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Original Article

Incidence and predictors of acute kidney injury in children with severe malaria

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Abstract

Background Acute kidney injury (AKI) is an underrecognized complication of severe malaria and an independent risk factor for mortality among children.

Objective To determine the incidence and factors predictive of AKI as defined by the pediatric risk, injury, failure, loss, and end-stage (pRIFLE) criteria in children with severe malaria and to assess in-hospital mortality rates in malarial AKI (MAKI).

Methods This was a prospective cohort study in 170 children aged 0.5 to 14 years with confirmed *Plasmodium falciparum* on peripheral blood smears and clinical and/or laboratory features of severe malaria. Serum creatinine was determined using the Jaffe method and glomerular filtration rate (eGFR) was estimated using the Schwartz equation. The primary outcome was the incidence of AKI as defined by the pRIFLE criteria. Secondary outcomes included in-hospital mortality comparison between AKI and non-AKI groups, as well as factors predictive of AKI.

Results The incidence of MAKI was 61.2% and was comparable between males (66.7%) and females (70.6%). Mean eGFR was lower among children with AKI than those without [42.00 (SD 22) *vs.* 98.7 (SD 3.9) mL/min/1.73m^2, respectively; P=0.005]. Children with MAKI were categorized as having risk (47/104; 45.2%), injury (33/104; 31.7%), or failure (24/104; 23.1%). Mortality rates in AKI and non-AKI subjects were comparable (4.8% *vs.* 4.6%; P=0.888). Predictors of MAKI were hemoglobinuria [adjusted OR (aOR) 3.948; 95%CI 1.138 to 8.030], deep acidotic breathing (aOR 2.991; 95%CI 3.549 to 66.898), and longer hospital stay (aOR 2.042; 95%CI 3.617 to 12.156). Children with MAKI were more likely to have a longer hospital stay by a mean of 2.5 days.

Conclusion Acute kidney injury is a common complication in children with severe malaria. Children with MAKI have a mortality rate comparable to those with severe malaria but without AKI. Hemoglobinuria, deep acidotic breathing, and longer hospital stay were predictive of MAKI. **[Paediatr Indones. 2022;62:44-50 ; DOI: 10.14238/pi62.1.2022.44-50**].

Keywords: *acute kidney injury; pRIFLE; severe malaria; children*

Malaria remains a major public health problem with high morbidity and mortality in most tropical countries. In 2018, 219 million cases of malaria and 435,000 deaths were recorded across the globe.[1,2] The high mortality of malaria is due to potentially severe aspects of the disease, including acute kidney injury.[3] Acute kidney injury (AKI) is defined as a sudden decline in renal function, retention of nitrogenous wastes, and disturbance of fluid and electrolyte balance.[4,5] The mechanism of AKI in severe malaria is multifactorial and poorly understood.[6] The pathogenesis of kidney injury in severe malaria includes mechanical obstruction of kidney microvasculature from parasitized red blood cells, immune dysregulation, and oxidative stress from intravascular hemolysis with resultant hypoperfusion, sequestration, and acute tubular necrosis.[6-8]

The incidence of AKI in malaria varies from 2-39%, with a mortality rate as high as 15-45%.[6-8] However, the actual burden of AKI associated with malaria in children remains underestimated because of varying criteria used in defining AKI in malaria. For

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example, the *World Health Organization* (WHO) criteria uses an absolute creatinine cut-off value of 3 mg/dL.[9-11] However, the WHO definition of malarial AKI may miss children with AKI in earlier stages, during which appropriate intervention may improve their outcomes. Thus, a highly sensitive diagnostic definition for AKI in malaria is needed, especially in the tropics where the disease is endemic and remains a leading cause of childhood death.

The Acute Dialysis Quality Initiative (ADQI) has proposed a uniform definition of AKI which applies across different clinical conditions.[12-14] The ADQI definition and staging of AKI include the *Risk, Injury, Failure, Loss, and End-stage* renal failure criteria (RIFLE criteria), which uses an increase in serum creatinine or a decline in estimated creatinine clearance from a baseline, and/or a decrease in urine output, rather than the using a single absolute creatinine value.[15,16] The RIFLE criteria have the advantage of providing diagnostic definitions for the early stage at which kidney injury can be prevented (risk stratum).[15-17]Akcan-Arikan *et al.*[18] validated the RIFLE criteria for AKI in children and referred to it as pediatric RIFLE (pRIFLE). There is, however, a paucity of data on the use of pRIFLE criteria in the diagnosis of AKI in children with severe malaria in malaria-endemic regions, including Nigeria. Hence, we aimed to determine the incidence and risk factors predictive of AKI diagnosed using the pRIFLE criteria in children with severe malaria. We also compared in-hospital mortality in subjects with and without malarial AKI.

Methods

This prospective cohort study was conducted at the children's emergency unit of the University of Ilorin Teaching Hospital from June 2016 to May 2017. We included children aged <14 years with confirmed falciparum malaria on peripheral blood smear microscopy, as well as clinical and/or laboratory features of severe malaria as defined by the WHO 2014 guidelines for severe malaria.[19] Children with chronic illnesses, including chronic kidney disease, human immunodeficiency virus infection, and severe malnutrition, were excluded.

Venous blood specimens were obtained from subjects aseptically in a vacutainer containing ethylene-diamine-tetra-acetic acid (EDTA) anticoagulant for confirmation of malaria parasites. We diagnosed malaria based on the presence of a malaria parasite on thick film. Serum samples were obtained from blood aliquots in a plain bottle after clotting and centrifuging at 3000 rpm. The sera were stored in other plain bottles and kept frozen at -20^{o}C until batch analysis of serum creatinine using the Jaffe alkaline assay methods.[20]

We classified malaria as severe based on the 2014 WHO criteria as follows: impaired consciousness, defined as a Glasgow coma scale (GCS) score 11 or Blantyre coma scale of 3; prostration, defined as the inability to sit upright in a child who can normally do so; more than two episodes of convulsions over 24 hours; circulatory shock, defined as a systolic blood pressure of <70 mmHg in older children and <50 mmHg in an infant; hypoglycemia, defined as blood sugar <40 mg/dL; severe anemia, defined as hematocrit <15% or hemoglobin <5 g/dL; spontaneous bleeding or evidence of disseminated intravascular coagulation (DIC); deep acidotic breathing or respiratory distress, defined as deep labored breathing or SpO_2 <92%; AKI, defined as serum creatinine >3 mg/dL; and hemoglobinuria, defined as the passage of dark-colored urine.[19]

We defined and classified AKI based on the pRIFLE criteria, using the percentage reduction in the estimated glomerular filtration rate (eGFR) calculated from serum creatinine.[18] In brief, patients were classified as "no AKI" if the decline in eGFR was ≤25%, "risk" if the decline in eGFR was >25% to 50%, "injury" if the decline in the eGFR was >50% to 75% and "failure" if the decline in the eGFR was >75%. The eGFR was calculated using the Schwartz equation: eGFR=K x L/serum creatinine, in which K was an empirical constant (0.45 for children <1-year-old, 0.55 for children 1 to 10 years old and female adolescents, and 0.77 for adolescent boys), L was height in centimeters, and serum creatinine was measured in mg/dL.[20] The primary outcome of this study was the incidence of AKI in children with severe malaria. Secondary outcomes were the associated risk factors and predictive factors of AKI and in-hospital mortality in children with severe malaria with AKI.

All subjects were managed according to the *National Guidelines for The Management of Severe Malaria*, which included administration of a minimum of three doses of intravenous artesunate.[3] We followed

this with artemisinin-based combination therapy when patients were fully conscious and able to take oral medication.[3] Subjects with AKI received conservative management which included appropriate fluid therapy, intravenous diuretics where indicated, avoidance of nephrotoxic drugs, and close monitoring. Children who had AKI with indications for dialysis, including oliguria, fluid retention, and hyperkalemia recalcitrant to medical treatment, received kidney replacement therapy (KRP) using peritoneal dialysis (PD).

All statistical analyses were done using *SPSS version 21.0* (*IBM*, Armonk, New York, USA). Age and eGFR were expressed as mean and standard deviation (SD). Some normally distributed variables (age, eGFR, length of hospital stay) were subjected to Student's t-test to identify significance. Categorical variables were expressed as proportion and frequency. The Chi-square test was used to determine possible risk factors (age, sex, length of hospital stay, clinical and laboratory features) for malarial AKI. Factors that were statistically significant ($P<0.05$) in the bivariate analysis were entered in the binary logistic regression analysis to determine those that were predictive of AKI. Statistical significance was set at a P value of <0.05. The study was approved by the Ethical Review Committee of the University of Ilorin Teaching Hospital and informed consent was obtained from parents or caregivers before the commencement of the study.

Results

This study involved 170 children with severe malaria. Most subjects (92/170; 54.1%) were five years old or younger. Subjects' mean age was 4.72 (SD 3.31) years. Males outnumbered females in the age group of 10 to 14 years. Mean age was comparable between males [4.98 (SD 3.49) years] and females [4.34 (SD 3.00) years]. The age and sex distribution of subjects is shown in **Table 1**.

The clinical features of severe malaria in our subjects are shown in **Figure 1**. The most common feature of severe malaria was severe anemia (86/170; 50.6%), while the least common was circulatory collapse (2/170; 1.2%). Sixty percent (102/170) of subjects had multiple features of severe malaria; out of these, 41.2% (42/102) had two features, 47.1% (48/102) had three, 8.8% (9/102) had four, and 2.9% (3/102) had more than four features.

The overall incidence of AKI was 61.2% (104/170) based on the pRIFLE criteria and 7.7% based on the WHO criteria. The incidence of AKI was comparable between males and females was comparable [66.7% (68/102) *vs.* 70.6% (40/68), respectively]. Amongst children with MAKI, 45.2% (47/104) were in the risk category, 31.7% (33/104) were in the injury category, and 23.1% (24/104) were in the failure category. The occurrence of AKI was significantly associated with older age ($P=0.031$), hemoglobinuria ($P=0.003$), deep acidotic breathing ($P=0.001$), and longer length of hospital stay ($P<0.001$) (**Table 2**). Mean eGFR was 96.23 (SD 45.9) mL/min/1.73m^2 overall, but lower in subjects with AKI than in those without [42.0 (SD 22.0) *vs.* 98.7 (SD 3.9) mL/min/1.73m^2; $P=0.005$)] (**Table 2**).

Subjects' overall mortality was 4.7% (8/170). In subjects with AKI, the mortality rate was 4.8% (5/104), which was not significantly different from subjects without AKI ($P=0.888$) (**Table 2**). Of all subjects with AKI, three underwent PD, one of whom died. On binary logistic regression, the significant predictors of AKI were hemoglobinuria [adjusted odds ratio (aOR) 3.95; 95%CI 1.138 to 8.030; $P=0.026$], deep acidotic breathing (aOR 36.85; 95%CI 3.549 to 66.898; $P=0.001$), and length of hospital stay (aOR 2.04; 95%CI 3.617 to 12.156; $P=0.001$) (**Table 3**).

Table 1. Age and sex distribution of the study population (N=170)

Age groups, years	Male, n (%)	Female, n (%)	Total, n (%)
0.5 to <1	3 (1.8)	1 (0.6)	4 (2.4)
1 to <5	48 (28.2)	40 (23.5)	88 (51.8)
5 to <10	39 (22.9)	24 (14.1)	63 (37.1)
10 to 14	12 (7.1)	3 (1.8)	15 (8.8)
Total	102 (60.0)	68 (40.0)	170 (100.0)

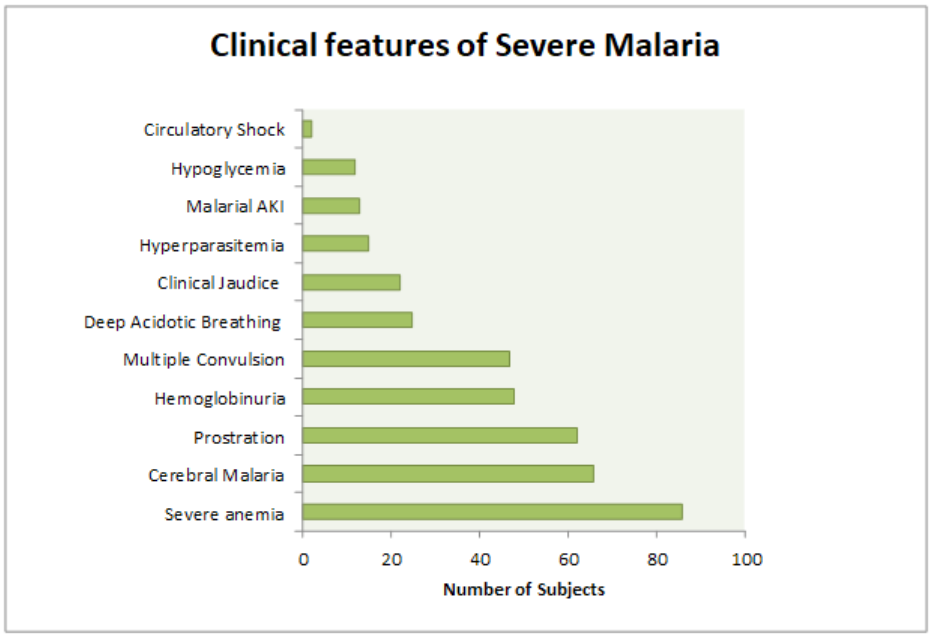

Figure 1. Clinical and laboratory features of severe malaria in study subjects

Table 2. Bivariate analysis of clinical and laboratory features and the presence of AKI

Variables	Total (N=170)	AKI (n=104)	No AKI (n=66)	P value
Age, n (%)				
0.5 - <5 years	92 (54.1)	58 (55.7)	34 (51.5)	0.031
5 - <10 years	64 (37.7)	42 (40.4)	22 (33.3)	
>10 years	14 (8.2)	4 (3.8)	10 (15.2)	
Sex, n (%)				
Male	102 (60.0)	64 (61.5)	38 (36.5)	0.607
Female	68 (40.0)	40 (38.5)	28 (26.9)	
Severe anemia, n (%)	86 (50.6)	51(49.0)	35 (33.7)	0.612
Cerebral malaria, n (%)	66 (38.8)	42 (40.4)	24 (23.1)	0.600
Prostration, n (%)	62 (36.5)	37 (35.6)	25 (24.0)	0.761
Multiple convulsions, n (%)	47(27.5)	34 (32.7)	13 (12.5)	0.065
Clinical jaundice, n (%)	22 (12.9)	12 (11.5)	10 (9.6)	0.494
Dehydration, n (%)	50 (29.4)	26 (25.0)	24 (23.1)	0.113
Deep acidotic breathing, n (%)	25 (14.7)	23 (22.1)	2 (3.0)	0.001
Hypoglycemia, n (%)	12 (7.1)	8 (7.6)	4 (3.8)	0.686
Oliguria, n (%)	12 (7.1)	10 (9.6)	2 (1.9)	0.102
Hyperparasitemia, n (%)	15 (8.8)	8 (7.6)	7 (6.7)	0.494
Hemoglobinuria, n (%)	48 (28.2)	38 (36.5)	10 (15.2)	0.003
Circulatory shock, n (%)	2 (1.20	2 (1.9)	0 (0.0)	0.258
Length of stay in days				
Mean (SD)	4.84 (2.6)	5.85 (1.2)	3.26 (2.8)	<0.001*
1-3 days, n (%)	75 (44.2)	26 (25.0)	49 (74.2)	<0.001
4-6 days, n (%)	56 (32.9)	39 (37.5)	17 (25.8)	
>7 days, n (%)	39 (22.9)	39 (37.5)	0 (0.0)	
Mean eGFR (SD), mL/min/1.73m^2	96.23 (45.9)	42.00 (22.1)	98.7 (3.9)	0.005*
Mortality, n (%)	8(4.7)	5 (3.8)	3 (2.9)	0.888

*independent T-test; all other analyses were done using the Chi-square test

Table 3. Predictors of acute kidney injury by logistic regression analysis

Variables	Beta coefficient	aOR	95%CI	P value
Age	1.410	3.353	0.450 to 10.564	0.333
Deep acidotic breathing	2.991	36.845	3.549 to 66.898	0.001
Hemoglobinuria	1.106	3.948	1.138 to 8.030	0.026
Length of hospital stay	1.892	2.042	3.617 to 12.156	0.001

Discussion

Malaria is a parasitic infection that affects multiple organ systems in humans, including the kidney. In our study, AKI meeting the pRIFLE criteria occurred in 61.2% of children with severe malaria. In comparison, when using the WHO criteria, only 7.7% of children with severe malaria had AKI. Our AKI incidence based on the pRIFLE criteria was comparable to that found in in a recent Nigerian study (59%),[11] and slightly higher than reported in Uganda (45.5%).[10] The incidence of AKI in our cohort was far higher than 0.6-4.9% reported in two large studies in Africa.[21,22] The higher incidence of malarial AKI (MAKI) could have been due to the use of more reliable creatinine criteria, that used a decline in the GFR rather than a single absolute creatinine value. Although the Nigeria[11] and Uganda[10] studies utilized the *Kidney Disease Improving Global Outcomes* (KDIGO) criteria, in contrast to our study which used pRIFLE, the high incidence of AKI showed that pRIFLE is able to detect more cases of AKI in a malaria-endemic region. In contrast to our findings, Prasad *et al*.[23] in India reported a lower incidence of AKI (19.9%) in children with severe malaria using the pRIFLE criteria. This difference in their findings compared to ours may have been due to differences in study methods and population, as our cohort was younger than that in Prasad's study.

Our study also showed that hemoglobinuria and deep acidotic breathing were predictive of AKI, while age was not. In contrast, a study in Nigeria found that age less than two years was predictive of AKI in children with severe malaria.[11] In Tanzania, male sex, hemoglobin <7.5 g/dL, and thrombocytopenia were predictive of AKI.[24] In India, jaundice, disseminated intravascular coagulopathy, and parasite density (>3+) were predictive of AKI.[23] The observation of hemoglobinuria and acidotic breathing as predictors of AKI may be related to their roles in the pathophysiology of severe malaria. Hemoglobinuria in severe malaria is due to acute intravascular hemolysis, while deep acidotic breathing is due to impaired tissue perfusion secondary to parasitized red blood cell (pRBC) sequestration, with a resultant accumulation of lactic acid and the release of free heme from the destruction of the pRBC.[25,26] The heme proteins released during the destruction of red blood cells in both conditions may precipitate cast formation that obstructs the renal tubules and results in necrosis of proximal tubular cells and AKI. A longer hospital stay was also predictive of AKI. A study also reported that children with malarial AKI were more likely to spend an additional 2 to 3 days in the hospital compared to those without AKI. The longer length of hospital stay may be a reflection of the progressive nature of AKI, with increased hospital stay as later stages of renal injury occur.[11]

The in-hospital mortality rate among children with severe malarial AKI was low and comparable to those without AKI. In contrast, higher mortality was reported in studies from India[23] and Lagos, Nigeria.[11] Our low in-hospital mortality may be a reflection of the availability of KRT and a dedicated pediatric nephrology unit with active management of children with AKI. In the Lagos study, the need for dialysis was amongst the factors identified as contributors to mortality in children with severe malarial AKI.[11] In addition, our lower mortality may have been due to the availability of appropriate anti-malaria chemotherapy, as well as early presentation to the health facility. Mortality among those who received KRT was 30.0%. Whereas KRT may improve outcomes in children with severe MAKI, the need for dialysis indicates an advanced AKI stage (failure), and such children may have other components of severe malaria that worsen their outcomes.

Our study is limited by the absence of subjects' baseline creatinine data; hence, we estimated baseline serum creatinine to determine the baseline eGFR. As such, we may have miscalculated the risk of AKI. In addition, serum bicarbonate levels were not measured;

rather, we relied on the clinical sign of deep acidotic breathing as a measure of lactic acid accumulation.

In conclusion, we found a high incidence of AKI in children with severe malaria due to the use of a more sensitive criteria capable of identifying more children with AKI and stratifying them based on severity. We also noted a low mortality rate among children with severe malaria with AKI. Children with malaria complicated by hemoglobinuria and deep acidotic breathing are more likely to develop AKI and have longer hospital stays.

Conflict of interest

None declared.

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