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## Renal Data from Asia–Africa

### **Acute Kidney Injury in Pediatric Patients with Malaria: A Prospective Cross-Sectional Study in the Shai-Osudoku District of Ghana**

Richard K. D. Ephraim<sup>1</sup>, Prince Adoba<sup>1</sup>, Samuel A. Sakyi<sup>2</sup>, Josephine Aporeigah<sup>1</sup>, Linda A. Fondjo<sup>2</sup>, Felix A. Botchway<sup>3</sup>, Rebecca P. Storph<sup>1</sup>, Emmanuel Toboh<sup>4</sup>

<sup>1</sup>Department of Medical Laboratory Science, School of Allied Health Sciences, University of Cape Coast, Cape Coast, <sup>2</sup>Department of Molecular Medicine, School Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, <sup>3</sup>Department of Chemical Pathology, School of Basic and Allied Health Sciences, University of Ghana, Legon, <sup>4</sup>Medical Laboratory Unit, Dansoman Polyclinic, Accra, Ghana

**ABSTRACT.** Acute kidney injury (AKI) is a highly fatal complication of malaria. We used the Kidney Disease Improving Global Outcomes (KDIGO) and Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease (pRIFLE) guidelines to assess AKI among children. One hundred children with *Plasmodium falciparum* malaria were recruited from the St. Andrew's Catholic Hospital. Admission and 48-h serum creatinine were estimated. Weight and height of the participants were measured, and AKI status determined with the KDIGO and pRIFLE guidelines. A questionnaire was used to collect the socio-demographic and clinical data of participants. Two percent and 5% of the participants had AKI according to the KDIGO and pRIFLE criteria, respectively. Per the KDIGO guidelines, 1% of the participants had Stage 2 and 1% also had Stage 3 AKI. Four percent had Stage 1 (risk) and 1% had Stage 2 (injury) AKI per the pRIFLE criteria. Participants with AKI were dehydrated, and neither had sepsis or on antibiotics when the KDIGO guideline was used. Participants who had AKI were dehydrated, with 80% having sepsis and 40% on antibiotics when the pRIFLE criteria were used. There was no association between the KDIGO and pRIFLE criteria with respect to AKI status of participants ( $k = -0.029$ ,  $P = 0.743$ ). Two percent and 5% of the study participants had AKI when the KDIGO and pRIFLE guidelines were used respectively. One percent of the participants had Stage 2 and 1% also had Stage 3 AKI per KDIGO; 4% had Stage 1 (risk) and 1% had Stage 2 (injury) AKI per the pRIFLE.

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Correspondence to:

Dr. Richard K. D. Ephraim,  
Department of Medical Laboratory Science,  
School of Allied Health Sciences, University  
of Cape Coast, Cape Coast, Ghana.  
E-mail: [rephraim@ucc.edu.gh](mailto:rephraim@ucc.edu.gh)

### **Introduction**

Malaria is a serious health problem in many parts of the world, especially tropical countries such as Ghana. It has a high morbidity rate and claims many lives in developing countries each year, majority of which are children. In

Ghana, malaria cases account for about 38.1% of all outpatient department attendances and 31.2% of children under five-year admissions in the country.<sup>1</sup>

Acute kidney injury (AKI) in malaria is often caused by *Plasmodium falciparum*. However, other species, such as *Plasmodium vivax* and *Plasmodium knowlesi*, have been reported as causes of AKI.<sup>2,3</sup> Adults from areas of low transmission and older children are more susceptible to develop AKI. The incidence of malarial AKI in Africa is reported to be low due to the high malaria endemicity of the region which confers naturally acquired immunity to inhabitants.<sup>4</sup> The pathogenesis of AKI in patients suffering from malaria is not clearly understood, with potentially many possible mechanisms such as blockage of renal microcirculation due to sequestration of infected erythrocytes, immune-mediated glomerular injury, and volume depletion being implicated.<sup>5,6</sup>

Studies have reported varying incidence rates of AKI in children presenting to the hospital with malaria.<sup>7-9</sup> However, there is a paucity of studies examining the development of AKI among pediatrics with malaria in Ghana. This study used both the Kidney Disease Improving Global Outcomes (KDIGO) and Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease (pRIFLE) criteria to assess the incidence of AKI among children admitted with malaria at the St. Andrew's Catholic Hospital in the Greater Accra Region of Ghana.

## Methods

### *Study setting/design/study population*

This prospective cross-sectional study was conducted from January to April 2018 at the St. Andrew's Catholic Hospital, Kordiabe, in the Shai-Osudoku District of the Greater Accra Region of Ghana. A total of 100 children aged 0–15 years with laboratory-confirmed *P. falciparum* malaria who were admitted to the pediatric ward of the hospital during the period were conveniently recruited into the study.

### *Ethical considerations*

Approval to conduct the study was sought

from the University of Cape Coast Institutional Review Board and the management of St. Andrew's Hospital. Written informed consent for enrollment and publication of research findings was sought from the caretakers of all the study participants. Management of the children that did not consent was not affected, and the participants had the freedom to withdraw from the study.

### *Anthropometry/collection of blood sample*

Height was measured to the nearest 0.1 cm without footwear, with a stadiometer (Lindels, Klippan, Sweden) and weight measured (to the nearest 0.1 kg) with a weighing scale. Blood samples were collected into serum separator gel tubes, allowed to clot, and centrifuged at 2000 ×g for 10 min. The serum obtained was aliquoted, properly labeled, and then stored in the freezer at –80°C until assayed. Demographic and clinical information such as age, sex, anti-malarial administered, hydration status, presence or absence of sepsis, and use of antibiotics were obtained from patient medical records and a questionnaire.

### *Acute kidney injury diagnosis and staging*

AKI status of the participants was determined and staged using the KDIGO guideline (KDIGO, 2012)<sup>4</sup> and pRIFLE criteria.<sup>10</sup> Patients' admission serum creatinine (Cr) was used as the baseline Cr, since previous Cr values of most of the participants were absent. For the pRIFLE criteria, estimated glomerular filtration rate (eGFR) of the participants was calculated using the Schwartz formula.<sup>11</sup>

### *Estimation of serum creatinine*

Serum Cr (SCr) was measured using Biosystems A25 autoanalyzer (Biosystems S.A., Barcelona) based on the Jaffe method (Kinetic).

## Statistical Analysis

Data were entered into a computer and analyzed using IBM SPSS Statistics version 20.0 for Windows (IBM Corp., Armonk, NY, USA). Differences and proportions were tested

by Chi-square tests and Student's *t*-tests for trend or independence as appropriate. Multiple logistic regression analysis was used to determine factors associated with AKI.  $P < 0.05$  was considered statistically significant.

### Results

Table 1 shows the general characteristics of the study participants. The female participants were insignificantly older than the males ( $6.0 \pm 3.1$  vs.  $5.6 \pm 2.8$ ,  $P = 0.579$ ). Most (44%) of the participants were within the age group of five to nine years, with 14% being more than 10 years. Majority of the males were within five to nine years, and most of the females were  $< 5$  years. Most of the participants were dehydrated, with 2% having concurrent sepsis. Admission SCr, eGFR, and urea were insignificantly higher among the males than the females ( $P > 0.05$ ).

Figure 1 illustrates the AKI stages of participants in relation to guideline used. When the KDIGO guideline was used, one (1%) of the participants had Stage 2 and 1% also had

Stage 3 (Figure 2). On the other hand, 4% had stage 1 (risk) and 1% had Stage 2 (injury) AKI when the pRIFLE criteria were used (Figure 3).

Table 2 presents the demographic and biochemical characteristics of study participants in relation to AKI status when the KDIGO guideline was employed. The participants with AKI were insignificantly older than those without AKI. Equal proportion of both males and females had AKI. All the participants who had AKI were dehydrated, and neither had sepsis or on antibiotics. Mean baseline admission Cr was insignificantly higher among participants without AKI than those with AKI. However, baseline eGFR and urea were insignificantly higher among those with AKI than those without AKI ( $P > 0.05$ ).

Table 3 shows the demographic and biochemical characteristics of study participants in relation to AKI stage when the KDIGO guideline was used. The participant with Stage 2 AKI was a male  $> 10$  years, whereas the one with Stage 3 AKI was a female  $< 5$  years. The participant with Stage 2 AKI was given

Table 1. General characteristics of study participants.

Parameter	Total	Male	Female	P
	(N=100)	(N=45)	(N=55)	
Age (years)	5.8±3.00	5.6±2.8	6.0±3.1	0.579
Age group (years)				0.889
<5	42 (42.0)	18 (40.0)	24 (43.6)	
5-9	44 (44.0)	21 (46.7)	23 (41.8)	
10	14 (14.0)	6 (13.3)	8 (14.5)	
Antimalarial				0.385
AL	41 (41.0)	18 (40.0)	23 (41.8)	
Artesunate	9 (9.0)	6 (13.3)	3 (5.5)	
AL/Artesunate	50 (50.0)	21 (46.7)	29 (52.7)	
Dehydration				0.949
Yes	67 (67.0)	30 (66.7)	37 (67.3)	
No	33 (33.0)	15 (33.3)	18 (32.7)	
Sepsis				0.114
Yes	2 (2.0)	2 (4.4)	0 (0.0)	
No	98 (98.0)	43 (95.6)	55 (100.0)	
Antibiotic				0.702
Yes	51 (51.0)	22 (48.9)	29 (52.7)	
No	49 (49.0)	23 (51.1)	26 (47.3)	
Admission creatinine (µmol/L)	56.85±14.44	57.97±15.55	55.93±13.54	0.485
Admission GFR (mL/min/1.72 m <sup>2</sup> )	108.97±115.96	121.41±169.98	98.78±29.58	0.334
Urea (mmol/L)	3.63±1.72	3.87±1.87	3.43±1.58	0.212

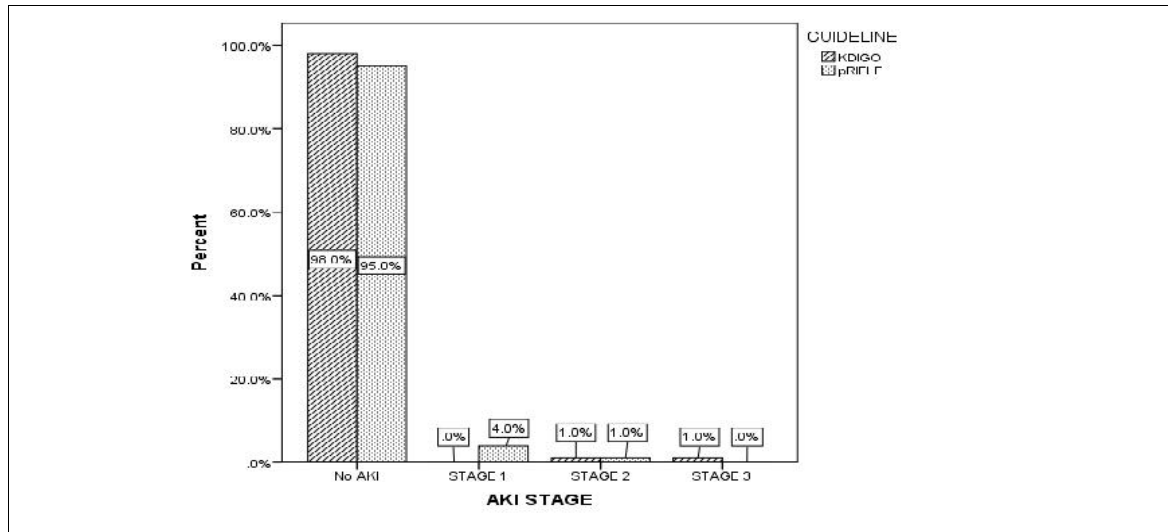


Figure 1. AKI stages of participants in relation to guideline used.

AKI: Acute kidney injury.

artemether-lumefantrine, whereas the one with Stage 3 AKI was given artemether-lumefantrine/artesunate. Mean baseline admission Cr was insignificantly higher among the participant with Stage 3 AKI than the one with Stage 2 AKI. However, baseline eGFR and urea were insignificantly higher among the one with Stage 2 AKI than the one with Stage 3 AKI ( $P > 0.05$ ).

Most of the participants with AKI were within the ages of five to nine years (60%) and

were males (60.0%). All the participants who had AKI were dehydrated, with 80% having sepsis and 40% on antibiotics. Mean baseline admission Cr was significantly higher among participants with AKI than those without AKI. However, baseline eGFR and urea were insignificantly higher among those without AKI than those with AKI ( $P > 0.05$ ) (Table 4).

Table 5 presents the demographic and biochemical characteristics of study participants

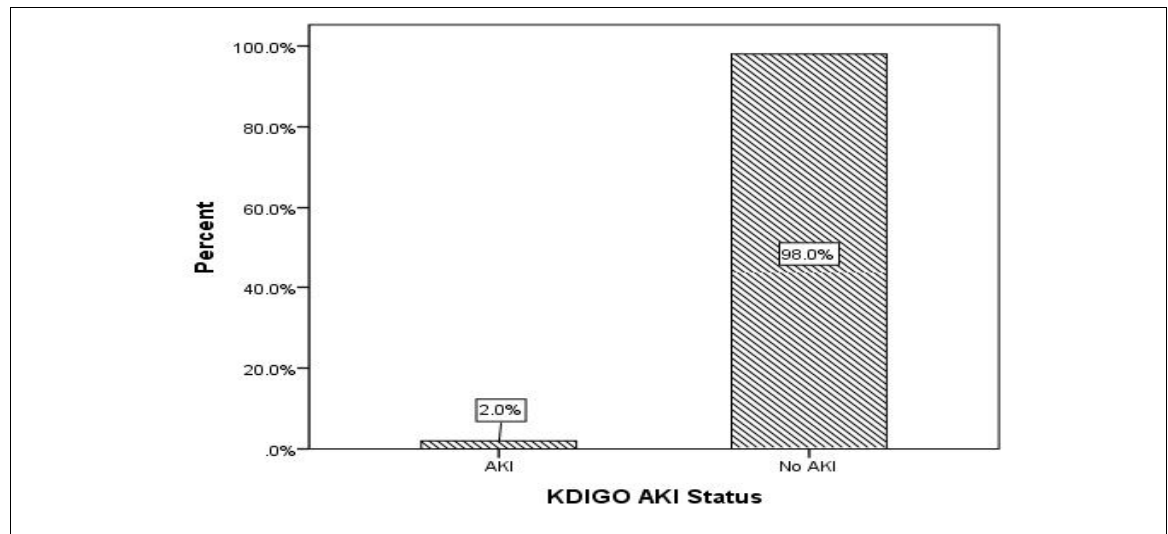


Figure 2. Prevalence of AKI using the KDIGO guideline.

AKI: Acute kidney injury, KDIGOs: Kidney Disease Improving Global Outcomes.

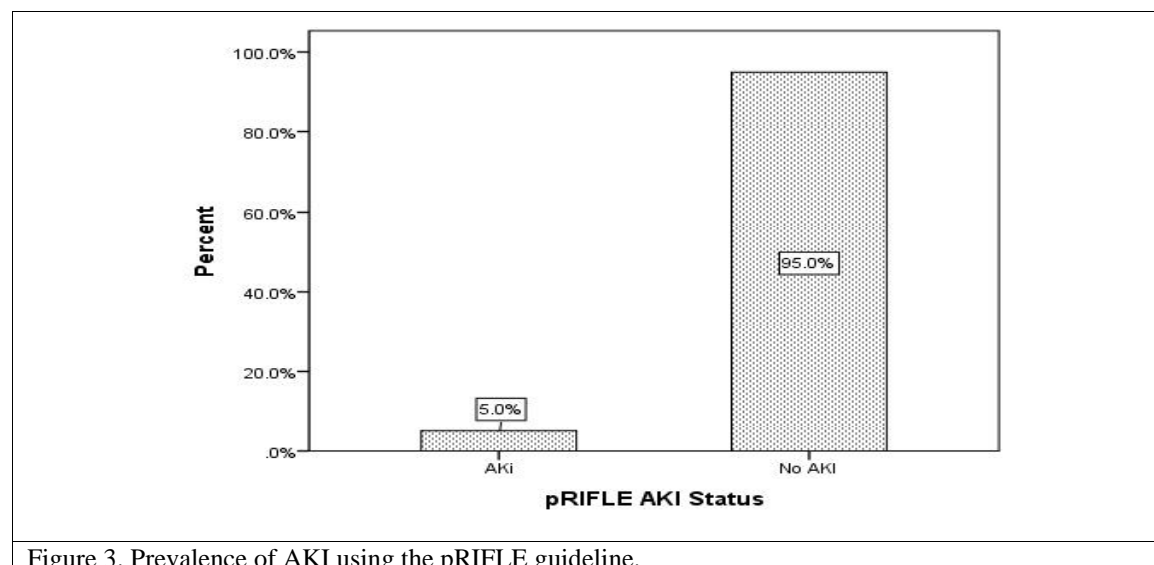


Figure 3. Prevalence of AKI using the pRIFLE guideline.

AKI: Acute kidney injury, pRIFLE: Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease.

Table 2. Demographic and biochemical characteristics of study participants in relation to acute kidney injury status when the Kidney Disease Improving Global Outcomes guideline was used.

Parameter	KDIGO		P
	AKI (n=2)	No AKI (n=98)	
Age (years)	7.0±4.2	5.8±3.0	0.580
Age group (years)			0.244
<5	1 (50.0)	41 (41.8)	
5–9	0 (0.0)	44 (44.9)	
10	1 (50.0)	13 (13.3)	
Gender			0.886
Male	1 (50.0)	44 (44.9)	
Female	1 (50.0)	54 (55.1)	
Antimalarial			0.894
Artemether-lumefantrine	1 (50.0)	40 (40.0)	
Artesunate	0 (0.0)	9 (9.2)	
Artemether-lumefantrine/artesunate	1 (50.0)	49 (50.0)	
Dehydration			0.316
Yes	2 (100.0)	65 (66.3)	
No	0 (0.0)	33 (33.7)	
Sepsis			0.838
Yes	0 (0.0)	2 (2.0)	
No	2 (100.0)	96 (98.0)	
Antibiotic			0.145
Yes	0 (0.0)	51 (52.0)	
No	2 (100.0)	47 (48.0)	
Admission creatinine (µmol/L)	55.8±31.2	56.9±14.2	0.914
Admission GFR (mL/min/1.72 m <sup>2</sup> )	132.25±98.64	108.49±116.67	0.776
Urea (mmol/L)	5.15±0.07	3.60±1.73	0.208

AKI: Acute kidney injury, KDIGOs: Kidney Disease Improving Global Outcomes.

Table 3. Demographic and biochemical characteristics of study participants in relation to acute kidney injury stage when the Kidney Disease Improving Global Outcomes guideline was used.

Parameter	KDIGO		P
	Stage 2 (n=1)	Stage 3 (n=1)	
Age (years)	10.00±0.00	4.0±0.0	0.319
Age group (years)			0.108
<5	0 (0.0)	1 (100.0)	
5–9	0 (0.0)	0 (0.0)	
10	1 (100.0)	0 (0.0)	
Gender			0.360
Male	1 (100.0)	0 (0.0)	
Female	0 (0.0)	1 (100.0)	
Antimalarial			0.655
Artemether-lumefantrine	1 (100.0)	0 (0.0)	
Artesunate	0 (0.0)	0 (0.0)	
Artemether-lumefantrine/artesunate	0 (0.0)	1 (100.0)	
Dehydration			0.605
Yes	1 (100.0)	1 (100.0)	
No	0 (0.0)	0 (0.0)	
Sepsis			0.979
Yes	0 (0.0)	0 (0.0)	
No	1 (100.0)	1 (100.0)	
Antibiotic			0.346
Yes	0 (0.0)	0 (0.0)	
No	1 (100.0)	1 (100.0)	
Admission creatinine (µmol/L)	33.70±0.00	77.80±0.00	0.096
Admission GFR (mL/min/1.72 m <sup>2</sup> )	202.00±0.00	62.50±0.00	0.673
Urea (mmol/L)	5.20±0.00	5.10±0.00	0.455

AKI: Acute kidney injury, KDIGOs: Kidney Disease Improving Global Outcomes.

in relation to AKI stage when the KDIGO guideline was used. Most of the participants with AKI were within the ages of five to nine years (75%), with equal proportions of males and females. All the participants who had risk (R) AKI were dehydrated and were not on antibiotics. The participant with Stage 2 injury (I) AKI was a male <5 years, was dehydrated, septic, and on antibiotic. Mean baseline admission Cr was significantly higher among participants with AKI than those without AKI ( $P = 0.005$ ). However, mean baseline eGFR and urea were insignificantly significantly higher among those with AKI than those without AKI ( $P > 0.05$ ).

Table 6 compares the KDIGO AKI guideline to the pRIFLE criteria among the study participants. None of the participants with AKI according to the KDIGO has AKI based on the pRIFLE criteria. No significant association

was found between the KDIGO and pRIFLE criteria with respect to AKI status of participants ( $k = -0.029$ ,  $P = 0.743$ ).

## Discussion

AKI is a common complication of malaria in adults, both in malaria-endemic countries and in nonendemic regions,<sup>12-14</sup> with a high fatality rate of over 70% in untreated patients.<sup>15</sup> This study used the KDIGO and pRIFLE guidelines to assess AKI among children with *P. falciparum* malaria. AKI was present in 2% and 5% of the study participants when the KDIGO guideline and pRIFLE criteria were used, respectively. All the participants who developed AKI were dehydrated, and no relationship was found between the KDIGO guideline and pRIFLE criteria for the diagnosis of AKI among the participants.

Table 4. Demographic and biochemical characteristics of study participants in relation to acute kidney injury status when the pRIFLE criteria were used.

Parameter	pRIFLE		P
	AKI (n=5)	No AKI (n=95)	
Age	4.8±2.4	5.9±3.0	0.434
Age group			0.592
<5	2 (40.0)	40 (42.1)	
5–9	3 (60.0)	41 (43.2)	
10	0 (0.0)	14 (14.7)	
Gender			0.489
Male	3 (60.0)	42 (44.2)	
Female	2 (40.0)	53 (55.8)	
Antimalarial			0.347
Artemether-lumefantrine	3 (60.0)	38 (40.0)	
Artesunate	1 (20.0)	8 (8.4)	
Artemether-lumefantrine/artesunate	1 (20.0)	49 (51.6)	
Dehydration			0.107
Yes	5 (100.0)	62 (65.3)	
No	0 (0.0)	33 (34.7)	
Sepsis			<b>0.003</b>
Yes	1 (20.0)	1 (1.1)	
No	4 (80.0)	94 (98.9)	
Antibiotic			0.614
Yes	2 (40.0)	49 (51.6)	
No	3 (60.0)	46 (48.4)	
Admission creatinine	77.04±11.20	55.78±13.83	<b>0.001</b>
Admission GFR	62.10±5.13	111.43±118.48	0.356
Urea	2.82±2.54	3.67±1.68	0.284

pRIFLE: Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease, AKI: Acute kidney injury, GFR: Glomerular filtration rate.

The 2% incidence of AKI among the participants when the KDIGO guideline was used is lower than the 3.3% reported in a retrospective study of patients with severe malaria admitted into the children emergency ward of the University of Port Harcourt Teaching Hospital, Nigeria.<sup>7</sup> It is also lower than the 12.4% prevalence observed by Romão,<sup>8</sup> in a study conducted in Luanda, Angola, and the 44.7% found by Thanachartwet et al<sup>9</sup> in a retrospective study conducted in Thailand among malaria patients. The different diagnostic criteria used, geographical area, and populations could have accounted for these differences observed. Furthermore, some studies used patients with severe malaria only or included patients infected with other species of *Plasmodium*, whereas this study used only patients infected with *P. falciparum*.

The 5% incidence when the pRIFLE criteria were used is, however, higher than the 3.3% reported by Okpere et al<sup>7</sup> but lower than the 12.4% prevalence observed by Brandão and Romão.<sup>8</sup> It is again lower than the 44.7% found by Thanachartwet et al<sup>9</sup> in a retrospective study conducted among malaria patients in Thailand. The differences in prevalence rates could also be associated with different diagnostic criteria used, use of patients with severe malaria only, or inclusion of patients infected with other species of *Plasmodium* in the other studies.

No association was found between the KDIGO and pRIFLE criteria with respect to AKI status of participants. None of the participants with AKI according to the KDIGO guideline developed AKI based on the pRIFLE criteria. This indicates an urgent need



Table 5. Demographic and biochemical characteristics of study participants in relation to acute kidney injury stage when the Kidney Disease Improving Global Outcomes guideline was used.

Parameter	pRIFLE		P
	R	I	
	(n=4)	(n=1)	
Age (years)	5.5±2.1	2.0±0.0	0.430
Age group (years)			0.534
<5	1 (25.0)	1 (100.0)	
5-9	3 (75.0)	0 (0.0)	
10	0 (0.0)	0 (0.0)	
Gender			0.526
Male	2 (50.0)	1 (100.0)	
Female	2 (50.0)	0 (0.0)	
Antimalarial			0.251
Artemether-lumefantrine	3 (75.0)	0 (0.0)	
Artesunate	1 (25.0)	0 (0.0)	
Artemether-lumefantrine/artesunate	0 (0.0)	1 (100.0)	
Dehydration			0.274
Yes	4 (100.0)	1 (100.0)	
No	0 (0.0)	0 (0.0)	
Sepsis			<b>0.000</b>
Yes	0 (0.0)	1 (100.0)	
No	4 (100.0)	0 (0.0)	
Antibiotic			0.358
Yes	1 (25.0)	1 (100.0)	
No	3 (75.0)	0 (0.0)	
Admission creatinine (µmol/L)	77.90±12.74	73.60±0.00	<b>0.005</b>
Admission GFR (mL/min/1.72 m <sup>2</sup> )	64.08±3.01	54.20±0.00	0.653
Urea (mmol/L)	2.68±1.34	1.00±0.00	0.281

pRIFLE: Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease, AKI: Acute kidney injury, GFR: Glomerular filtration rate.

for further evaluation of the KDIGO and pRIFLE criteria in the diagnosis of AKI in the pediatric population.

The findings of a study conducted by Conroy et al<sup>16</sup> showed that hypoperfusion/renal ischemia was associated with AKI among a pediatric population with severe malaria. This is supported by the observation of all participants who developed AKI being dehydrated

in our study when both criteria were used. The kidney responds to prerenal conditions by concentrating the urine maximally and re-absorbing sodium in order to maintain or increase intravascular volume and normalize renal perfusion. Prolonged or profound prerenal azotemia results in ischemic damage to the kidney.<sup>17</sup>

The participant with injury (I) AKI when the

Table 6. Comparison of the Kidney Disease Improving Global Outcome acute kidney injury A guideline to the pRIFLE criteria among the study participants.

	pRIFLE		Kappa	P
	AKI	No AKI		
<b>KDIGO</b>			-0.029	0.743
AKI	0 (0.0)	2 (2.1)		
No AKI	5 (100.0)	93 (97.9)		

KDIGOs: Kidney Disease Improving Global Outcomes, AKI: Acute kidney injury, pRIFLE: Pediatric Risk, Injury, Failure, Loss, End-Stage Kidney Disease.

pRIFLE criteria was used was a male <5 years, was dehydrated, septic, and on antibiotic. This could be attributed to the fact that dehydration, sepsis, and nephrotoxic effects of certain antibiotics have been implicated in the pathogenesis of AKI in several previous studies.<sup>17,18</sup> Hence, several risk factors concurrent in this patient might have led to the development of injury (I) in this patient.

The findings of this study show the development of AKI in children infected with *P. falciparum* and that dehydration/renal hypoperfusion might be the major etiological factor. Routine assessment of kidney function of children with malaria is, therefore, necessary in order to curtail any progression of AKI developed into chronic kidney disease. Although the study has strength in it being the first study to assess AKI among children with malaria in Ghana to the best of our knowledge, it is limited by the non-availability of urine out-put and inability to estimate parasite density. Furthermore, the limitations of Cr as a marker of kidney function might have over- or under-estimated the prevalence rate obtained.

### Conclusion

AKI was recorded among 2% and 5% of the study participants when the KDIGO guideline and pRIFLE criteria were used respectively. Renal hypoperfusion as a result of dehydration was the major cause of AKI as all the participants with AKI were dehydrated. No association was found between the KDIGO guideline and pRIFLE criteria in assessing the AKI status of participants. Routine assessment of kidney function of children with malaria is, therefore, necessary for early diagnosis of AKI in pediatrics with malaria, and further evaluation of the KDIGO and pRIFLE criteria in the diagnosis of pediatric AKI is imperative.

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**Conflict of interest:** None declared.

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