

Original Research Article

The prevalence of acute kidney injury among children with severe malaria in a tertiary hospital in South-West Nigeria

Korede O. Oluwatuyi¹, Adanze Asinobi², Adebowale Ademola², Olumuyiwa A. Alonge¹, Ifedayo O. Fasoranti¹, Qasim O. Salau¹, Tolulope O. Jegede¹, Abiodun J. Kareem^{1*}, Olajumoke M. Aiyeku¹, Olusoji O. Olayinka¹, Datonye C. Briggs³, Temitayo O. Bewaji¹, Opeyemi O. Akinmadelo¹, Stanley E. Obasohan¹, Olukemi C. Ilori¹, Samiah G. Ajana¹

¹Department of Paediatrics, Federal Medical Centre, Owo, Ondo state, Nigeria

²Department of Paediatrics, University College Hospital, Ibadan, Oyo state, Nigeria

³Department of Paediatrics, Rivers State University Teaching Hospital, Port Harcourt, Rivers state, Nigeria

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*Correspondence:

Dr. Abiodun J. Kareem,

E-mail: biodunkareem13@gmail.com

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ABSTRACT

Background: Acute kidney injury (AKI) is a dire complication of severe malaria with a high mortality rate. AKI worsens the prognosis of children with malaria. Despite the poor prognostic index, there is scarce data on the prevalence of AKI in severe malaria in Nigeria. Therefore, this study aimed to document the prevalence of AKI in severe malaria among children in a tertiary hospital in South-West Nigeria.

Methods: This was a cross-sectional study. Children with WHO-defined severe malaria were recruited, and AKI was defined using the KDIGO and WHO criteria. The serum creatinine was measured, and the data were analysed, with a $p < 0.05$ considered significant.

Results: A total of 126 children aged 1-15 years, comprising 70 (55.6%) males with a male-to-female ratio of 1.25:1, were studied. The prevalence of AKI was 23.8% using KDIGO and 11.9% using WHO criteria, with a statistically significant difference ($p = 0.001$). The majority (50%) were in stage 1 AKI, while 36.7% were in stage 3. The haemoglobin concentration was statistically significantly associated with the occurrence of AKI.

Conclusions: The prevalence of AKI using KDIGO doubles that of the WHO criteria in the presence of severe malaria. There is a need to review the criteria for AKI diagnosis in severe malaria.

Keywords: Acute kidney injury, Children, Malaria, Prevalence

INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome characterized by sudden deterioration in kidney function resulting in the inability of the kidneys to maintain fluid and electrolyte homeostasis.¹ It was formally called acute renal failure (ARF), first described by Homer Smith in 1951.² This term was however, dropped for AKI which involves the whole spectrum of events in the kidney dysfunction syndrome rather than just the terminal stage

that requires renal replacement therapy (RRT) connoted by ARF.^{2,3}

AKI is seen in 1-3% of children admitted to tertiary paediatric centres.^{1,4} The burden of AKI appears to be on the rise globally with prevalence generally ranging between 0.6-82% in children.^{5,6} The reported general prevalence of AKI in various parts of Nigeria ranged between 3.0-82.9%, similar to Halle et al that reported AKI incidence of 84% in a retrospective study of Cameroonian children.⁷⁻⁹ In a meta-analysis of the global

incidence of AKI from a large cohort from 2004-2012 where 154 studies from various countries were reviewed, world AKI incidence was reported to be 33.7% in Caucasian children.¹⁰

AKI occurs as a complication of one or a combination of several conditions such as primary renal disorders, sepsis, human immunodeficiency virus (HIV), diabetes mellitus, and severe malaria.¹¹⁻¹⁵ AKI is one of the most dire complications of severe malaria, contributing to 45% mortality in children with severe malaria.^{7,16-18} Severe malaria has been shown in Nigeria and other developing countries to be a significant aetiology of AKI¹⁹ and this is more severe in children due to the ongoing growth of their kidney.

Severe malaria and its accompanying AKI complication are seen in all age groups still, they are more commonly seen in under-five children who have not developed adequate immunity enough to protect them from severe forms of malaria.^{19,20} AKI worsens the outcome in children with severe malaria and is a risk factor for future CKD and neurocognitive impairment.^{21,22} Kidney failure was reported as one of the significant predictors of death in patients with severe malaria.¹⁸

There is a paucity of data on the incidence of AKI in Nigerian children with severe malaria, as most studies quoted the proportion of AKI in severe malaria as part of a broad study on AKI. Therefore, this study aimed to determine the prevalence of AKI using KDIGO and WHO criteria in children aged one to 15 years with severe malaria admitted to the Children's Emergency ward in Federal Medical Centre, Owo, Nigeria.

The objectives are to determine the prevalence of AKI among children with severe malaria and the associated factors. This will help to put measures in place to help in curbing the factors responsible for the increase prevalence of AKI among children with severe malaria.

METHODS

Study site

The study was carried out at the Children's Emergency Ward (CHEW) of Federal Medical Centre (FMC), Owo, a 22-bed ward. The Federal Medical Centre is a federal tertiary hospital that sub-serves the entire state including neighbouring Edo, Ekiti and Kogi States. The population of Owo LGA is 218,886.²³ The CHEW and Children Outpatient (CHOP) are the points of entry of all patients (except neonates) admitted to the Department of Paediatrics and it receives an average of 6-10 admissions per day.

Study design

This was a hospital-based cross-sectional study.

Study duration

The period of study was from 1st November 2024 to 30th September 2025.

Subjects' recruitment

This study was conducted among children aged one to fifteen years who presented to the CHEW of FMC, Owo who met the WHO clinical and /or laboratory criteria for severe malaria.^{20,24} Children with established/background renal disease were excluded from the study.

Sample size

The minimum sample size was calculated using the formula below.²⁵

$$N = \frac{(Z\alpha + Z\beta)^2 pq}{d^2}$$

Where, N=sample size,

p=The best-estimated prevalence hypothesized value obtained from literature²⁶=0.176,

Z α =standard normal deviate, usually set at 1.96 (95% level of significance),

Z β =is the standard normal deviate corresponding to the power of 1- β set as 0.84 (at 80% power),

d=margin of error allowable=10%=0.10

q=1.0-p

q=1-0.176=0.824

N=(1.96+0.84)²×0.176×0.824/0.10×0.10

N=114

The minimum sample size was 126 participants including an attrition rate of 10%.

Sampling technique

All consecutive admissions into the children's emergency ward were noted, while those aged one to fifteen years with severe malaria who met the inclusion criteria were recruited. They were tested for the presence of an asexual form of *plasmodium falciparum* using the microscopy method.

Those who tested positive for the asexual form of *plasmodium falciparum* and whose parents had given consent were recruited into the study until the sample size was completed.

Study procedure

All consecutive admissions into the CHEW who met the inclusion criteria during the study period were recruited. Data on the history, examination and laboratory investigations were collected in a proforma. The information obtained was the socio-demographic data including age, sex, renal symptoms and clinical presentations. The socio-economic class of the subjects was determined using Ogunlesi's classification of social class.²⁷ A thorough general physical and systemic examination was carried out on all subjects recruited looking out for features of severe malaria that were not captured in the history. Also, features suggestive of a kidney injury such as body swelling were sought. The temperature was taken with a digital thermometer, placed in the armpit of each subject for one minute before reading.

The weight (in kilogram, kg) was measured to the nearest one decimal place using a pre-calibrated digital weighing scale (EBSA-20, CHINA) for children between the ages of one to two years or weight less than 13 kg, while a pre-calibrated beam balance weighing scale (MA-DONAX Model: RGZ-160, ENGLAND) was used for children who were able to stand unsupported. Children who could not stand had their weights measured by checking their mother/caregiver's weight alone and deducted from the combined weight of both caregiver and child earlier obtained. The difference was taken as the child's weight.

Height was assessed using a stadiometer with a degree of precision of 0.1 cm. Each subject was made to stand against the stadiometer on a flat wall with the occiput, buttocks and heels touching the wall and instructed to focus horizontally on a distant object. The caliper was then adjusted to the crown of the head at a right angle from the level of the caliper. Length was measured for subjects whose ages were less than two years or those older but could not stand. This was measured with the child lying supine on a flat firm couch and the lower limbs held together with feet parallel on the couches. A marker was used to mark the head (vertex) and soles of the feet on the couches. The child's length was taken as the distance between the two marks measured with an inelastic tape.

Sample collection and laboratory investigation

At admission, two millilitres of blood was collected from a peripheral vein using a 21G hypodermic needle while maintaining a strict aseptic technique. A few drops of the blood were placed directly on two glass slides for thin and thick films for the malaria parasite. At the point of recruiting, drops of blood were collected directly on a pre-cleaned slide for thin and thick film smears. The thick films were used for the presence of trophozoites of Plasmodium while the thin films were for parasite species identification.

One millilitre of the withdrawn blood sample was placed in a plain bottle for serum electrolyte, urea, and creatinine estimation. The aliquots of samples were allowed to clot and serum was extracted by centrifuging at 3000 revolutions per minute for five minutes in a bench-top centrifuge. The serum obtained was analyzed for serum creatinine (Scr), urea and electrolyte (potassium and bicarbonate). Another one millilitre of blood was collected for a repeat Scr estimation at 36 hours after admission. The assay was done in batches of 50 serum samples.

The serum creatinine at admission and the 36th hour of admission were estimated. The method used for the creatinine estimation was Jaffe's picric kinetic method using the creatinine kit (CR 510) from RANDOX laboratories, Ireland. The serum creatinine was determined using the following calculation.

Serum creatinine (mg/dl) = $\frac{\text{Absorbance at A2} - \text{A1}}{\text{Absorbance at A2} - \text{A1 of standard}} \times 2$

A1 = Absorbance at admission; A2 = Absorbance at 36 hours.

Principle of Jaffe's reaction method: Creatinine in an alkaline solution reacts with picric acid to form a coloured complex (red-orange). The amount of the complex formed is directly proportional to the concentration of creatinine in the serum. The intensity was measured at 510 nm and compared with the standard.

Urinary output was monitored over 24 hours to determine those who had oliguria/anuria by placing a penile conduit around the penile shaft and an adhesive urine bag attached to the female perineum held by a diaper to hold the bag firmly to avoid leakages. The urine volume was measured in a calibrated urine jar and then recorded. Five millilitres of urine was collected at admission into a universal bottle which was subsequently subjected to urinalysis using a Combi-9 Dipstick (MissionR Expert 11UW by ACON).

AKI definition in the study

The KDIGO definition of AKI in this study was any subject with a rise in serum creatinine of at least 0.3 mg/dl between the admitting serum creatinine and that obtained at 36 hours of admission as well as urine output less than 0.5 ml/kg/hour lasting 6-12 hours of admission.²⁸ Subjects with serum creatinine levels greater than 3 mg/dl (>265 μmol/l) and /or 24-hour urine output less than 12 ml/kg were considered to have WHO-defined AKI.²⁹

Data analysis

Statistical analysis was done using the statistical package for social science (SPSS) version 22.0 (SPSS for Windows Inc, Chicago LL, USA) statistical software.

Continuous variables like age and the serum creatinine were summarized using mean and standard deviation while categorical variables- sex, age group, and presence of AKI were presented using frequencies and proportions in tables and charts. The independent sample t-test was used to compare two means of normally distributed variables. The prevalence of AKI using both the KDIGO and WHO criteria was presented in percentages of the severe malaria recruited.

Pearson’s Chi-square test was used to determine the factors of AKI. A p value less than 0.05 was set as the level of significance. The unadjusted and multivariate model analysis was used to determine the independent factors of AKI.

RESULTS

Socio-demographic characteristics of the study population

The study period spanned between November, 2020 and September, 2021. During this period, a total of 521 children were admitted into the Children Emergency Room, out of which 126 subjects who met the inclusion criteria were recruited for the study.

Socio-demographic characteristics of the study population

Table 1 shows the socio-demographic characteristics of the study population. The majority (62.7%) were under-five years of age. There were 70 (55.6%) males with a median age of 3.17 (IQR 2.08-5.54) years. The parents of 52 (41.3%) of the children were from socio-economic class IV and no parent was from socio-economic class I.

Prevalence of AKI in severe malaria using the WHO, and KDIGO criteria

The number of subjects with AKI diagnosed using serum creatinine-based WHO and KDIGO criteria were 15 and 30 giving a prevalence of 11.9% (95% CI: 8.4-24.7) and 23.8% (95% CI: 20.2-42.8) respectively and the difference was statistically significant (p=0.001). Figure 1 shows the bar chart of the prevalence of AKI using WHO and KDIGO criteria.

Socio-demographic/Clinical characteristics and the occurrence of AKI using the WHO criteria

Table 2 shows the relationship between the socio-demographic/clinical characteristics and occurrence of AKI using the WHO criteria. There was no significant difference between the ages and sex of those who had AKI and those who did not, although a higher proportion 7 (46.7%) of the 47 subjects aged 5 years and above had WHO-defined AKI. The mean haemoglobin concentration of those who had AKI (6.1±2.0 g/l) was lower than those without AKI (7.4±2.9 g/l) while a higher

proportion of those who had WHO-defined AKI, 13 (86.7%) had taken herbal mixture prior to presentation.

Table 3 shows the relationship between socio-demographic/clinical characteristics and the occurrence of AKI using KDIGO criterion. Most of the subjects 19 (63.3%) with KDIGO-defined AKI were under five years of age. There is female preponderance 17 (56.7%) among the children with KDIGO-defined AKI. The presence of haemoglobinuria and jaundice was not significantly associated with KDIGO AKI. The mean haemoglobin concentration of subjects with KDIGO-defined AKI was statistically significantly higher than those without KDIGO-defined AKI (6.4±2.6 vs 7.5±2.8 g/l, p=0.038). Of the various pre-referral treatment received by the participants, KDIGO AKI occurred in 24 (80.0%) of the subjects who had used herbal mixture prior to presentation, though not statistically significant.

Staging of AKI in the study population based on KDIGO criteria

Table 4 shows KDIGO staging of the 30 subjects with AKI. Majority 15 (50.0%) were in stage 1 while 11(36.7%) were in stage 3.

Outcomes of the studied population

Three (2.4%) of the subjects had dialysis (peritoneal). There were 7 (5.6%) deaths out of all the 126 participants. Of the 119 survivors, 2 (1.7%) subjects discharged against medical advice (DAMA) because of lack of fund while the remaining 117 (98.3%) subjects were discharged to be followed up at the paediatric nephrology clinic.

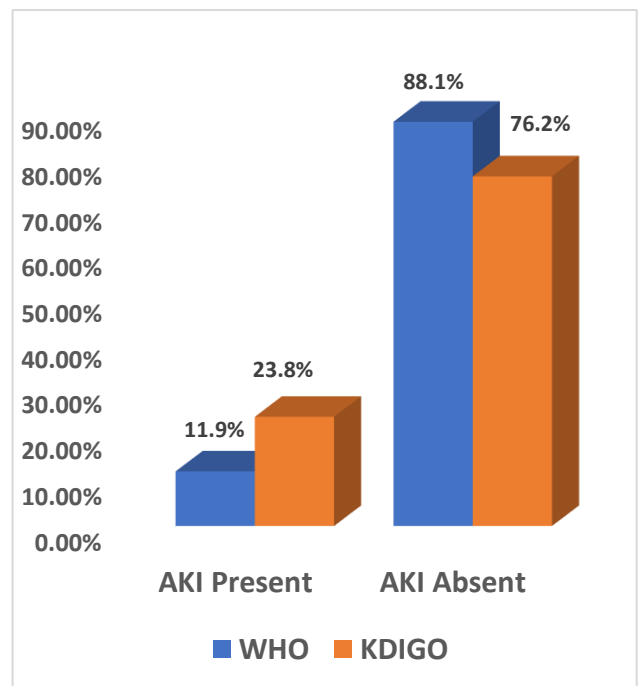


Figure 1: Prevalence of AKI using WHO and KDIGO.

Table 1: Socio-demographic characteristics of the study population, (n=126).

Variables	N	Percentages (%)
Age (in years)		
<5	79	62.7
≥5	47	37.3
Sex		
Male	70	55.6
Female	56	44.4
Parent ethnicity		
Yoruba	87	69.0
Ibo	15	11.9
Hausa	12	9.5
Others	12	9.5
Pre-referral treatment		
Herbal	96	76.2
Non-herbal	30	23.8
Socioeconomic class		
Class I	0	0
Class II	12	9.5
Class III	32	25.4
Class IV	52	41.3
Class V	30	23.8

Table 2: Relationship between socio-demographic/clinical characteristics and AKI using WHO criteria.

Variables	AKI present, n=15 (%)	AKI absent, n=111 (%)	Total, n=126 (%)	X ²	P value
Age median (IQR)⁺ (in years)	3.25 (2.00, 5.25)	3.17 (2.00,6.00)	3.17 (2.08,5.54)		0.878
Age group (in years)					
<5	8 (53.3)	71 (63.9)	79 (62.7)	0.639	0.570
≥5	7 (46.7)	40 (36.0)	47 (37.3)		
Sex					
Male	9 (60.0)	61 (55.0)	70 (55.6)	0.136	0.787
Female	6 (40.0)	50 (45.0)	56 (44.4)		
Haemoglobinuria					
Yes	5 (33.3)	32 (29.1)	37 (29.6)	0.114	0.473
No	10 (66.7)	78 (70.9)	88 (70.4)		
Hb concentration level (g/l)	6.1±2.0	7.4±2.9	21.7±8.4	1.678*	0.096
Pre-referral treatment					
Herbal	13 (86.7)	83 (74.8)	96 (76.2)	1.03	0.310
Non-herbal	2 (13.3)	28 (25.2)	30 (23.8)		
Jaundice					
Yes	2 (13.3)	15 (13.5)	17 (13.5)	0.000	0.670
No	13 (86.7)	96 (86.5)	109 (86.5)		

*T test, ⁺Mann-Whitney test, IQR: Interquartile range, others-Chi square test

Table 3: Socio-demographic/clinical characteristics and the occurrence AKI using KDIGO criteria.

Variables	AKI present, n=30 (%)	AKI absent, n=96 (%)	Total, n=126 (%)	X ²	P value
Age median (IQR) (in years)	2.5 (2.0, 5.0)	3.0 (2.0, 6.0)	3.0 (2.0, 6.0)		0.619 ⁺
Age group (in years)					
<5	19 (63.3)	60 (62.5)	79 (62.7)	0.007	1.000
>5	11 (36.7)	36(37.5)	47 (37.3)		
Sex					
Male	13 (43.3)	57 (59.4)	70 (55.6)	2.382	0.144
Female	17 (56.7)	39 (40.6)			

Continued.

Variables	AKI present, n=30 (%)	AKI absent, n=96 (%)	Total, n=126 (%)	X ²	P value
Haemoglobinuria					
Yes	7 (23.3)	30 (31.6)	37 (29.6)	0.744	0.494
No	23 (76.7)	65 (68.4)			
Hb concentration level (g/l)	6.4±2.6	7.5±2.8	7.2±2.8	2.017	0.038*
Pre-referral treatment					
Herbal	24 (80.0)	72 (75.0)	96 (76.2)	0.315	0.633
Non-herbal	6 (20.0)	24 (25.0)			
Jaundice					
Yes	3 (10.0)	14 (14.6)	17 (13.5)	0.411	0.568
No	27 (90.0)	82 (85.4)			

*T-test, †Mann-Whitney test, IQR: Interquartile range, #= Chi square test

Table 4: Staging of AKI in the study population based on KDIGO criteria.

Stages	N	Percentages (100%)	X ²	P value
Stage 1	15	50.0	43.9	<0.001
Stage 2	4	13.3		
Stage 3	11	36.7		
Total	30	100		

*KDIGO-kidney disease: improving global outcomes

DISCUSSION

This study aimed to determine the prevalence of AKI among children with severe malaria who were aged 1-15 years using the WHO and KDIGO criteria.

The prevalence of KDIGO-defined AKI observed in this study was similar to that reported by Gunther et al but lower than what was reported by Afolayan et al and Oshomal et al.^{15,30,31} Unlike the present study wherein a serial elevation of creatinine over 36 hours was used, Afolayan et al utilised an estimated baseline serum creatinine KDIGO criterion. It has been observed that utilising an estimated baseline serum creatinine was associated with a higher incidence of AKI.^{8,31} The higher prevalence observed by Oshomal et al could be due to the differences in the AKI definition used.¹⁵ In addition to utilizing subjects with a creatinine rise of 0.3 mg/dl, they also utilized estimated creatinine rise from baseline as well as urine output to define KDIGO AKI. In the present study, none of the studied subjects had oliguria and as such, the urine output component of the KDIGO criteria did not contribute to the prevalence of KDIGO-defined AKI in this study. The absence of oliguria does not rule out the presence of AKI, therefore, reliance on urine output as defining criteria for AKI may miss a large number of subjects that will thereafter progress to require RRT. In the study by Oshomal et al only 4.2% of the 144 severe malaria children with KDIGO AKI had oliguria.¹⁵

Some other studies that utilized KDIGO were silent about urine output.^{30,31} This may imply that urine output is an insensitive criterion of AKI diagnosis in children with severe malaria. This may also be due to the difficulty in measuring urine output in young paediatric patients.

The prevalence of WHO-defined AKI in this study was comparable with that reported by Afolayan et al but higher than that reported by Okpere et al.^{19,31} The difference in the reported prevalence may be due to the study methodology, the sample size, and the nutritional status of recruited subjects. The implication of the high threshold level of creatinine used in the WHO criterion in the diagnosis of AKI in severe malaria is that less severe forms of renal dysfunction were not considered for and may thus be missed by the WHO criteria. These missed subjects may progress to require RRT with other poor outcome measures as reported by Concroy et al and Oshomal et al.^{15,32} This is so because serum creatinine utilized by WHO coincides with stages 2-3 of KDIGO criteria.

In this study, the KDIGO criterion was able to detect all the subjects who had WHO-defined AKI at admission. Seventy-three percent of the subjects with WHO-defined AKI were in stage 3 while the remaining four were in stage 2 of the KDIGO criteria. This further reiterates the fact that the WHO criteria will only detect severe diseases with a higher tendency of missing those with the early stage of AKI in severe malaria.

In this study, herbal treatment was an alternative to orthodox care. This finding may be ascribed to the rural nature of the study location and the prevailing low socioeconomic status of the people found in this study. The use of herbal treatment may result from factors such as poverty and sociocultural practices.³³ Herbal mixtures have been associated with 35% of all cases of AKI in Africa.³⁴ They are concocted chemical and biological products which may cause toxic nephropathy by one or a combination of several processes depending on the

components. These processes include but are not limited to direct effects on renal tissues, hypersensitivity reaction and renal ischaemia that are capable of causing intravascular haemolysis with resultant ATN and AKI. Kadiri et al reported traditional herbal remedies as the most common aetiology of AKI in the adult population.³⁵ Anochie et al in a retrospective study found herbal drugs as the second highest factor that contributed to mortality in children with AKI.⁴ However, in this study, the herbal mixture was not an independent predictor of AKI.

The limitation of this study was the inability to compare the immediate and short-term outcome of the participants defined by the two criteria.

CONCLUSION

There is a significant difference in the prevalence of severe malaria-associated AKI obtained from serum creatinine-based KDIGO and WHO criteria. Therefore, there is a need to review the WHO criteria for AKI diagnosis in severe malaria to allow for the inclusion of KDIGO criteria in order to capture subjects with subclinical changes in renal function.

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