Sultan Qaboos University Med J, November 2020, Vol. 20, Iss. 4, pp. e312–317, Epub. 21 Dec 20
Submitted 23 Dec 19
Revision Req. 21 Apr 20; Revision Recd. 4 May 20
Accepted 3 Jun 20
https://doi.org/10.18295/squmj.2020.20.04.006

CLINICAL & BASIC RESEARCH

Acute Kidney Injuries in Children with Severe Malaria

A comparative study of diagnostic criteria based on serum cystatin C and creatinine levels

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إصابات الكلى الحادة عند الأطفال المصابين بملاريا حادة

دراسة مقارنة للمعايير التشخيصية المبنية على قياس تركيزي السيستاتين سي والكرياتنين في مصل الدم

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ABSTRACT: ***Objectives:*** Serum creatinine levels are often used to diagnose acute kidney injury (AKI), but may not necessarily accurately reflect changes in glomerular filtration rate (GFR). This study aimed to compare the prevalence of AKI in children with severe malaria using diagnostic criteria based on creatinine values in contrast to cystatin C. ***Methods:*** This prospective cross-sectional study was performed between June 2016 and May 2017 at the University of Ilorin Teaching Hospital, Ilorin, Nigeria. A total of 170 children aged 0.5–14 years old with severe malaria were included. Serum cystatin C levels were determined using a particle-enhanced immunoturbidmetric assay method, while creatinine levels were measured using the Jaffe reaction. Renal function assessed using cystatin C-derived estimated GFR (eGFR) was compared to that measured using three sets of criteria based on creatinine values including the Kidney Disease: Improved Global Outcomes (KDIGO) and World Health Organization (WHO) criteria as well as an absolute creatinine cut-off value of >1.5 mg/dL. ***Results:*** Mean serum cystatin C and creatinine levels were 1.77 ± 1.37 mg/L and 1.23 ± 1.80 mg/dL, respectively (P = 0.002). According to the KDIGO, WHO and absolute creatinine criteria, the frequency of AKI was 32.4%, 7.6% and 16.5%, respectively. In contrast, the incidence of AKI based on cystatin C-derived eGFR was 51.8%. Overall, the rate of detection of AKI was significantly higher using cystatin C compared to the KDIGO, WHO and absolute creatinine criteria (P = 0.003, <0.001 and <0.001, respectively). ***Conclusion:*** Diagnostic criteria for AKI based on creatinine values may not indicate the actual burden of disease in children with severe malaria.

Keywords: Biomarkers; Acute Kidney Injury; Renal Failure; Glomerular Filtration Rate; Cystatin C; Creatinine; Malaria; Nigeria.

الملخص: الهدف: كثيرا ما تستخدم مستويات كرياتنين لتشخيص إصابة الكلى الحادة. غير أن ذلك لا يعكس بالضرورة التغييرات في معدل التصفية الكبيبي. تهدف هذه الدراسة لمقارنة مدى انتشار إصابات الكلى الحادة عند الأطفال المصابين بملاريا حادة باستخدام معايير تشخيصية تعتمد على قيم كرياتنين في مقابل قيم سيستاتين سي. **الطريقة:** هذه دراسة استباقية ومقطعية-عرضية أجريت بين يونيو 2106م ومايو 2017م بمستشفى جامعة إلورين، في مدينة إلورين بنيجريا. شملت الدراسة 170 طفلا مصابين بملاريا حادة. وتم قياس تركيز سيستاتين سي عن طريق مقايسة مناعية عكرة معززة بالجسيمات، وتم قياس تركيز كرياتنين عن طريق تفاعل جافي. وتمت مقارنة وظائف الكلى التي أجريت عن طريق تقدير معدل التصفية الكبيبي المستمد من سيستاتين سي بتلك التي قيست بثلاث معايير تعتمد على تركيز كرياتنين، إضافة إلى ''أمراض الكلى: تحسين النتائج العالمية''، ومعايير منظمة الصحة العالمية، والقيم الحدية المطلقة للكرياتنين (أكثر من 5.1 مجم /100 مل). **النتائج:** كان متوسط تركيزي سيستاتن سي وكرياتنين هما 1.37 ± 1.77 مجم/لتر، و1.80 ± 1.23 مجم /100 مل، على التوالي (P = 0.002). وبحسب معياري ''أمراض الكلى: تحسين النتائج العالمية'' و''منظمة الصحة العالمية'' والقيم الحدية المطلقة للكرياتنين، بلغ معدل تواتر (تكرار) إصابة الكلي الحادة 32.4% و7.6% و16.5%، على التوالي. وفي المقابل، كان معدل وقوع إصابة الكلي الحادة المعتمد على تقدير معدل التصفية الكبيبي المستمد من سيستاتين سي يساوي 51.8%. وعلى وجه العموم كان معدل اكتشاف حالات إصابة الكلي الحادة عن طريق سيستاتين سي أعلى بصورة يعتد بها إحصائيا من تلك الطرق المعتمدة على ''أمراض الكلى: تحسين النتائج العالمية''، ومعايير منظمة الصحة العالمية، والقيم الحدية المطلقة للكرياتنين (<0.001 and <0.001، P = 0.003) على التوالي. **الخلاصة:** قد لا تكشف المعايير التشخيصية لمرض إصابة الكلي الحادة عن طريق قياس قيم كرياتنين عن العبء الحقيقي للمرض عند الأطفال المصابين بالملاريا الحادة.

الكلمات المفتاحية: المؤشرات الحيوية؛ إصابة الكلي الحادة؛ القصور الكلوي؛ معدل التصفية الكبيبي؛ سيستاتن سي؛ الملاريا؛ نيجيريا.

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Advances in Knowledge

- *Serum creatinine is the most widely used method of estimating glomerular filtration rate (GFR) for the diagnosis of renal injuries. However, creatinine is affected by extrarenal factors and may not accurately indicate a decline in renal function. Hence, there is a need for a more reliable endogenous marker of changes in GFR.*
- *This study confirmed that serum creatinine-based diagnostic criteria underestimated the actual burden of acute kidney injury (AKI) in a cohort children with severe malaria.*
- *In contrast, cystatin C-derived estimated GFR resulted in a significantly increased detection rate of AKI in children with severe malaria compared to traditional diagnostic criteria based on creatinine values.*

Application to Patient Care

- *The early recognition of AKI in children allows for more rapid intervention, potentially halting the progression of renal injury and improving patient outcomes. Healthcare practitioners should therefore be aware that the use of creatinine-based diagnostic criteria may under-represent the actual prevalence of AKI in severe paediatric malaria.*

Acute kidney injury (AKI) is a well-recognised complication of severe malaria in adults; however, its incidence in paediatric patients is not commonly reported, presumably as a result of under-diagnosis.[1,2] According to criteria outlined by the World Health Organization (WHO), a diagnosis of malarial AKI should be made based on the measurement of serum creatinine values, either with a single-point value of 3 mg/dL (265 mmol/L) or a blood urea level of >20 mmol/L.[3] Different creatinine cut-off values have also been proposed for use in children with malaria.[4,5] In turn, the Kidney Disease: Improving Global Outcomes (KDIGO) criteria diagnoses malarial AKI according to an acute rise in serum creatinine from baseline, or a percentage rise in its level, thus enabling identification of a minor acute reduction in kidney function which may not be clinically apparent, rather than just relying on a single creatinine value[6–9] Nevertheless, although both the WHO and KDIGO diagnostic criteria for AKI rely heavily upon its use, serum creatinine is an unreliable marker of AKI because of its delayed rise following a decrease in glomerular filtration rate (GFR).[8–10] As a result, more reliable endogenous markers of GFR changes are necessary to accurately detect cases of malarial AKI.

Serum cystatin C is one such candidate which has demonstrated promising applicability in clinical practice.[11] Cystatin C is a non-glycosylated low-molecular-weight 13-kD basic protein that is freely filtered by the renal *glomeruli*, catabolised in the tubules and is not secreted or reabsorbed as an intact molecule.[12,13] Moreover, unlike creatinine, serum cystatin C concentration is independent of age, gender, inflammatory process, muscle mass and protein intake.[12,13] However, few studies have sought to assess the utility of cystatin C in malaria and, of these, most focus exclusively on adult populations.[14–16] Hence, this study aimed to determine and compare the incidence of AKI in children with severe malaria by assessing estimated GFR (eGFR) using serum cystatin C in contrast to traditional creatinine-based criteria.

Methods

This prospective cross-sectional analytical study was conducted between June 2016 and May 2017 at the paediatric emergency unit of the University of Ilorin Teaching Hospital in Ilorin, the capital of Kwara State, Nigeria. This hospital is a tertiary health facility with a 650-bed capacity and is located in a region with a high transmission of malaria year-round.[17,18] A total of 170 children between six months and 14 years of age with clinical and/or laboratory features of severe malaria were included. In each case, the child's medical history was obtained from the caregiver and a physical examination was conducted to confirm the presence of clinical features of severe malaria. Children with chronic illnesses including HIV infection, chronic renal failure, sickle cell disease and diabetes mellitus were excluded from the study, as were children with severe malnutrition or those currently taking steroids.

Features of severe malaria were defined according to the WHO criteria as follows: (1) impaired consciousness (Glasgow coma scale score of 11 or Blantyre coma scale of 3); (2) prostration (inability to sit upright in a patient that could normally do so); (3) multiple convulsions (>2 episodes over 24 hours); (4) circulatory shock (systolic blood pressure of <70 and <50 mmHg in older children and infants, respectively); (5) hypoglycaemia (blood sugar levels of <40 mg/dL); (6) severe anaemia (haematocrit of <15% or haemoglobin levels of <5 g/dL); spontaneous bleeding or evidence of disseminated intravascular coagulation; and (7) haemoglobinuria (passage of dark-colored urine).[3] In terms of treatment, all children received a minimum of three doses of intravenous artesunate, followed by artemisinin combination therapy when they were fully conscious and able to tolerate oral medications. Other complications, including severe

anaemia, multiple convulsions, hypoglycaemia and respiratory distress, were managed according to the standard protocols of the department.

At admission, each child underwent a pinprick test using a rapid malaria diagnostic test (RDT) strip for the detection of histidine-rich protein 2 (SD BIOLINE Malaria Ag P.f/Pv test, Abbott Laboratories, Chicago, Illinois, USA). Subsequently, venous blood samples were obtained aseptically from all patients with positive RDT results and collected in a vacutainer containing ethylenediaminetetraacetic acid anticoagulant. A thick peripheral blood smear was prepared, stained with Giemsa and examined under light microscopy at a minimum of 100 high-power fields. Malaria was diagnosed based on the presence of *Plasmodium* parasites on the thick film. The remaining blood was then aliquoted into a plain bottle and allowed to clot. The clotted blood sample was centrifuged at 3,000 rpm using a bench-top centrifuge in order to obtain serum samples. The *sera* were then aliquoted into another plain bottle and kept frozen at –20°C for batch analysis of serum cystatin C and creatinine.

Serum creatinine levels were determined according to a modified Jaffe reaction using alkaline picric acid. Levels of cystatin C were measured using an automated latex-enhanced immunoturbidimetric method (Latex Cystatin C Assay, Biobase Group, Jinan, Shandong, China). Thereafter, GFR was estimated using the original Schwartz formula as k × L/serum creatinine in mg/dL, where k was an empirical constant with a value of 0.45 in children aged 0.5–1 year, 0.55 in children aged 1–10 years and adolescent girls and 0.7 in adolescent boys. Based on the turbidimetric assay, the cystatin C-derived eGFR in mL/minute/1.73 m^2 was determined for children aged ≤14 years using the following equation:[19]

$$eGFR = 84.69 \times \text{cystatin } C^{-1.68} \times 1.384 \quad \text{[Equation 1]}$$

The incidence of AKI was then assessed according to four different criteria: (1) creatinine-based KDIGO criteria; (2) creatinine-based WHO criteria; (3) an absolute creatinine cut-off value of >1.5 mg/dL; and (4) cystatin C-derived eGFR.[3,6] Due to the lack of availability of baseline serum creatinine levels for the children, baseline levels of serum creatinine for the KDIGO criteria were backcalculated using the Schwartz formula, assuming an estimated creatinine clearance equal to 120 mL/minute/1.73m^2 ($eCCl_{120}$). The use of $eCCl_{120}$ to define normal baseline renal function has been shown to be closely reflect actual baseline renal function with little bias.[20] The incidence of AKI was then determined based on the percentage increase in creatinine from baseline, with children who had undergone renal replacement therapy included in stage 3.[6]

The statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS), Version 21.0 (IBM Corp., Armonk, New York, USA). Age and serum cystatin C and creatinine levels were presented as means and standard deviations, while categorical variables were presented as proportions and frequencies. Prior to the use of a student's t-test for analysis, both serum cystatin C and creatinine were log-transformed to ensure a normal distribution of data. A Chi-squared test was used to assess differences between categorical variables while odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the strength of any associations. A *P* value of <0.050 was considered statistically significant.

Ethical approval for this study was obtained from the Human Ethical Review Committee of the University of Ilorin Teaching Hospital (ERC PAN/2016/04/1523). The parents or caregivers of the children provided informed consent on their behalf.

Results

A total of 170 children were included in the study, of which 102 (60%) were male. Moreover, 92 (54.1%) were under the age of five, with a mean age of 4.72

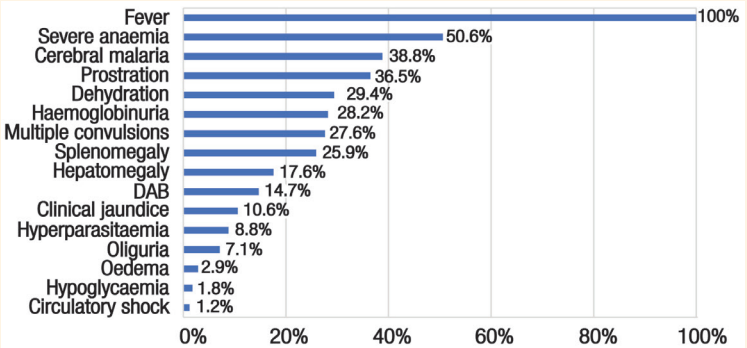

Figure 1: Clinical and laboratory features of children with severe malaria (N = 170).
DAB = deep acidotic breathing.

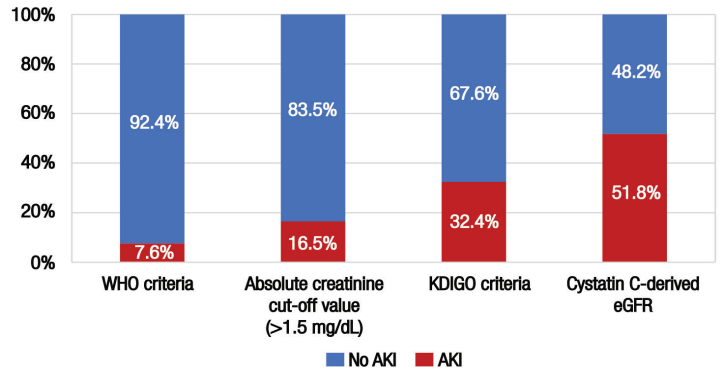

Figure 2: Incidence of acute kidney injury using diagnostic criteria based on cystatin C versus creatinine values in children with severe malaria (N = 170).

AKI = acute kidney injury; WHO = World Health Organization; KDIGO = Kidney Disease: Improved Global Outcomes; eGFR = estimated glomerular filtration rate.

Table 1: Comparison of incidence of acute kidney injury using diagnostic criteria based on cystatin C versus creatinine values in children with severe malaria (N = 170)

Category A	Category B	Incidence of AKI, n (%)		χ^2	*P* value	OR (95% CI)
		Category A	Category B			
Cystatin C-derived eGFR	KDIGO criteria	88 (51.8)	55 (32.4)	13.14	0.003*	2.2 (1.445–3.485)
Cystatin C-derived eGFR	WHO criteria	88 (51.8)	13 (7.6)	79.23	<0.001*	13.0 (6.829–24.560)
Cystatin C-derived eGFR	Absolute creatinine cut-off value (>1.5 mg/dL)	88 (51.8)	28 (16.5)	47.11	<0.001*	5.4 (3.286–9.016)

*AKI = acute kidney injury; OR = odds ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease Improved Global Outcome; WHO = World Health Organization. *Significant at P <0.050.*

± 0.25 years. The majority (80%) had multiple clinical and laboratory features of severe malaria, with fever (100%), severe anaemia (50.6%), cerebral malaria (38.8%) and prostration (36.5%) being most common. The least common features were circulatory shock (1.2%), hypoglycaemia (1.8%), oedema (2.9%) and oliguria (7.1%) [Figure 1]. The mean temperature was 38.58 ± 1.05°C, while mean systolic and diastolic blood pressure was 89.64 ± 10.73 mmHg and 52.20 ± 11.16 mmHg, respectively.

The mean serum cystatin C level was 1.77 ± 1.37 mg/L, while the mean creatinine level was 1.23 ± 1.80 mg/dL (t = –3.113; *P* = 0.002). Based on cystatin C-derived eGFR, AKI was present in 88 children (51.8%). In contrast, AKI was detected in 55 (32.4%), 28 (16.5%) and 13 (7.6%) patients according to the KDIGO criteria, absolute creatinine cut-off value and WHO criteria, respectively [Figure 2]. Overall, the use of cystatin C as a biomarker of eGFR resulted in a significant increase in the detection of AKI cases compred to the KDIGO criteria (OR: 2.2, 95% CI: 1.445–3.485). Similarly, cystatin C detected a significantly greater number of AKI cases compared to both the absolute creatinine cut-off value (OR: 5.4, 95% CI: 3.286–9.016) and the WHO criteria (OR: 13.0, 95% CI: 6.829–24.560) [Table 1].

Table 2: Comparison of estimated glomerular filtration rate using cystatin C versus creatinine values in children with severe malaria (N = 170)

Variable	Mean eGFR ± SD in mL/minute/1.73 m^2		t value	*P* value
	Cystatin C-derived rate	Creatinine-derived rate		
Age in years				
0.5–4.9 (n = 92)	83.68 ± 41.30	89.60 ± 46.70	0.956	0.956
5–9.9 (n = 63)	84.26 ± 40.89	91.06 ± 44.79	0.910	0.366
10–14 (n = 15)	89.87 ± 42.17	124.79 ± 34.79	2.533	0.024*
Gender				
Male (n = 102)	82.21 ± 40.88	95.47 ± 44.57	2.237	0.027*
Female (n = 68)	86.29 ±41.42	84.58 ± 61.14	0.034	0.973
Total	80.42 ± 41.01	96.23 ± 45.91	1.943	0.045*

*SD = standard deviation; eGFR = estimated glomerular filtration rate. *Significant at P <0.050.*

In addition, the mean eGFR using cystatin C was significantly lower compared to the mean eGFR calculated using serum creatinine values (80.42 ± 41.01 versus 96.23 ± 45.91 mL/minute/1.73m^2; *P* = 0.045).

When stratifying by age group, both methods of deriving eGFRs were comparable, except in adolescents wherein eGFR values derived using cystatin C were significantly lower than those calculated using serum creatinine values (89.87 ± 42.17 versus 124.79 ± 34.79 ml/minute/1.73 m^2; $P = 0.024$). Based on gender, eGFRs calculated using both methods were comparable for females; however, cystatin C-derived eGFRs were lower than those calculated using creatinine values for males (82.21 ± 40.88 versus 95.47 ± 44.57 ml/minute/1.73 m^2; $P = 0.027$) [Table 2].

Discussion

This study revealed that the assessment of renal function using cystatin C-derived eGFR resulted in the significantly higher detection of AKI among children with severe malaria compared with traditional creatinine-based criteria.[3,6] Overall, cystatin C-derived eGFR indicated that AKI was present in 88 children (51.8%). Previous research has revealed similar rates of AKI detection using cystatin C values (54.6–62.5%).[14,15] However, Burchard *et al*. reported a lower incidence of 17%; this may be because the study was conducted among children in Ghana with uncomplicated and less severe forms of malaria.[16] In contrast, the current study focused on children with severe forms of malaria who were more likely to have multiorgan dysfunction, including kidney involvement.

In comparison with traditional creatinine-based criteria, the higher incidence of AKI obtained from cystatin C values likely reflects the fact that the latter biomarker can indicate subclinical derangement in renal function much earlier compared to the former. This is because the level of serum cystatin C is mainly determined by GFR.[21,22] Therefore, any increase in serum cystatin C is identified by a GFR decrease, indicating a preclinical state of kidney dysfunction which is otherwise undetected when assessing levels of serum creatinine or measuring creatinine-derived GFR.[23] Hence, an acute change in serum cystatin C levels from baseline may be a true reflection of renal impairment, in contrast to changes in creatinine. Indeed, a recent systematic and meta-analysis revealed that serum cystatin C has a higher prognostic value for predicting AKI in children compared to other methods.[24] Moreover, a previous study of children with severe malaria found that admission levels of cystatin C were a predictor of early mortality.[1]

In the current study, the incidence of AKI according to the KDIGO criteria was 32.4%; in contrast, previous researchers have reported higher incidence rates using the same method (45.5–55.8%).[1,14] This difference could be because one study was conducted among a large population of adults with severe malaria, while the other focused on 180 children randomised to inhale nitric oxide, a substance which increases the risk of developing AKI in critically ill individuals.[1,14,25] In addition, the present study found that the incidence of AKI was higher when applying the KDIGO criteria compared to rates detected using the WHO criteria or an absolute creatinine cut-off value of >1.5 mg/dL. Other studies assessing the prevalence of malarial AKI using a single creatinine value (0.7–3 mg/dL) revealed similar findings when compared to the KDIGO criteria.[5,26,27] However, there is a possible drawback to the use of the KDIGO criteria in that they rely on a change in serum creatinine levels as a marker of renal filtration, which may not adequately reflect a change in GFR as serum creatinine does not rise until there is a 50% decline in GFR.[11]

The present study also reported a significantly higher mean eGFR value obtained from creatinine compared to the eGFR derived from cystatin. This could be due to an overestimation of GFR within the Schwartz equation.[28] However, it is more likely that the lower eGFR values obtained using cystatin more accurately reflect changes in GFR, while creatinine levels lag behind, thereby accounting for the higher mean eGFR value. Hence, careful interpretation of eGFR values obtained using creatinine-based formulae is necessary in children with severe malaria.

Conclusion

This study showed that the detection of AKI was significantly higher using serum cystatin C-derived eGFR compared to traditional creatinine-based criteria, including the KDIGO and WHO criteria as well as an absolute creatinine cut-off value of >1.5 mg/dL. As such, healthcare practitioners should be aware that the assessment of renal function using serum creatinine-based formulae may not accurately indicate the actual burden of AKI in children with severe malaria.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

No funding was received for this study.

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