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Original Article

Clinical and Laboratory Predictors of Acute Kidney Injury in Childhood Severe Malaria

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Abstract

Introduction: Despite being responsible for the highest burden of global malaria infection, there are limited data on malaria-associated acute kidney injury (MAKI) among Nigerian children for inform decision. This study described the incidence and predictors of MAKI among a cohort of 541 children in northwestern Nigeria.

Methods: This was a retrospective review of malaria cases from 1st January 2019 to 31st December, 2020. We extracted socio-demographics, clinical features, and laboratory parameters from the records of the children with confirmed cases of severe malaria. AKI was defined and staged according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria. We carried out bivariate analysis and entered variables that were significant into binary logistic regression in order to determine predictors of AKI.

Results: Out of 541 children, 208 (38.4%) had MAKI. Of 208 children with AKI, 165 (79.3%) were in stage 1, 26 (12.5%) were in stage 2, and 17 (8.2%) were in stage 3. Clinical features associated with AKI included hypoxemia, respiratory distress, loss of consciousness, prostration, passage of dark-colored urine, and shock ($p < 0.05$). Laboratory parameters associated with AKI included acidosis, leukocytosis, hyponatremia, and hyperkalemia ($P < 0.05$). Factors that independently predicted AKI included the passage of dark-colored urine with an adjusted odds ratio (AOR) - 3.853 (95% CI 2.417, 6.143), hyponatremia - AOR 2.346, (95% CI 1.287, 4.277), and hyperkalemia - AOR 3.122, (95% CI 1.031, 9.393).

Conclusion: The incidence of MAKI is high among children in northwestern Nigeria. The presence dark-colored urine, hyponatremia, and hyperkalemia strongly predict the risk for AKI.

Introduction

Malaria is an infectious disease, with approximately 50% of the world's population at risk.[1] Though there has been progress with a decline in the burden of malaria globally, the disease still affected approximately 247 million individuals with 619,000 deaths in 2021.[2] More than 50% of the burden of malaria is recorded in the eleven high burden countries. Nigeria is one of the countries with a "high burden" and is ranked highest globally in terms of morbidity and mortality.[3] In 2022 World Malaria Report, the country accounted for 27% and 31% of the global morbidity and mortality, respectively.[2] Although Nigeria has the largest of global malaria, it achieved some progress in the past decades, with a decline in childhood severe

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malaria from a prevalence of 42% in 2010 to about 22% in 2021.[4] This was due to improved case management, sustained distribution of long-insecticidal nets, improved access to diagnostic services, and effective anti-malaria interventions, among others, such as residual indoor spray in some parts of the country.[5] However, they are far short of the sustainable development goal of ending death from preventable disease by the year 2020.

In Nigeria, the severe forms of malaria are common among the vulnerable populations, including children. Among Nigerian children, severe malaria accounts for as much as 30% of under-five mortality.[6] Most of the deaths from childhood severe malaria result from multiple organ dysfunctions.[7] Kidneys are one of the commonest organs involved in severe malaria, with manifestations that range from proteinuria to acute kidney injury (AKI). The incidence of AKI could be as high as 61% and may lead to possible progression to acute kidney disease, and subsequent chronic kidney disease, and later death.[8-11]

There are a few studies on AKI in childhood malaria in Nigeria conducted outside of the northwest zone of Nigeria.[8,12] In addition, improving the outcomes of MAKI will include tracking of laboratory results and clinical features that could predict its occurrence with appropriate response. Identifying these factors will allow for targeted intervention, ultimately improving both short-term outcomes and long-term complications of MAKI. We therefore aim to determine the incidence of childhood AKI and clinical and laboratory features that are predictive of AKI among a cohort of 541 children with severe malaria managed at a tertiary health facility in northwestern Nigeria.

Methods

This was a retrospective study of children admitted with severe malaria from 01 Jan 2019 to 31 Dec 2020 at the Federal Teaching Hospital, Katsina, Katsina State, Nigeria. The Paediatric Department has 28-bed emergency unit for the care of acutely ill children, including those with severe malaria. We estimated the minimum sample size for this study using an online sample size calculator (http://www.raosoft.com/samplesize.html). Using a 27.9% prevalence documented at the facility, at a confidence level of 95% and a 5% level of precision, we obtained a minimum sample size of 305.[13] However, all the children (541) that met the study eligibility criteria were included in the final data analysis. The study included children from three months to 14 years with a confirmed diagnosis of severe malaria based on the parasitological confirmation (Positive rapid diagnostic test and / or malaria parasite on microscopic slides) and the presence of clinical and laboratory features of severe malaria based on the 2015 WHO guidelines for severe malaria.[14] We excluded children with underlying chronic kidney disease (from history and clinical findings), chronic illnesses such as malignancy, chronic liver disease etc.

The children were managed according to national guidelines for severe malaria, which included a minimum of three doses of intravenous artesunate, fluid support, and blood transfusion for those with anemia, among others.[15] Children with seizures or impaired consciousness had a lumbar puncture, and treated with third generation cephalosporins. Patients who developed AKI received conservative management and dialysis (peritoneal dialysis or hemodialysis) where indicated. Children were discharged for follow-up upon improvement in their clinical conditions.

AKI was defined based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) criteria as a rise in the serum creatinine of 26.5 umol / L or more from the baseline within 48 hours or a rise of 1.5 times the baseline in the preceding seven days.[16] AKI was staged into 1 (a rise of up to 1.9 times the baseline), stage 2 (a rise of more than 2.0 – 2.9 times the baseline), and stage 3 (a rise of 3.0 times the baseline or serum creatinine above 4 mg / dl or the need for renal replacement therapy (RRT). We extracted the socio-demographics, clinical history, physical findings, and laboratory parameters at presentation from the electronic health record into the Excel spread sheet. The data was analyzed with SPSS 25 for Windows. The bedside Schwartz formula [estimated glomerular filtration = (0.413 x height) / serum creatinine] was used to back-calculate baseline serum creatinine at a glomerular filtration of 120 ml / 1.73 m^2.[17] Continuous variables (age, serum urea, serum creatinine and length of hospitalization) that were not normally distributed were summarized as median with interquartile range. The discrete variables were summarized as frequency and percentages. The clinical and laboratory features were compared between those who developed AKI and those without AKI using Mann-Whitney U and Chi-squares for continuous and discrete variables, respectively. Variables that were significant on bivariate analysis along with age and sex were entered into a binary logistic regression to determine the independent predictor of AKI, and results were expressed as adjusted odds ratios (AOR) with a 95% confidence interval. For all levels of statistical significance, the p value was set at less than 0.05. Institutional Ethical Review Committee approved this study, FMCNHREC.REG.N003/0830425. The data was anonymized during analysis and handled with absolute confidentiality.

Results

The demographic characteristics of the study population is represented in Table 1. The incidence and various stages of AKI in the study population is depicted in Table 2. The clinical and laboratory parameters of the children are shown respectively in Table 3 and 4. Table 5 elucidates the predictors of AKI in severe malaria.

Table 1: Sex and age distribution of children with severe malaria

Age group (years)	Total N = 541; (%)	Male N = 300; (%)	Female N = 241; (%)
Less than 2	67 (12.4)	39 (13.0)	28 (11.6)
2 to 5	268 (49.5)	149 (49.7)	119 (49.4)
6 to 10	148 (27.4)	80 (26.7)	68 (28.2)
11 to 14	58 (10.7)	32 (10.6)	26 (10.8)

Table 2: Incidence of acute kidney injury based on gender and age groups.

Variable	Total N = 541	AKI		AKI		
		Yes N = 208 (38.4%)	No N = 333 (61.6%)	Stage 1 N = 165 (79.3%)	Stage 2 N = 26 (12.5%)	Stage 3 N = 17 (8.2%)
Gender						
Male	300	121 (40.3)	179 (59.7)	90	20	11
Female	241	87 (36.1)	154 (63.9)	75	6	6
Age group (years)						
< 2	67	31 (46.3)	36 (53.7)	18	10	3
2 - 5	268	108 (40.3)	160 (59.7)	90	12	6
6 - 10	148	48 (32.4)	100 (67.6)	41	2	5
11 - 14	58	21 (36.2)	37 (63.8)	16	2	3

Table 3: Clinical features among children with severe malaria AKI

Variable	Subgroup	Total (N)	AKI (N = 208)	No AKI (N = 333)	Test	p
Median (IQR)-years		4 (2.5 to 8)	4 (2 to 7)	5 (3 to 8)	31096.50[U]	0.045
Age (years)	< 5	283 (52.3)	118	165	2.834	0.243
	5 to 10	199 (36.8)	68	131		
	> 10	59 (10.9)	22	37		
Sex	Male	300 (55.5)	121	179	1.012	0.314
	Female	241 (44.5)	87	154		
Fever	Yes	502 (92.8)	198	304	2.913	0.088
	No	39 (7.2)	10	29		
Vomiting	Yes	102 (18.9)	43	59	0.731	0.429
	No	439 (81.1)	165	274		
Passage of loose stool	Yes	32 (5.9)	10	22	0.744	0.456
	No	509 (94.1)	198	311		
Temperature (Mean) (SD)		38.1 (1.2)	38.0 (1.2)	38.1 (1.2)	-1.530	0.127
Hypoxemia	< 90	26 (4.8)	16	10	6.154	0.013
(SpO_2 in %)	≥ 90	515 (95.2)	192	323		
Resp. distress	Yes	64 (11.8)	32	32	4.094	0.043
	No	477 (88.2)	176	301		
Tachypnoea	Yes	318 (58.8)	122	196	0.002	0.962

	No	223 (41.8)	86	137		
Tachycardia	Yes	270 (49.9)	99	171	0.722	0.395
	No	271 (50.1)	109	162		
Loss of consciousness	Yes	114 (21.1)	53	61	3.949	0.047
	No	427 (78.9)	155	272		
Convulsions	Yes	285 (52.7)	108	177	0.078	0.078
	No	256 (47.3)	100	156		
Prostration	Yes	64 (11.8)	12	52	11.900	0.001
	No	477 (88.2)	196	281		
Dark color urine	Yes	108 (20.0)	68	40	34.269	< 0.001
	No	433 (80.0)	140	293		
Jaundice	Yes	22 (4.1)	12	10	2.511	0.113
	No	519 (95.9)	196	323		
Shock	Yes	8 (1.5)	7	1	8.256	0.004
	No	533 (98.5)	201	322		
LOH median (IQR)-days		3.00 (1.00 to 6)	3.00 (2.00 .to 8.00)	2 (1.00 to 5.00)	31439.00[U]	0.068

IQR-Interquartile range; Temp-temperature; SD-Standard deviation; LOH-length of hospitalization; U- Mann-Whitney U test

Table 4: Laboratory findings (baseline) among children with severe malaria AKI

Variable	Subgroup n (%)	Total (N)	AKI* (N) 208	No (AKI) 333	χ2/U	p
Acidosis*	< 15	21 (3.9)	13	8	5.080	0.024
	≥ 15	520 (96.1)	195	325		
Hypoglycaemia	Yes	5 (0.9)	3	2	0.991y	0.594
	No	536 (99.1)	205	331		
White cell counts	> 10	128 (23.7)	62	66	7.071	0.008
(X 10^9/L)	≤ 10	413 (76.3)	146	267		
Neutrophils (%)	> 60	267 (49.6)	106	161	0.350	0.554
	≤ 60	274 (50.6)	102	172		
Lymphocytes (%)	> 40	199 (36.8)	79	120	0.208	0.648
	≤ 40	342 (63.2)	129	213		
PCV (%)	≤15	92 (17.0)	41	51	1.753	0.185
	> 15	449 (83.0)	167	282		
Platelets (X 10^9 / L)	≥ 150	345 (63.8)	124	221	2.526	0.112
	< 150	196 (36.2)	84	112		
Sodium (mmol / L)	≥ 130	475 (87.8)	169	306	13.536	< 0.001
	< 130	66 (12.2)	39	27		
Potassium (mmol / L)	≥ 5.5	23 (4.3)	17	6	11.2505	0.001
	< 5.5	518 (95.7)	191	327		
Urea median (IQR) mmol / L		3.2 (2.10 to 5.63)	5.6 (3.06 to 8.00)	2.4 (1.60 to 4.30	16706.00[U]	< 0.001
Creatinine median (IQR) mg / dL		0.55 (0.43 to 0.73)	0.78 (0.68 to 0.98)	0.44 (0.37 to 0.53	2140.00[U]	< 0.001

*Bicarbonate less than 15 mmol/L; PCV-Packed cell volume; IQR-Interquartile range; y-Yates corrected Chi-square; U-Mann-Whitney U test; □2 -Chi square

Table 5: Independent predictors (baseline) of AKI in children with severe malaria AKI

Variables	categories	n	OR	95% CI	AOR	95% CI	P
Age (years)	< 2		1		1		
	2-5		0.784	0.457, 1.343	0.761	0.421, 1.374	0.364
	6-10		0.557	0.309, 1.006	0.534	0.278, 1.026	0.060
	11-14		0.659	0.321, 1.353	0.636	0.273, 1.482	0.295
Sex	Female		1				
	Male		1.197	0.843, 1.698	1.012	0.690, 1.486	0.950
Hypoxemia (SpO_2 in %)	≥ 90		1				
	< 90		2.692	1.197, 6.051	2.199	0.883, 5.477	0.091
Resp. distr.	No		1				
	Yes		1.710	1.013, 2.888	1.198	0.655, 2.191	0.558
LOC	No		1				
	Yes		1.525	1.004, 2.315	1.488	0.936, 2.367	0.093
Prostration	No		1				
	Yes		0.331	0.172, 0.636	0.505	0.242, 1.055	0.069
Dark urine	No		1				
	Yes		3.558	2.293, 5.521	3.853	2.417, 6.143	< 0.001
Shock	No		1				
	Yes		11.562	1.412, 94.664	3.340	0.333, 33.549	0.306
Acidosis*	≥ 15		1				
	< 15		2.708	1.103, 6.651	1.929	0.713, 5.215	0.195
WBC (X 10^9 / L)	≤ 10		1				
	> 10		1.718	1.150, 2.566	1.332	0.852, 2.081	0.208
Sodium (mmol / L)	≥ 130		1				
	<130		2.615	1.547, 4.423	2.346	1.287, 4.277	0.005
Potassium (mmol / L)	< 5.5		1				
	≥ 5.5		4.851	1.880. 12.513	3.122	1.031, 9.393	0.044

Resp. distr.-respiratory distress, LOC - Loss of consciousness; WBC - white blood counts; *bicarbonate less than 15 mmol / L; OR - Odds ratio; AOR - adjusted odds ratio; SpO_2 - Oxygen saturation

Discussion

AKI is one of the organ dysfunctions associated with poor outcomes in children with severe malaria. This study showed that approximately 40% children with severe malaria developed AKI. The incidence of 38.4% of AKI obtained in this study falls within the range of values (24 – 59%) reported in a review of AKI in African children with severe malaria.[9] However, the incidence of AKI is slightly higher compared with 32% in northcentral Nigeria, and 35.1% among Ugandan children.[11,18] In contrast to our findings, 59% incidence was reported from southwestern Nigerian children.[12] While the present study, like those mentioned above, was based on the KDIGO criteria for AKI, the differences in our study compared with others may be due to the retrospective nature of this study. The high burden of severe MAKI calls for a pragmatic approach, including making an effort at early diagnosis. The early diagnosis of MAKI will allow for early intervention and ultimately improved outcomes.

The baseline clinical features that were associated with AKI included hypoxemia, respiratory distress, loss of consciousness, prostration, passage of dark-colored urine, and shock. These findings contrast the observations made in southwestern Nigeria, where only loss of consciousness was found to be associated with AKI.[12] In north-central Nigeria, only the passage of dark-colored urine was identified among the clinical features as a risk factor for AKI.[8] In India, factors that were associated with AKI included hypoglycemia, pulmonary edema, and disseminated intravascular coagulation.[19] The

various factors identified in our study as risk factors for the occurrence of AKI may have acted together to accentuate the development of AKI. Respiratory distress and shock may lead to impaired tissue oxygenation that will affect the kidneys, while passage of dark-colored (due to red cell hemolysis) may cause tubular occlusion, leading to pre-renal and intrinsic renal injury. The presence of these multiple factors should alert the physicians to an increased risk of a child with severe malaria developing AKI.

The present study showed that the presence of acidosis, leukocytosis, hyponatremia, and hyperkalemia were associated with AKI. In contrast to our findings, the two Nigerian studies identified only acidosis being associated with AKI amongst the laboratory parameters [8,12] Worthy of note is the fact that a similar study in India also observed hyponatremia and hyperkalemia as being associated with AKI.[19] In Tanzania, levels of parasitemia, hemoglobin, and platelets were associated with AKI. These laboratory findings (acidosis, hyponatremia, and hyperkalemia) probably reflect early changes in the kidney's functions due to its role in the acid-base balance and electrolyte balance hemostasis in the human body.[20] These findings also call for careful monitoring of electrolytes and acid-base balance in a child with severe malaria.

Our observation of elevated WBC being associated with AKI contrasts with the findings in Ugandan children with severe where WBC was not associated with AKI.[11] Part of the pathogenesis of malaria associated AKI includes immune dysregulation, which increases pro-inflammatory markers and probably causes the elevated WBC.[21,22] This study also shows the independent predictors of AKI as passage of dark-colored urine, hyponatremia, and hyperkalemia. These findings contrast with the study in southwestern Nigeria, where age less than two, multiple convulsions, and hypoglycemia were the independent predictors of AKI.[12] Also, a study in northcentral Nigeria identified hemoglobinuria and acidosis as the predictors of AKI.[8] In Tanzanian study, male sex, low hematocrit, and low platelets, were the predictors of AKI.[20] A multi-center study in Zambia and Malawi among children with cerebral malaria identified age and hyperpyrexia as independent factors associated with AKI.[23] Dark-colored urine in children with severe malaria is a reflection of ongoing hemolysis that spilled into urine with a tendency for tubular blockade, causing renal ischemia and subsequent renal injury. Besides, released free heme has also been found to cause oxidative stress and accentuate the intrinsic renal damage.[21,22] Thus, the need for adequate hydration and close monitoring of children with severe malaria who passed dark-colored urine.

Although the present research has shown significant results, it is limited by its retrospective nature and small sized single centric study. Besides, the baseline creatinine in the past three months was not available and Schwartz formula was used to calculate creatinine. Due to absence of detailed documentation of urinary outputs in the case records, the urine output criteria of KDIGO were not used.

These facts may have caused errors in the calculation of AKI incidence in the present study. However, we expect that this research should encourage further, larger, multi centric prospective studies in the future.

Conclusion

The incidence of malaria associated AKI is high among children in northwestern Nigeria. The presence dark-colored urine, hyponatremia, and hyperkalemia strongly predict the risk for AKI.

Conflict of interest: None

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