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RESEARCH

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Impact of methods of estimating baseline Serum Creatinine (bSCr) on the incidence and outcomes of acute kidney injury in childhood severe malaria

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Abstract

Background Estimated baseline serum creatinine (bSCr) affects the incidence and outcomes of childhood severe malaria. Herein, we estimated baseline serum creatinine (bSCr) levels of 541 children with severe malaria using Pottel and Scwartz formulas for AKI incidence, hospitalization outcomes, and evaluated risk factors for death.

Methods This was a retrospective review of malaria cases from January 2019 to December 2020 at a tertiary health facility in northern Nigeria. We extracted relevant data from the electronic health record. AKI definition and staging was based on the 2012 Kidney Disease Improving Global Outcomes (KDIGO).

Results The estimated bSCr using Pottel's method was lower with a mean (standard deviation) bias of -0.039 (0.013) mg/dl, an upper limit of agreement (-0.014 mg/dl), and the lower limit of agreement (-0.063 mg/dl). All (100%) of the estimated bSCr using Pottel's method fell within 30% of the Schwartz method's estimated bSCr. The incidence of AKI from Pottel's method was higher than the Schwartz's method (43.3% vs. 38.4%, $p < 0.001$). The incidence of AKI derived from Pottel's method was highest among those under 5 years old ($p < 0.001$). The mortality rate was 6.1% (33 deaths out of 541 admissions). Pottel's method detected more deaths (57.6%; 19 out of 33) vs. Schwartz's method (48.5%; 16 out of 33), $p < 0.001$. Factors that were associated with malaria AKI death included acidosis with an adjusted odds ratio (AOR) of 9.2 (95% CI 1.671 to 50.097), the first 72 h [AOR 7.0 (95% CI 1.358, 35.840)], and KDIGO stage 3 of AKI [AOR 14.4 (95% CI 3.073, 66.969)].

Conclusion Among Nigerian children with severe malaria, bSCr back-calculated from Pottel's equation showed a minimal bias, narrow limit of agreement, and high degree of accuracy. Also, Pottel's method detected more AKI and deaths.

Keywords Malaria, Acute kidney injury, Creatinine, Child, Incidence, Mortality

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Background

Malaria is an acute infectious disease, with an estimated half of the world's population at risk [1]. Though stalled in recent years due to the impact of coronavirus disease (COVID-19), the past decades have witnessed substantial reductions in the global malaria burden [2, 3]. Malaria incidence per 1000 population at risk declined from 82 in 2000 to 57 in 2019 [2]. The progress in malaria spanned all world health organization (WHO) regions, including the WHO African region, where Nigeria belonged. In Nigeria, malaria prevalence also declined by 50% from 2010 (42%) to 2021 (22%) [4].

Malaria is a disease that affects people of all ages, but it has a greater impact on vulnerable populations, including children [5]. Malaria has a greater impact on children, particularly those under the age of five, with deaths resulting primarily from the severe form of the disease [5]. Severe forms of childhood malaria are characterised by system-organs damage with the kidney being one of the primary targets [6]. Malaria affectations of the kidney, mostly in the form of acute Kidney injury (AKI) could be as high as 61% with a poor outcome especially in those that present late [7]. Though a few studies in Nigeria estimated the burden of AKI using consensus definitions, the outcomes of childhood severe malaria AKI are usually lumped together with other complications of severe malaria [8, 9]. This therefore makes it difficult to delineate factors that are associated with deaths in children who developed malaria AKI when compared with those who survived with similar AKI.

In addition, the few studies that applied the consensus definitions of AKI, such as the Kidney Disease Improving Global Outcomes (KDIGO) 2012 malaria AKI in Nigeria, rely on estimation of baseline serum creatinine, which remains one of the critical challenges with AKI diagnosis in low- and middle-income countries (LMICs) [7, 9, 10]. This is because the measured baseline serum creatinine in the preceding three months is not readily available [10]. Thus, the baseline serum creatinine values are usually estimated using a formula, with the most popular being the Schwartz equation [11]. Schwartz formula "back" calculates baseline serum creatinine using an estimated glomerular filtration rate (GFR) of 120 ml per 1.73 m^2 [12]. The estimation of baseline renal function is important in children with severe malaria-related kidney injury because it forms the basis for the diagnosis of AKI incidence and subsequent staging [13]. This is due to the fact that an inaccurate baseline serum creatinine may lead to an underestimation of the actual burden of childhood severe AKI, with subsequent short-term adverse outcomes and the associated long-term progression to chronic kidney disease [14–16].

Despite its continued usage for estimation of baseline among children, early research in Nigeria showed the Schwartz formula may overestimate GFR among children [17]. Furthermore, the Schwartz formula requires a child's height or length, which are not always available and may be impractical in a busy emergency situation with a very sick child [18]. In contrast to Schwartz's height-dependent equation, Pottel's formula is a height-independent equation for the estimation of GFR in children and adolescents. Study shows that its estimation of GFR has higher precision than the updated bedside Schwartz's equation [19]. Pottel formula has been validated among Belgian children and recently among Ugandan children [19, 20]. Thus, the Pottel formula may be applicable in the Nigerian situation.

We therefore hypothesized that estimating baseline serum creatinine determined from the height-independent method (Pottel formula) would perform better than the height-dependent method (Schwartz method) with regard to assessing the incidence and outcomes of AKI in children with severe malaria. We also hypothesized that there are variables that are associated with poor hospitalization outcomes (death) among children with severe malaria AKI.

Hence, we set out to compare the baseline serum creatinine levels of 541 children with severe malaria using the Pottel formula (a height-independent method) versus the Scwartz formula (a height-dependent method). We also compared the two methods' incidence of AKI and hospitalization outcomes (death or discharge) in children with severe malaria. Furthermore, we identified risk factors for poor hospitalization outcomes (death) in children with severe malaria AKI.

Methods

Study design

This study was retrospective review of cohort of childhood severe malaria cases from 1st January 2019 to 31st December 2020 at a tertiary health facility in northwestern Nigeria.

Study site

This study took place at the Federal Teaching Hospital, Katsina, a tertiary health facility located in the northwestern part of Nigeria. The hospital is the only referral tertiary health facility for the pediatric age group in the state, with an estimated total population of eight million. The pediatric department has a 24-bed emergency unit and manages children younger than or equal to 14 with acute emergencies, including those with severe malaria. Children with severe malaria are mostly referred from hospitals in the state and parts of neighboring Kano, Zamfara, Kaduna, and Niger Republic.

This study involved children aged 14 years and below with a diagnosis of severe malaria. The diagnosis of severe malaria was based on the presence of parasitological evidence of malaria infection (a positive rapid diagnostic test or malaria parasites on microscopic slides) and features of severe malaria based on the WHO guidelines [21]. In brief, the features of severe malaria used for this study included children with a Blantyre coma score of less than 3 or a Glasgow coma score of less than 11 in older children (impaired consciousness); an inability to drink or sit without support in older children (prostration); two or more episodes of convulsions within 24 h (multiple convulsions); hemoglobin less than 5 g/dl or packed cell volume of less than 15% (severe anemia), random blood sugar of less than 40 mg/dl (hypoglycemia), bicarbonate of less than 15 (acidosis), systolic blood pressure less than 50 mmHg in infants and less than 70 mmHg in older children (circulatory shock), labored breathing with a pulse oximeter reading less than 92% (respiratory distress), spontaneous bleeding or evidence of disseminated intravascular coagulation (DIC), and serum creatinine greater than 3 mg/dl (renal impairment).

Inclusion and exclusion criteria

This study included all cases of severe malaria managed during the study period (2019–2020). We excluded children with underlying renal diseases (chronic kidney diseases such as nephrotic syndrome, glomerulonephritis, renal stones, and those with underlying congenital anomalies of the kidney and urinary tract), those with malignancy or another diagnosis managed during the study period, and nine children without complete laboratory results (creatinine and urea).

Sample size estimation

Using a previous 59% obtained based on the KDIGO criteria defined AKI among children with severe malaria in a Nigerian study [9], we estimated the minimum sample of 365 using online calculator for sample size (http://www.raosoft.com/samplesize.html). The minimum sample size was estimated at a confidence level of 95% with a 5% margin of error.

Data collection

The following information was obtained from the patients' electronic health records: age, gender, presenting complaints, durations of presenting complaints, features of severe malaria, durations of hospitalization, hospitalization outcomes (defined as discharged or deaths), anthropometrics (weight and height), electrolytes, complete blood counts, urea, and creatinine. The data extraction was done by one of the co-authors and verified by another co-author.

Patients' management

Children with severe malaria were managed based on the national guidelines for severe malaria [22]; which included the administration of intravenous artesunate for a minimum of three doses; provision of blood transfusion with those with anemia (Packed cell less than 15%); intravenous fluids where indicated, close monitoring and other supportive cares as indicated. Those with convulsions, an altered sensorium, or who were unconscious routinely had a lumber puncture for cerebrospinal fluid (CSF) analysis to rule out bacterial meningitis. Before the results were made available, such children had a third-generation cephalosporin added to their treatment pending the outcome of the CSF analysis. Children with negative CSF had the antibiotics discontinued after 72 h. Those with malaria AKI without indications for dialysis were managed conservatively. Eight children received dialysis (five had peritoneal dialysis and three had hemodialysis). The dialysis modalities were based on age and weight, with peritoneal dialysis for those under 10 years of age weighing less than 25 kg. For children ten years and above and weighing at least 25 kg underwent hemodialysis. The children were discharged upon improvement in their clinical conditions.

Definition of AKI

We defined AKI based on KDIGO 2012 definition criteria and staging. In brief, AKI was defined as a rise in serum creatinine (SCr) of $\geq$ 0.3 mg/dl within 48 h or a rise in SCr of 1.5 to 1.9 times the baseline in the preceding seven days (Stage 1). Stage 2 was defined as a SCr of 2.0 to 2.9 times the baseline values. Stage 3 was defined as an increase in SCr of 3.0 times baseline, an increase in SCr to 4.0 mg/dL, or the initiation of kidney replacement therapy.

Study outcomes

Our primary outcome of this study was the impact of estimated baseline SCr on the incidence and outcomes of severe malaria AKI derived from the Pottel method (height-independent) and the Schwartz method (height-dependent). Our secondary outcomes were the factors associated with hospitalization mortality in children with malaria AKI.

Statistical analysis

We analyzed the data with IBM Statistical Package for the Social Sciences® software version 25. The age was summarized as the median with an interquartile range (not normally distributed). The baseline serum creatinine (bSCr) from the Pottel method was estimated with a back-calculated estimated bSCr derived from the Pottel

age-based equation, where eGFR = 107.3 (SCr/Q), assuming a normal GFR of 120 mL/min per 1.73 m^2 (height-independent). The constant, Q = 0.0270*age + 0.2329 [20]. We also back-calculated the estimated bSCr from the bedside Schwartz's equation [eGFR = (0.413*height)/SCr], assuming a normal GFR of 120 mL/min per 1.73 m^2 (height-dependent); this was used as the study's reference. For paired samples comparison of the two methods, we used the pair t-test and the Wilcoxon test for the mean and median values, respectively. To evaluate the levels of agreement between the two methods, we used Bland–Altman plots and expressed the results as mean bias (with 95% confidence) and percentage of mean bias (with a 95% confidence interval). To evaluate the accuracy, we compared the percentage of estimated bSCr values derived from Pottel's method that fell within 10% (p10) and 30% (p30) of the estimated bSCr derived from the Schwartz's method. For the AKI, we used the chi-square test for differences to evaluate the differences in the incidences and outcomes. Kappa statistics were also used to evaluate the levels of agreement between the two methods regarding the detected incidences and outcomes of AKI. We also compared factors that were associated with the occurrence of AKI and hospitalization outcomes (deaths) and expressed the results as odds ratios with a 95% confidence interval. Factors that were significant on the bivariate analysis, along with age and sex for the AKI outcomes, were entered into the binary logistic regression, and results were expressed as adjusted odds ratios (AOR) with 95% confidence intervals. In all the statistical tests, the p value was set at less than 0.05.

Results

General characteristics

In total, 541 cases of severe childhood malaria during the study period were included in the data analysis. The median age of the children was 4 (interquartile range: 2.5 to 8); the minimum and maximum ages were three months and 14 years, respectively. There were more males (300; 55.5%). Based on the age groups, most of the children were younger than five years (283; 52.3%), as shown in Table 1.

Table 1 Demographic distribution of children admitted with severe malaria

Variables	Total *n* = 541(%)	Male *n* = 300 (%)	Female *n* = 241 (%)
Age groups (years)			
Less than five	283 (52.3)	163 (54.3)	120 (49.8)
5 to 10 years	199 (36.8)	105 (35.0)	94 (39.0)
Greater than 10	59 (10.9)	32 (10.7)	27 (11.2)

% Column percentage

Estimated baseline serum creatinine using the two methods

The mean estimated bSCr using the Pottel's method was lower compared with the Schwartz's method, with a mean (standard deviation) bias of -0.039 (0.013) mg/dl. For the mean bias, the upper limit of agreement was -0.014 mg/dl and the lower limit of agreement was -0.063 mg/dl (Table 2). The mean (standard deviation) percentage bias was 11.97% (4.4%). Also, the mean serum estimated bSCr using the Pottel's method was also significantly less than the estimated values from the Schwartz's method, $p < 0.001$, across the age groups (Table 2). Furthermore, all (100%) and 32% of the estimated bSCr using the Pottel's method fell within the range of 30% and 10% of the Schwartz method's estimated bSCr, respectively (Table 2).

Incidence of acute kidney injury using the methods

The incidence of AKI obtained from the Pottel's method was significantly higher than the incidence from the Schwartz's method (43.3% vs. 38.4%, $p < 0.001$). There were also significant differences in the AKI stages detected by both methods (Table 3). Furthermore, in both males and females, the Pottel's method detected more AKI compared with the Schwartz's method (54.7 vs. 40.3% and 41.9 vs. 36.1%, $p < 0.001$, respectively). In the age groups, the incidence of AKI derived from the Pottel's method was also higher than the incidence from Schwartz's method, with the highest differences in those younger than five years (47.0 vs. 41.7%, $p < 0.001$), as shown in Table 3. On the level of agreement between the methods, there was a very good level of concordance with the detection of AKI between the two methods, with a Kappa statistic of 0.890 (Table 3).

Hospitalization outcomes among children with severe malaria AKI

The overall mortality rate for the children with severe malaria was 6.1% (33 deaths out of 541 admissions). The probable causes of death included cerebral malaria (19; 57.6%), cerebral malaria and anemia (5; 15.2%), anemia (4; 12.1%), cerebral malaria, anemia, acidosis (1; 3.0%), disseminated intravascular coagulation (1; 3.0%), disseminated intravascular coagulation, acute kidney injury, cerebral malaria (1; 3.0%), and multiple convulsions and anemia (1, 3.0%). Further details are shown in Supplementary Table 1 Based on the Pottel's method, the mortality rate among children with AKI was 8.0%, which was not statistically significantly different from that of children without AKI (4.6%), $p = 0.100$. Using the Schwartz's method, the mortality rate was 7.7%, which was also not significantly different when compared with

Table 2 Comparison of baseline serum creatinine estimated using Pottel and Schwartz equations ($n = 541$)

Variables	Pottel method	Schwartz method	Test	*p* value
Mean (SD)- mg/dl	0.33 (0.08)	0.38 (0.08)	-0.038(0.01)[a]	< 0.001
Median (IQR)- mg/dl	0.31 (0.27–0.40)	0.36 (0.32–0.43)	-20.147[b]	< 0.001
Minimum, Max- mg/dl	0.21, 0.55	0.21, 0.56		
< 2 years (67)				
Mean (SD)- mg/dl	0.24 (0.01)	0.26 (0.02)	-0.026(0.01)[a]	< 0.001
Median (IQR)- mg/dl	0.23 (0.23–0.25)	0.26 (0.26–0.28)	-14.574[b]	< 0.001
Min, Max- mg/dl	0.21, 0.25	0.21, 0.29		
Age 2 to 10 years (415)				
Mean (SD)- mg/dl	0.33 (0.06)	0.37 (0.05)	-0.044(0.01)[a]	< 0.001
Median (IQR)- mg/dl	0.31 (0.28, 0.38)	0.36 (0.33, 0.42)	-12.232[b]	< 0.001
Min, Max,—mg/dl	0.26, 0.45	0.30, 0.47		
Age > 10 years (59)				
Mean (SD)- mg/dl	0.51 (0.03)	0.52 (0.02)	-0.016(0.01)[a]	< 0.001
Median (IQR)- mg/dl	0.50 (0.47, 0.52)	0.52 (0.50, 0.54)	-6.680[b]	< 0.001
Min, Max,—mg/dl	0.46, 0.55	0.49, 0.56		
Mean bias, mg/dL, SD, (95% CI)	-0.039, 0.013 (-0.040, to -0.038)	-		< 0.001
Upper limit of agreement (95% CI)	-0.014 (-0.016, to -0.012	-		
Lower limit of agreement (95% CI)	-0.063 (-0.065 to -062)	-		
Mean percentage bias, %, SD (95% CI)	-11.97, 4.4 (-11.97 to -11.21)			< 0.001
95% limits of agreement of percent bias, % lower limit (95% CI)	-20.34 (-21.03 to -19.74)			
95% limits of agreement of percent bias, % upper limit (95% CI)	-2.80 (-3.45 to -2.15)			
Percentage within ± 30% of Schwartz estimated baseline SCr, %	100.0%			
Percentage within ± 10% of Schwartz estimated baseline SCr, %	32.2%			

SD Standard deviation, *IQR* Interquartile range

[a] pair t-test for mean, *Min* Minimum, *Max* Maximum, *CI* Confidence interval, *SCr* Serum creatinine

[b] Wilcoxon test for paired samples for median

Table 3 Incidence of acute kidney injury using the two methods of baseline estimations

Variables	Subgroups	Pottel Method n (%)	Schwartz Method n (%)	χ2	*p*
AKI	Yes	237 (43.8)	208 (38.4)	33.453	< 0.001
	No	304 (56.2)	333 (61.6)		
KDIGO Stages	1	178 (75.1)	166 (79.8)	968.240	< 0.001
	2	31 (13.1)	24 (11.5)		
	3	28 (11.8)	18 (8.7)		
Sex	Males (300)	136 (54.7)	121 (40.3)	240.862	< 0.001
	Females (241)	101 (41.9)	87 (36.1)	185.006	< 0.001
Age group (Years)	< 5 (283)	133 (47.0)	118 (41.7)	224.622	< 0.001
	5 to 10 (199)	80 (40.2)	68 (34.2)	149.900	< 0.001
	> 10 (59)	24 (40.7)	22 (37.3)	47.315	< 0.001
Agreement (95% CI)	0.890 (0.851 to 0.928) [a]				

[a] Kappa statistics between AKI detected by both methods; *CI* Confidence interval

children without AKI (5.1%), $p=0.221$). Of the 33 deaths in this study, 19 children were identified as having AKI (57.6%) according to Pottel's method. In contrast, out of the 33 deaths in this study, only 16 children (48.5%) had AKI based on Scwartz's method, which was significantly lower than that based on Pottel's method ($p<0.001$) (Supplementary Table 1). Based on the age groups, there were no differences in the level of mortality detected by either of the methods, and both demonstrated increased mortality with an advanced stage of KDIGO AKI classifications (Table 4). Furthermore, there was a very good level of agreement in the level of mortality measured by the two methods, with a Kappa statistic of 0.819 (Table 4).

Factors that are associated with outcomes of hospitalization among children with AKI

On multivariable analysis, age and sex were not related to poor hospitalization outcomes (death) in Table 5. Similarly, most of the clinical features and laboratory findings were not related to hospitalization deaths among children with AKI, except for acidosis, which an adjusted odds ratio (AOR) of 9.2 (95% CI 1.671 to 50.097). In those who developed severe malaria AKI, the first 72 h and KDIGO stage 3 of AKI were also significantly associated with death, with adjusted odds ratios of 7.0 and 14.4 respectively (Table 5).

Discussion

The bSCr values are important in the true estimation of burden of severe malaria associated AKI. In this study, we looked at the impact of the estimated bSCr back-calculated from a height independent formula for GFR (Pottel's equation) [20] compared with bSCr values back-calculated from Bed-side Schwartz formula on the incidence and outcomes of childhood severe malaria [12]. Overall, Pottel derived bSCr values showed minimal bias (-0.04) with a narrow limit of agreement (0.05). The mean differences estimated bSCr values were also small across the various age strata. This observation is consistency with the observation among the Uganda children where the Pottel's derived bSCr shows small bias when compared with actual measured serum creatinine among

Table 4 Hospitalization outcomes (death) among severe malaria AKI based on the two methods

Variable	Total	Discharge	Death	Mortality rate	OR	Test		*p*-value
Total	541	508	33	6.1				
No AKI (Pottel)	304	290	14	4.6		2.706	0.100	
AKI (Pottel)	237	218	19[a]	8.0				
No AKI (Schwartz)	333	316	17	5.1		1.496	0.0221	
AKI (Schwartz)	208	192	16[a]	7.7				
AKI stages (Pottel) 1	178	169	9	5.1	1			0.002
2	31	28	3	9.7	2.012	0.513, 7.890		0.316
3	28	21	7	25.0	6.259	2.111, 18.558		**0.001**
AKI stages (Schwartz)	166	158	8	4.8	1			
2	24	21	3	12.5	2.821	0.694, 11.474		0.147
3	18	13	5	27.8	7.596	2.171, 26.575		**0.002**
Age (Pottel)	Pottel							
< 5 years	133	123	10	7.5	1			
5 to 10 years	80	73	7	8.8	1.179	(0.430, 3.233),		0.748
> 10 years	24	22	2	8.3	1.118	(0.229, 5.453),		0.890
Age (Schwartz)								
< 5 years	118	110	8	6.8	1			
5 to 10 years	68	62	6	8.8	1.331	(0.441, 4.011)		0.612
> 10 years	22	20	2	9.1	1.375	(0.272, 6.956)		0.700
Correlation						**Spearman's rho**		
Pottel AKI stages[b]						0.207		0.001
Schwartz AKI stages[b]						0.227		0.001
Pottel vs Schwartz[c]						0.914		< 0.001

CI Confidence interval

[a] chi-square for comparing mortality between the two methods = 19.638, $p<0.001$

[b] Vs mortality

[c] Mortality rate by both methods. K-Kappa's statistics- K = 0.819, (95% CI 0.627 to 1.000)

Table 5 Factors that are associated with poor hospitalization outcomes (death) among children with AKI[c]

Variable	Subgroup $n=16$	OR	95% CI	AOR	95% CI	*P*
Age	< 5 (8)	1		1		
	5 to 10 (6)	1.331	0.441, 4.011	0.946	0.247, 3.628	0.935
	> 10 (2)	1.375	0.272, 6.956	1.134	0.177, 7.282	0.894
Sex	Males (7)	0.532	0.190, 1.489	0.314	0.087, 1.127	0.076
Fever	Yes (16)	142,019,747.3	0.000			
Vomiting	Yes (4)	1.308	0.400, 4.277			
Loose stool	Yes (1)	1.356	0.161,11.430			
Temp	≥ 38.5 (3)	0.431	0.119, 1.564			
Hypoxemia	Yes (2)	1.816	0.375, 8.803			
Acidosis[a]	< 15 (4)	6.778	1.820,25.237	9.150	1.671, 50.097	**0.011**
Respiratory distr	Yes (3)	1.297	0.348, 4.836			
Tachypnoea	Yes (13)	3.3	0.911,11.956			
Tachycardia	Yes (10)	1.929	0.674, 5.518			
LOC	Yes (6)	1.851	0.639,5.366			
Convulsions	Yes (10)	1.599	0.559, 4.573			
Prostration	Yes (0)	0.000	0.000			
Dark color urine	Yes (4)	0.667	0.207, 2.149			
Shock		2.067	0.233,18.308			
Hypoglycaemia	Yes (0)	0.000	0.000			
Jaundice	Yes (2)	2.600	0.518,13.041			
WBC (X 10^9/L)	> 10 (8)	2.556	0.913, 7.153			
Lymphocytes (%)	> 40 (7)	1.296	0.463, 3.631			
Neutrophils (%)	> 60 (6)	0.552	0.193, 1.579			
PCV (%)	≤ 15 (20	0.560	0.122, 2.569			
Platelets (X 10^9/L)	≤ 150 (10)	0.376	0.131, 1.079			
Sodium (mmol/L)	< 130 (4)	1.495	0.455, 4.912			
Potassium (mmol/L)	≥ 5.5 (1)	0.733	0.091, 5.917			
Urea	> 20 (13)	1.830	0.502, 6.667			
LOH (days)	≤ 3 (14)	5.800	1.283,26.218	6.977	1.358, 35.840	**0.020**
AKI stages (Cr)[b]	1 (8)	1				
	2 (3)	2.821	2.171,26.575	1.836	0.335,10.079	0.484
	3 (5)	7.596	2.171,26.575	14.345	3.073, 66.969	**0.001**

OR Odds ratio, *AOR* Adjusted odds ratio, *CI* Confidence interval; [a]bicarbonate less than 15 mmol/L, *LOC* Loss of consciousness, *PCV* Packed cell volume, *distr* Distress, *LOC* Loss of consciousness, *LOH* Length of hospitalization; [b]KDIGO serum creatinine criteria. [c]AKI derived from Schwartz's method

healthy children [19]. A study among Indian children that also compared estimated GFR derived from the Pottel and Schwartz's formulae found a minimal bias with narrow width of agreement [23]. Based on degree of accuracy, bSCr derived values from Pottel's equation showed a high degree of accuracy with 100% of the derived values within ± 30% estimated bSCr obtained from bedside Schwartz formula. In contrast, the study in Uganda shows that 79% estimated bSCr fall within ± 30% [19]. The differences in our study compared with Uganda study may be due to the fact we compared with bed-side Schwartz formula as the reference standard. Our finding of a small mean bias from the Pottel's equation derived bSCr reinforces a previous report that shows that the height-independent formula by Pottel has a better precision especially at value a lower GFR than the Schwartz formula when compared head-to-head with the gold standard of measured GFR using inulin clearance [24]. The importance of our findings of observed narrowed limit of agreement, and a high accuracy in the estimating bSCr make Pottel's formula more suitable for sick children with malaria-associated AKI especially in the busy emergency, and where the height of a child is not readily available.

Our study shows that Pottel's method detected more AKI across both sex and all the age groups

(highest among under five) when compared with the bed Schwartz's method. This observation is supported by research conducted in Uganda among children with Malaria AKI [19]. A study among critically ill children in Korea also affirmed the observation that the Schwartz's method underestimated AKI incidence [25]. Our observation further corroborated the earlier findings that baseline serum creatinine significantly influence the actual incidence of AKI with possible under estimation by Schwartz equation [26]. Worthy of note is the good level of agreement in the measured AKI by both methods, which suggested that Pottel's formula can be used in place of Schwartz's formula with a better performance among Nigerian children. Using the Pottel's method in children with severe malaria in our environment will probably improve the estimation of true burden of childhood malaria AKI, allow for more intervention and ultimately improved their outcomes.

Among children with severe malaria AKI, we found that the Pottel's formula detected more deaths compared with Schwartz formula. This finding supported the observation among Ugandan children with severe malaria where Pottel formula had the best sensitive to predict mortality [19]. In addition, both methods showed a good level of agreement in the mortality measured and demonstrated an increased mortality with advance stage of KDIGO. Thus, Pottel's equation detection of more deaths offers additional benefit improve stratification of childhood malaria AKI related death and may be used to identify those with poor prognosis.

Factors that were associated with death among children with AKI included acidosis with an AOR of 9.1 (95% confidence interval, 1.671 to 50.097), a shorter hospital stay (less than 72 h on admission), and stage 3 KDIGO. Though there is limited literature on factors associated with deaths in children with severe malaria AKI, a recent study in Uganda found acidosis to be an important predictor of death [19]. Acidosis results from 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 [27]. In line with previous research, we discovered that the first 72 h were associated with fatalities in children with severe malaria AKI. In contrast, a study in India observed that AKI death was associated with a prolonged hospital stay [28]. The observation of more deaths in the first 72 h affirmed the challenges faced by a child with severe malaria AKI in the first few days of the illness, with attendant high mortality [10]. Some of the challenges in the early phase include fluid and electrolyte derangements, with studies showing bolus fluids for the correction of hypovolemia associated with severe malaria may worsen the outcomes of AKI [29, 30]. As a result, there is a need for more research in the early stages of severe malaria, particularly on fluids and the outcomes of AKI. This observation also called for close monitoring and meticulous management of AKI in the first few days while a child is on admission. The observation of KDIGO stage 3 AKI being associated with deaths affirmed previous studies and suggested the need for more early intervention before a child progressed to the advanced stage [10].

Limitations

Despite the relatively large sample size of 541 children with severe malaria, our study has some limitations. The estimated baseline derived from Pottel's method was compared with Schwartz's formula, as none of the study children had their baseline measured in the preceding three months.

Conclusions

This study showed that bSCr back-calculated from Pottel's equation (a height independent) showed a minimal bias, narrow limit of agreement and high degree of accuracy compared with the bSCr obtained from the besides Schwartz's formula among Nigerian children with severe malaria. Also, among children with severe malaria, Pottel's method detected more AKI, and identified more deaths compared with Schwartz methods. Both methods show a good level of agreement in the measured incidences of AKI and associated outcomes (hospitalization deaths). We recommend estimating the true burden of severe childhood malaria with acute kidney injury in Nigeria using bSCr back-calculated from Pottel's formula instead of Schwartz's formula.

Abbreviations

AKI	Acute kidney injury
KDIGO	Kidney Disease Improving Global Outcomes
bSCr	Baseline serum creatinine

Supplementary Information

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Additional file 1: Supplementary Table 1. Details of the mortality-among children with childhood severe malaria.

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Authors' contributions

ORI conceptualized the study, was involved in the study design, data collection, analysis, draft and revision of the manuscript. FMA was involved in the study design, data analysis and interpretation, draft and revision of the manuscript. MAA was involved in the conceptualization, study design, data analysis and interpretation, draft and revision of the manuscript study conception and

design. BM was involved in the study design, data collection, interpretation, draft and revision of the manuscript. BMS was involved in study design, data collection, interpretation, draft and critical appraisal of the manuscript. OTA was involved study design, data analysis and interpretation, draft and critically appraised the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was carried out in accordance with the Helsinki Declaration. The Federal Teaching Hospital Katsina (FTHK) ethical review committee approved this study FMCNHREC.REG.N003/0830425. Being a retrospective study, the Federal Teaching Hospital, Katsina ethical review also waived the informed consent, and the data was anonymized during analysis and handled with absolute confidentiality.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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