis OR melaena
Shock	Compensated: Capillary refill ≥ 3 sec or temperature gradient (leg); Decompensated: SBP < 70 mm Hg (children) or < 80 mm Hg (adults) + signs of impaired perfusion
Hyperparasitaemia	*P. falciparum* parasitaemia > 10%

Table1. Diagnostic criteria for severe malaria.

Data collection

A data collection form was drawn up. Data were collected from patients' records. A detailed history and a clinical examination were recorded for each patient (age, sex, chief complaint, history of present illness, history, family history, personal history, treatment history, and the presence of risk factors). On admission, routine hematological investigations, plasma glucose tests, liver function tests, renal function tests, serum electrolytes, and malarial parasite tests (malaria rapid diagnostic tests (RDT), quantitative buffy coat, microscopy examination of thick blood films (METBF)) were performed.

Statistical analysis

Data analysis was carried out with SPSS (Statistical Package for Social Sciences) version 21 software. The descriptive study was carried out with the calculation of frequencies and proportions for the qualitative variables and the calculation of the means and standard deviations for the quantitative variables. The analytical study was done with cross tables. To compare the frequencies, we used the Pearson chi-square test or the bilateral Fisher exact test depending on their conditions of applicability; the comparison of the means was made with the analysis of variance test with a threshold of significance of $p < 0.05$. In multivariable analysis, binomial logistic regression with the stepwise method was used. This method consists of eliminating non-significant variables one by one in the model. It should be noted that only variables with a bivariate p-value of less than 25% were taken into account. The significance threshold used in this work is $p < 0.05$.

Results

During the study period, we collected 321 cases (Figure 1). There were 158 patients with AKI, representing a prevalence of 49.2%. The mean age was 36.25 years (12 and 86 years). The study population comprised 244 (76.0%) men and 77 (24.0%) women, giving a sex ratio of 3.14. The median length of hospital stay was 11 days (IQR, 1-14). Hypertension and diabetes mellitus were the most common comorbidities, with prevalence of 9.6% and 4.3%, respectively. Anuria was present in 64.3% of cases, oliguria in 26.8%, and edema in 7.14% (Table 2). Among patients with AKI, 88 (55.7 %) had pre-renal kidney failure, and 70 (44.3%) had AKI due to acute tubular injury. The KDIGO prognostic classification of AKI in our patients showed stage 1 in 34%, stage 2 in 25 %, and stage 3 in 41% of cases (Figure 2). RDT was performed in 258 patients and was positive in 249. METBF were

carried out in 277 patients and were positive in 247 in patients. The Quantitative Buffy Coat (QBC) was performed on 3 patients and was positive in all cases.

For the entire cohort, mean blood urea was 1.2 g/L ± 2.6 and mean creatinine was 34.7 mg/L ± 40.1. For patients with AKI, mean blood urea was 2.1 g/L ± 2.3 and mean creatinine was 60.2 mg/L ± 48.1. Hyponatremia was noted in six patients, four of whom developed AKI. Hyperkalemia was noted in 25 patients, all of whom developed AKI. Artesunate was used for all patients. Rehydration was performed in 96.8% of cases. Hemodialysis was performed in 19 patients, with an average of 1.89 sessions. The indications for hemodialysis were hyperkalemia (12 patients), followed by uremic encephalopathy (10 patients) and pulmonary edema (2 patients). There were 5.3 % of patients who required invasive mechanical ventilation and 12.5% to high-flow nasal oxygen. The median non-renal SOFA score of all patients was 2 (IQR, 1–3). Patients with AKI exhibited a significantly higher non-renal SOFA score than patients with no AKI (3 [IQR, 2–4] vs 1 [IQR, 0–1]). Death occurred in 41 (12.77 %) patients, 78 % with AKI. Among patients with AKI, 111 (70.25 %) had complete remission of renal function and 12 (7.59%) had partial remission of renal function before leaving the hospital. For patients who were on dialysis, nine had complete remission of renal function and two had partial remission of renal function before leaving the hospital. In univariable analysis, the risk factor significantly associated with the occurrence of AKI was herbal medicine (p = 0.029), hypertension (p = 0.051); diabetes mellitus (p = 0.014); respiratoiry distress (p = 0.011); anemia (p = 0.001). In multivariate analysis, AKI-associated factors were herbal medicine (p = 0.045 [OR = 1.509; IC95%: [0.513-4.439]), diabetes mellitus (p = 0.044 [OR = 3.375; IC95%: [0.850-13.393]), respiratory distress (p = 0.034; OR = 2.758; IC95%: [0.907-8.389]) and anemia (p = 0.002; OR = 0.407; IC95%: [0.232-0.713]) (Table 3). In univariable analysis, risk factors significantly associated with the occurrence of death were Thrombopenia (p = 0,0001), respiratory distress (p = 0,0001) ; anemia (p = 0,049) ; leukocytosis (p = 0,018) ; AKI (p = 0,001). In multivariable analysis, the factors associated with death were gender (p = 0,0022; OR = 2,790; IC95%: [1,160-6,710]), respiratory distress (p = 0,047; OR = 2,745; IC95%: [0,863-8,735]); leukocytosis (p = 0,024; OR = 2,582; IC95%: [1,135-5,871]); thrombopenia (p = 0,004; OR = 0,098; IC95%: [0,020-0,476]); AKI (p = 0,004; OR = 3,584; IC95%: [1,467-8,754]) (Table 4).

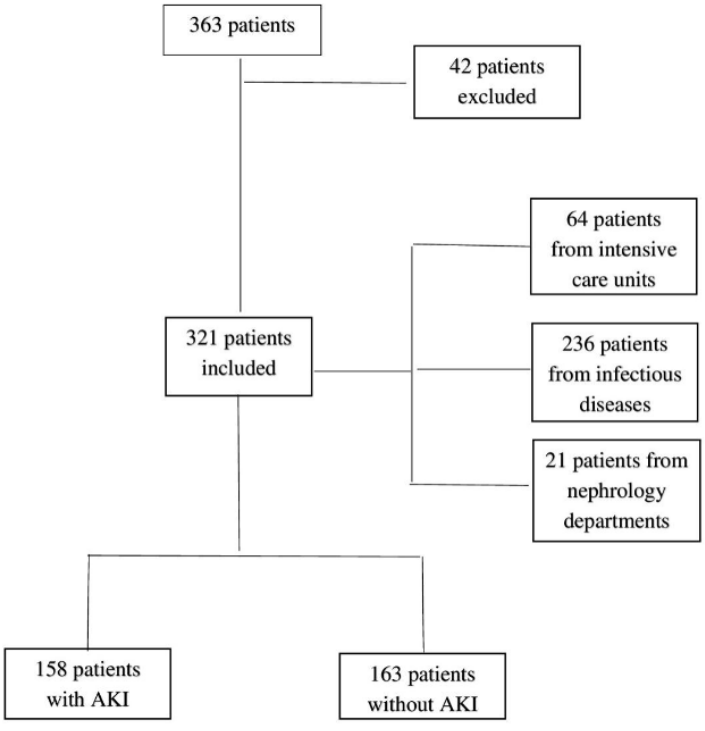

Figure 1. Diagram of flow.

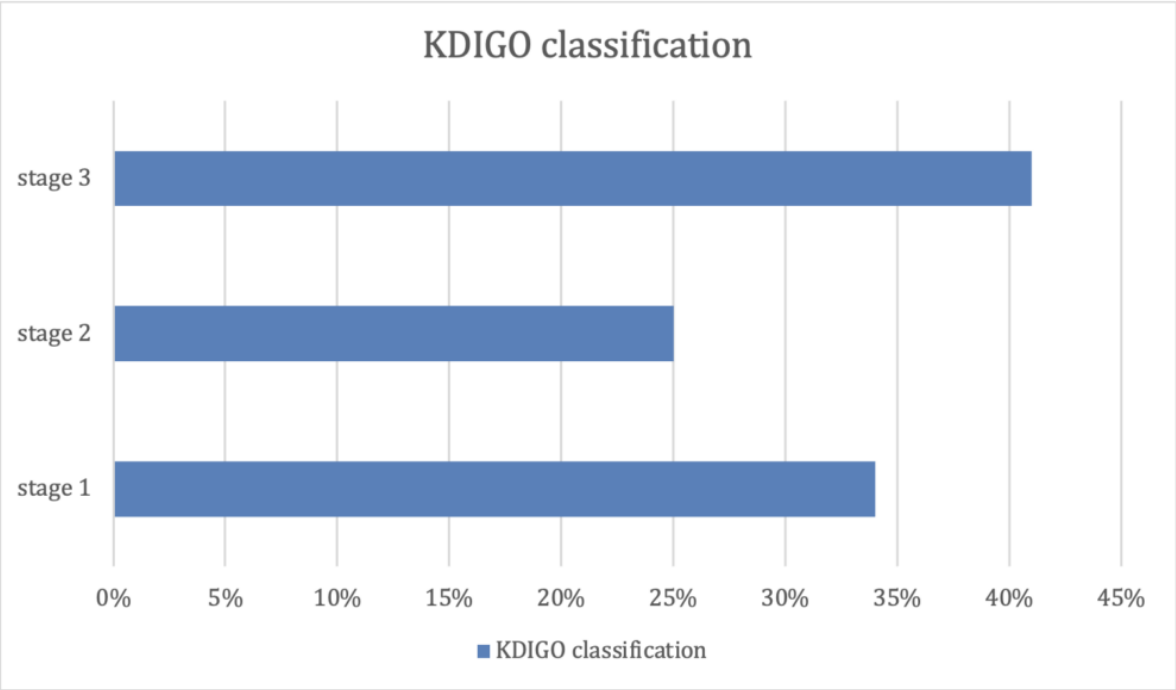

Figure 2. Distribution of patients according to KDIGO AKI classification.

Variables		All patients	AKI	No AKI	P value
Mean age (years)		36.25	36.3	36.1	0.926
Age > 60 years		49	27 (55.10%)	22 (44.90%)	0.371
Gender	Men	244	118 (48.36%)	126 (51.64%)	0.583
	Women	77	40 (51.95%)	37 (48.05%)	
Herbal medicine		18	11 (61.10%)	7 (38.90%)	0.029
Smoking		45	22 (48.90%)	23 (51.10%)	0.962
Hypertension		31	17 (54.84%)	14 (45.16%)	0.051
Diabetes mellitus		14	4 (28.57%)	10 (71.43%)	**0.014**
Respiratory distress		21	16 (76.20%)	5 (23.80%)	**0.011**
Jaundice		119	64 (53.80%)	55 (46.20%)	0.210
RDT		249	130 (52.20%)	119 (47.80%)	0.838
Anemia		229	130 (56.80%)	99 (43.20%)	**0.0001**
Thrombocytopenia		235	114 (48.50%)	121 (51.50%)	0.674
Leukocytosis		153	97 (63.40%)	56 (36.60%)	**0.0001**

Table 2. Characteristics of the study population. RDT = Malaria rapid diagnostic tests.

Variables	Odds Ratio	95% CI	p value
Sex	1.002	[0.555-1.808]	0.996
Age > 60 years	1.878	[0.822-4.288]	**0.013**
Hypertension	0.703	[0.256-1.927]	0.493
Diabetes mellitus	3.375	[0.850-13.393]	**0.044**
Respiratory distress	2.758	[0.907-8.389]	**0.034**
Anemia	0.407	[0.232-0.713]	**0.002**
RDT	0.776	[0.429-1.404]	0.402
Leukocytosis	2.349	[1.485-3.715]	**0.0001**
Thrombocytopenia	1.114	[0.637-1.949]	0.706
Jaundice	1.292	[0.773-2.157]	0.328
Herbal medicine	1.509	[0.513-4.439]	**0.045**

Table 3. Factors associated with AKI (multivariable analysis). RDT = Malaria rapid diagnostic tests.

Variables	Odds Ratio	95% CI	p value
Age > 60 years	1.482	[0.455-4. 826]	0.514
Sex	2.79	[1.160-6. 710]	**0.022**
Hypertension	2.54	[0.414-15.576]	0.314
Diabetes mellitus	0.752	[0.074-7.623]	0.809
Respiratory distress	2.745	[0.863-8.735]	**0.047**
Anemia	0.731	[0.270-1.982]	0.539
RDT	3.560	[1.427-8.877]	**0.006**
Leukocytosis	2.582	[1.135-5.871]	**0.024**
Thrombocytopenia	0.098	[0.020-0.476]	**0.004**
Jaundice	0.733	[0.325-1.654]	0.455
Hyponatremia	0.735	[0.312-1.733]	0.482
Hyperkaliemia	0.148	[0.045-0.487]	**0.002**
Herbal medicine	0.859	[0.088-8.421]	0.896
AKI	3.584	[1.467-8.754]	**0.004**

Table 4. Factors associated with death for all patients (multivariable analysis). RDT= malaria rapid diagnostic tests; AKI = Acute kidney injury.

Discussion

In our study, the prevalence of AKI was 49.2%. The prevalence of AKI is variable in the literature. This variation in prevalence would be related to differences in socio-economic living conditions and the definition of AKI in the different studies. The World Health Organization (WHO) definition of renal impairment in severe malaria is a creatinine value >3mg/dl irrespective of patient age or baseline creatinine. This definition leads to substantial underestimation of AKI in patients with lower creatinine levels [6]. The 2023 WHO definition of AKI in severe malaria would therefore only detect stage 3 AKI; the stage at which AKI is present or imminent, and dialysis is often required for survival [7]. There are emerging data using consensus definitions to define AKI in severe malaria, reporting AKI in 24-59% of children hospitalized with severe malaria [8–12]. More recent data using the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines demonstrate that AKI is common in children hospitalized with malaria occurring in 19-59% of children with severe malaria [13].

Use of herbal medicine was a factor associated with AKI in our study. A systematic review of AKI in African children identified nephrotoxins in 16% of pediatric AKI [14]. Traditional herbal remedies or toxins can also contribute to AKI [14, 15]. In Africa, the population often resorts to traditional medicine due to the lack of doctors and healthcare facilities. Herbal medicine is not sufficiently studied in Africa and can lead to or worsen AKI.

In our study, anemia was associated with AKI. Anemia during severe malaria is caused by hemolysis. The primary contributors to hemolysis in malaria-endemic areas include *P. falciparum* infection, G6PD deficiency, sickle cell anemia, and other hemolytic anemias. Hemolysis-mediated kidney injury occurs due to increased oxidative stress, inflammation, endothelial dysfunction, and reduced nitric oxide bioavailability, all of which are implicated in severe malaria pathogenesis. Paracetamol represents a potential treatment to prevent AKI through its action as a potent inhibitor of hemoprotein-catalyzed lipid peroxidation (eg, cell-free hemoglobin, myoglobin) [16–18].

High levels of endogenous nephrotoxins, which are caused by haemolysis that releases cell-free haemoglobin and free heme, which are nephrotoxic and cause AKI through elevated oxidative stress [19, 20].

In our study, AKI was an independent factor of mortality. The identification of elevated blood urea nitrogen as a risk factor for prolonged hospitalization and neurologic deficits at discharge is novel in the context of malaria-associated AKI. AKI is a risk factor for long-term cognitive and behavioral problems [13] and disabilities [21]. AKI is a well-established risk factor for mortality in children with

severe malaria and is associated with prolonged duration of hospitalization [8]. AKI is associated with increased post-discharge mortality in severe malaria [9]. Mortality would be higher in Low- and Middle-Income Countries (LMICs), due to delayed diagnosis of malaria and especially of AKI. Human resources and equipment are not often available to allow for early diagnosis [1]. AKI screening markers such as serum creatinine (measured in the laboratory) are not always accessible in LMICs. Currently, we should focus more on tools that are more accessible and less expensive, such as urine dipsticks and point-of-care testing like creatinine meters [22]. Often, screening is only possible in urban areas where nephrologists can be found. A reorganization with decentralization is needed to improve screening methods. Primary health practitioners, nurses, and community personnel in remote areas must be trained to screen for AKI. The integration of community and rural personnel in the screening, diagnostic and therapeutic management of AKI can play an important role. The ISN 0by25 trial successfully demonstrated the utility of a symptom-based health assessment risk score coupled with a point of care creatinine and urine dipstick test in early recognition of kidney disease and appropriate triaging and management of patients presenting to primary healthcare centers in LMICs [23].The lack of adequate care also increases mortality. Today, even though antimalarials are much more accessible in Africa, there are still problems in managing severe malaria, particularly with renal involvement. Renal replacement therapies are not often accessible in LMICs. A systematic review showed that in sub-Saharan Africa, when dialysis was needed, the pooled dialysis access rate was 33% in adults and 64% in children [24]. The high cost of kidney replacement therapy (KRT) necessitates that LMICs strategize to improve accessibility for the general population. LMICs should take inspiration from Hong Kong's example (71.9 % of the dialysis patients were on peritoneal dialysis (PD)) and resort to the least expensive KRT such as PD [25].

Programs like Saving Young Lives that promote acute PD, with local production of dialysate and bedside insertion of PD catheters, would make dialysis more accessible [26, 27].

The present study has some limitations. First, it was a retrospective cohort study, in which a high proportion of patients was lost during the long-term follow-up. The reliance of clinical adjudication to determine whether patients had acute tubular injury or prerenal azotemia increases the risk of patient misclassification.

Conclusion

AKI is common during severe malaria. It is associated with the severity of malaria, the presence of comorbidities and use of nephrotoxic products. AKI is independently associated with increased risk of death in severe malaria.

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