Diagnosis of Acute Kidney Injury in Children Hospitalized in a Sub-Saharan African Unit by Saliva Urea Nitrogen Dipstick Test

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Keywords

Acute kidney injury · Blood urea nitrogen · Developing countries · Diagnostic tools · Saliva urea nitrogen · Saliva dipstick

Abstract

Introduction: Acute kidney injury in pediatric patients (pAKI) is common in developing countries and leads to significant morbidity and mortality. Most nephrology services in developing countries are only in larger cities and for that reason many cases remain undiagnosed. We evaluated the performance of a saliva urea nitrogen (SUN) dipstick to diagnose pAKI in Sudan. **Methods:** We collected demographic and clinical information, serum creatinine (SCr), blood urea nitrogen (BUN), SUN, and urine output (UO) in children with pAKI. pAKI was diagnosed based on different criteria (Risk, Injury,

Failure, Loss of kidney function, and end-stage kidney disease, Acute Kidney Injury Network and Kidney Disease Improving Global Outcomes). We also recorded hospital and 3-months' mortality and progression to chronic kidney disease (CKD) as outcomes. **Results:** We studied 81 patients (mean age 10.7 ± 7 years, 51.9% females) and divided them by age into (a) neonates (<120 days; $n = 21$; 25.9%); (b) infants (120–365 days; $n = 18$; 25.9%); and (c) children (>365 days; $n = 42$; 53.1%). Diagnosis using different pAKI definitions resulted in differences in AKI staging. SUN reliably reflected BUN over the entire study period, regardless of treatment modality or pAKI severity. Neither pAKI staging, SUN, BUN, nor SCr were associated with mortality or progression to CKD. UO predicted all-cause mortality during the 3-months follow-up. **Conclusion:** Diagnosis of pAKI using different criteria differs in triage and staging. SUN reflects BUN particularly at higher BUN levels and allows monitoring of treat-

ment responses. Despite the lack of predictive power of SUN to predict hard outcomes, measurement of SUN by dipstick can be used to identify, screen, and monitor pediatric patients with pAKI.

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Introduction

The term acute kidney injury (AKI) includes all manifestations of renal impairments ranging from minor changes in biochemical markers of renal function to immediate requirement of renal replacement therapy (RRT) [1]. The considerably high incidence of AKI in developing countries and the substantial risk of consequent mortality represent a significant burden to public health particularly in resource-limited countries. Epidemiology, causes, and incidence of AKI in the adult population differ between developed and developing countries, where community-acquired AKI prevails [2–6].

Consistent in both adult and pediatric population, AKI (pAKI for pediatric patients) in developing countries is mainly caused by infective illness and renal hypoperfusion instead of primary congenital kidney diseases, which predominate in children in developed countries [2, 7–9]. Generally, in developed countries comorbid older patients are affected by multifactorial AKI, while in contrast in developing countries otherwise healthy children and young adults are affected by it due to a single, often treatable and preventable cause, including bacterial, viral, and parasitic infectious diseases, volume depletion due to severe diarrhea, pregnancy-related events, or animal envenomation [5]. Therefore, AKI epidemiology, risk factors, incidence, and outcome need to be considered on an individual level for each country.

Sudan is the third largest African country and the seventeenth largest in the world and AKI is considered an important cause of morbidity and mortality (13th most often reported cause of death). The country has a total population of 37,345,935, notably with 40.5% of the total population being under 15 years old [10]. Furthermore two-thirds of the population lives in rural areas with poor infrastructure and limited access to clean water and health care facilities [11]. Consistent with data from the International Society of Nephrology (ISN) Snapshot study, infectious diseases such as malaria, sepsis, diarrheal diseases, and respiratory tract infections are common causes of AKI in Sudan [11, 12]. Around 50% of nephrology services are located in Khartoum state, whereas the other

half is scattered in big cities and is inaccessible to a majority of patients. Those that require dialysis must travel long distances in order to be able to reach dialysis centers, which results in additional costs for transportation and accommodation related to accessing care. In contrast to most African countries where RRT is private and needs to be fully paid out of pocket [13], Sudan provides RRT (hemodialysis and PD) free at the point of delivery for all patients. Intermittent peritoneal dialysis, continuous ambulatory peritoneal dialysis, kidney transplantation, and immunosuppressive medications are also funded by the government.

In most developing countries, a divergent distribution of health care resources relative to the population is present. While the majority of population lives in rural areas, health facilities are mainly located in urban areas, complicating the diagnosis and timely treatment of kidney disease. While most secondary and tertiary hospitals have the laboratory equipment necessary to measure indicators of kidney function, on the primary healthcare level, physical exam and history taking are often the only diagnostic means [14]. Point of care (POC) devices providing the required diagnostic accuracy to diagnose AKI early, may solve the problem, but their widespread use is limited due to high costs, and often their dependence on refrigerated storage of reagents [14]. A low-cost alternative are salivary urea nitrogen (SUN) dipsticks, which have been proposed as a simple noninvasive, non-expensive POC tool to detect kidney injury. In our previous SUN studies, this simple test demonstrated good diagnostic performance to detect chronic kidney disease (CKD) and AKI, including obstetric-related AKI, in both developed and developing settings [15–19] (Table 1).

In this study, we aimed (a) to describe the demographics and clinical characteristics of a pAKI population in Sudan including a comparison of diagnosis of pAKI severity using different criteria, (b) to evaluate the agreement between SUN and blood urea nitrogen (BUN) at presentation and during AKI management, and (c) to investigate the diagnostic performance of SUN vis-à-vis BUN and serum creatinine (SCr) to (1) discriminate AKI at stage “failure” as per the pediatric Risk, Injury, Failure, Loss of kidney function, and end-stage kidney disease (pRIFLE) urine output (UO) criteria from less severe stages, (2) determine the risk to develop CKD in a population, and (3) determine the risk of mortality. As an ancillary analysis, we also aimed to analyze the association between the distance of the patient from the hospital and outcomes.

Table 1. Overview of currently published journal articles on the use of SUN dipsticks

Study	Period of study	Country	Type of study	Population	Study size	No of SUN measurements	Outcome	Sensitivity	Specificity	AUC ROC (95% CI)
Raimann et al. [19], 2011	2006	Austria and USA		CKD Stages 1–5D	68 patients	120	SUN dipstick is a reliable method to detect abnormal BUN levels in CKD patients	0.77	0.85	0.85 (0.85–0.95)
Calice-Silva et al. [15], 2014	February to May 2013	Brazil	Cross sectional	AKI	44 patients		SUN dipsticks allow the discrimination of different AKI stages	0.91	0.79	0.91 (0.80–1.0)
Raimann et al. [18], 2016	2015	Brazil and USA	International multicenter-prospective	AKI	37 patients	120	SUN reflects BUN especially in severe AKI and allows monitoring treatment responses			0.81 (0.63–0.98)
Evans et al. [17], 2016	April to July 2015	Malawi	prospective observational study	AKI and CKD	742 patients	986	Agreement between BUN and SUN dipsticks at different levels of BUN and can be used for monitoring of renal function	0.72	0.87 (0.97 when SUN combined with UO)	0.82 (0.59–1.0)
Evans et al. [16], 2017	September to December 2015	Malawi	prospective observational study	Women who were >20 weeks gestation or <6 weeks post-partum at risk of obstetric AKI	301 obstetric patients	301	SUN dipstick was specific but insensitive in obstetric patients most likely due to physiological changes in pregnancy	0.12	0.97	0.55
Current study	March 2015 to December 2016	Sudan		AKI	81 patients	465				

BUN, blood urea nitrogen; SUN, saliva urea nitrogen; CKD, chronic kidney disease; AKI, acute kidney injury; AUC ROC, area under the receiver operator curve.

Methods

Study Design, Setting, and Participants

All pAKI patients admitted between March 2015 and December 2016 to the pediatric nephrology unit at Soba University Hospital (SUH), Sudan, were approached and invited to participate in this study. Patients with CKD or renal transplantation were excluded. Patients who were discharged within 3 days of hospitalization were excluded, as were those from whom informed consent was not obtained.

Patients were classified into 3 groups by age: (1) neonates (28 days or less), (2) infants (29–365 days), and (3) toddlers and older children (1–18 years).

The study protocol was approved by the Ethics Committee at SUH and conducted according to the Declaration of Helsinki. Subjects (or their parents or guardians) have given written informed consent to participation. Only de-identified data as per US law were used for analysis in compliance with local and US regulations.

Measurements

Age, gender, length of hospital stay, biochemical markers, comorbidities, medications, in-hospital death, and outcomes were retrieved from SUH medical records. Urine was collected using indwelling urinary Foley catheters throughout the study periods. UO

rate was standardized by body weight and reported in mL/kg/h. BUN (mg/dL) and sCr (mg/dL) were measured daily in the SUH laboratory. Estimated GFR was calculated using the bedside Schwartz formula [20].

For the primary analysis, AKI severity was determined using the pRIFLE UO classification. In addition, we applied other diagnostic systems (Table 2), namely, the pRIFLE; the Acute Kidney Injury Network (AKIN) and the Kidney Disease Improving Global Outcomes (KDIGO) classifications. As opposed to the other criteria that define severity as stage 1–3, the pRIFLE criteria subdivide AKI into 3 severity stages (risk, injury, and failure). For simplicity in interpretation we labeled Risk, Injury and Failure categories to stages 1, 2, and 3.

We explored the following outcomes: (1) renal function recovery; (2) development of CKD (as per KDIGO criteria); (3) need for permanent RRT; (4) loss to follow-up or death. These outcomes were recorded during hospitalization and up to 3 months after discharge.

SUN Measurements

Unstimulated saliva was collected concurrent with blood. Patients were asked to refrain from drinking and eating for at least 15 min prior to saliva collection. Older children collected saliva in a plastic cup, while in neonates and younger children we used swabs. The colorimetric SUN dipstick (Integrated Biomedical

Table 2. Different published classifications for the diagnosis of AKI in pediatric patients

pRIFLE			AKIN		KDIGO		Neonatal KDIGO		Neonatal RIFLE	
category	eGFR	UO	eGFR	UO	eGFR	UO	eGFR	UO	eGFR	UO
Stage 0	–	–	–	–	–	–	No change in SCr or rise <0.3mg/dL	>1 mL/kg/h	–	–
Stage 1	Decreased by 25%	<0.5 mL/kg/h for 8 h	Increase in creatinine of ≥50% or Absolute increase in creatinine of 0.3 mg/dL	<0.5 mL/kg/h for >6 h	Increase in creatinine of ≥50% or Absolute increase in creatinine of 0.3 mg/dL	<0.5 mL/kg/h for >6 h	SCr rise ≥0.3 mg/dL within 48 h or SCr rise ≥1.5–1.9 x *reference SCr within 7	<0.5 mL/kg/h for 6–12 h	–	<1.5 mL/kg/h for 24 h
Stage 2	Decreased by 50%	<0.5 mL/kg/h for 16 h	Increase in creatinine of ≥100%	<0.5 mL/kg/h for >12 h	Increase in creatinine of ≥100%	<0.5 mL/kg/h for >12 h	SCr rise ≥2.0–2.9 x *reference SCr	<0.5 mL/kg/h for ≥12 h	–	<1.0 mL/kg/h for 24 h
Stage 3	Decreased by 75% or <35 mL/min per 1.73 m ²	<0.3 mL/kg/h for 24 h or anuric for 12 h	Increase in creatinine of ≥200%	<0.3mL/kg/hr for 24 h, or anuria for 12 h	Increase in creatinine of ≥200% or Need for RRT or decrease in eGFR to ≤35 mL/min per 1.73 m ²	<0.3 mL/kg/h for ≥24 h or Anuria for ≥12 h	SCr rise ≥3 x *reference SCr or **SCr ≥2.5 mg/dL or Need for RRT	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h	–	<0.7 mL/kg/h for 24 h or anuric for 12 h

eGFR was estimated using the Schwartz method.

* Reference SCr will be defined as the lowest previous SCr value.

** SCr value of 2.5 mg/dL represents <10 mL/min/1.73 m².

pRIFLE, pediatric Risk, Injury, Failure, Loss of kidney function, and end stage kidney disease; AKI, acute kidney injury; AKIN, AKI network; KDIGO, kidney diseases improving global outcomes; RRT, renal replacement therapy; SCr, serum creatinine; UO, urine output; eGFR, Glomerular GFR.

Technology, Elkhart, IN, USA) was moistened with the saliva. After 60 s, the color of the test pad was compared to 6 standardized color fields indicating SUN concentrations of 5–14 (color pad #1), 15–24 (#2), 25–34 (#3), 35–54 (#4), 55–74 (#5), and ≥75 (#6) mg/dL respectively [16]. SUN measurements were performed by the same pediatric nephrologist on site.

Statistical Analysis

Descriptive statistics included measures of central tendency (mean, median) and spread (SD, quartiles). SUN was transformed to a continuous variable by choosing the midpoint for each range. Diagnostic performance of SUN was expressed in terms of sensitivity, specificity, and area under the receiver operating characteristic curve. For the CKD outcome analyses (with demised or censored patients being excluded), we constructed logistic regression models with SUN, BUN, SCr, and UO at baseline or as changes between day 1 and 2. In addition, we constructed a logistic regression models using the same predictors with pAKI stage 3 or death as a co-primary outcome.

Google maps were used to calculate the distance between patients' home city and SUH and patients were grouped into 5 distance categories (Fig. 2). We built regression models to explore if the distance between the patient's home and SUH was a predictor of pAKI stage 3 or death.

We also constructed linear mixed effects models to account for repeated within-patient measurements to further investigate the temporal association between BUN and SUN. A two-sided *p* value

<0.05 was considered statistically significant. Analyses were done in R version 3.4.1 (codename "Single Candle"; R Foundation for Statistical Computing; Vienna, Austria [21]) and the packages *pROC*, *doBy*, *survival*, *dplyr*, *maptools*, *RgoogleMaps* and *maps*.

Results

Eighty-one eligible patients (age 10.7 ± 7 years, 51.9% females) were enrolled. Figure 1 displays the study flow-chart. Twenty-one (25.9%) were neonates, 18 (25.9%) infants, and 42 (53.1%) were toddlers and children. Age of neonates, infants, and the older children were 16 ± 12 days, 6 ± 5 months, and 12 ± 5 years respectively. Demographic and clinical characteristics and pAKI causes are shown in Table 3. All patients had SCr, BUN, SUN, and UO measurements throughout the study period. SUN was measured in all 81 children on the first 3 days of admission, in 66 on day 4, in 60 on day 5, and in 48 on days 6 and 7. Distance to SUH was <50 km in 29 patients (35.8%), 51–100 km in 16 (19.8%), 101–150 km in 13 (16%), 151–200 km in 3 (3.7%), over 200 km in 20 (24.7%; Table 3, Fig. 2). SUN, BUN, and SCr declined significant-

Fig. 1. Study flowchart. SCr, serum creatinine; SUN, saliva urea nitrogen; UO, urine output; CKD, chronic kidney disease; ESRD, end-stage renal disease; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis.

ly during hospitalization (Table 4, Fig. 4, 5). Fifty-eight patients (72%) were treated conservatively and 23 (28%) were dialyzed within the first 2 days of admission. Dialysis indications were severe fluid-overload, pulmonary edema, electrolytes disturbances unresponsive to medical treatment, and uremic encephalopathy. All neonates who needed RRT received peritoneal dialysis. Twelve patients received intermittent hemodialysis (Table 1). Antibiotic drug doses were adjusted to Estimated GFR.

AKI Classification and Incidence

pAKI severities based on different definitions are shown in Figure 3 (for simplicity pRIFLE was converted from “Risk”, “Injury,” and “Failure” to stage 1–3). Per KDIGO and pRIFLE based on SCr, all patients had AKI stage 3. By the AKIN criteria, pAKI stage 3 was present in 78 patients (96.3%). Per pRIFLE UO criterion (all 3 are similar) pAKI occurred in 54 patients (66.7%); per pRIFLE 12 (14.8%) patients were stage 3. Per KDIGO and AKIN criteria with the same UO criterion (Fig. 2) 35 patients (43.2%) had pAKI.

Outcome Analysis

The development of CKD of any stage during the 3-months of follow-up was predicted neither by baseline SUN, BUN, SCr, and UO, nor by their changes between day 1 and 2.

Similarly, neither death nor AKI stage 3 were predicted by these indicators. High UO at admission (OR 0.11 [95% CI 0.01–0.71]) and an UO rise between days 1 and 2 (OR 0.23 [95% CI 0.005–0.86]) were inversely associated with either death or AKI stage 3.

Distance between patients’ homes and SUH was not associated with composite outcome of AKI stage 3 per pRIFLE or death.

Agreement between SUN and BUN

SUN, BUN, and Scr decreased in parallel during hospitalization (Fig. 4, 5) in all age groups. SUN and BUN agreed consistently (Fig. 6; Table 4, 5).

Table 3. Descriptive statistics of the studied patient cohort

Variable	All 81 (100%)	Neonates ≤28 days 21 (25.9%)	Infants 29–365 days 18 (21%)	Children ≥366 days 42 (53.1%)
Gender, female, <i>n</i> (%)	42 (51.85)	13 (16.04)	9 (11.11)	20 (24.70)
Cause of AKI, <i>n</i> (%)				
Infections/sepsis	36 (44.45)	20 (24.70)	7 (8.64)	9 (11.11)
GN	16 (19.8)	–	–	16 (19.75)
CAKUT	15 (18.51)	1 (1.23)	6 (7.40)	8 (9.88)
HUS	6 (7.40)	–	2 (2.46)	4 (4.94)
TLS	3 (3.69)	–	1 (1.23)	2 (2.46)
SLE	3 (3.69)	–	–	3 (3.69)
Cause unknown	2 (2.46)	–	1 (1.23)	1 (1.23)
Comorbidities, <i>n</i> (%)				
Cardiovascular	1 (1.23)	1 (1.23)	–	–
Auto-immune encephalitis	4 (4.94)	–	–	4 (4.94)
CP	6 (7.40)	–	–	6 (7.40)
HIE	2 (2.46)	2 (2.46)	–	–
MS	1 (1.23)	–	–	1 (1.23)
Trisomy 21 (Down syndrome)	1 (1.23)	1 (1.23)	–	–
Multisystem Disease	6 (7.40)	–	1 (1.23)	5 (6.17)
Convulsions/Epilepsy	9 (11.11)	6 (7.40)	1 (1.23)	2 (2.46)
Therapy, <i>n</i> (%)				
Conservative management	58 (71.60)	18 (22.22)	12 (14.82)	28 (34.56)
IHD	12 (14.82)	–	1 (1.23)	11 (13.58)
IPD	11 (13.58)	3 (3.69)	4 (4.94)	4 (4.94)

AKI, acute kidney injury; GN, glomerulonephritis; CAKUT, congenital anomalies of the kidney and urinary tract; HUS, hemolytic uremic syndrome; TLS, tumor lysis syndrome; SLE, systemic lupus erythematosus; CP, cerebral palsy; HIE, hypoxic-ischemic encephalopathy; MS, multiple sclerosis; RRT, renal replacement therapy; IHD, intermittent hemodialysis; IPD, intermittent peritoneal dialysis.

Discussion

Our research resulted in several important new insights: First, pAKI classifications based on SCr are very sensitive and categorize almost all patients as falling into the highest pAKI severity class. Criteria based on UO are less sensitive, possibly due to a delayed UO decline in pAKI. Second, SUN and BUN results were concordant, indicating that BUN measurements could be complemented or even replaced by SUN. Third, SUN, BUN, or SCr predicted subsequent CKD of any stage or death. Fourth, high UO at baseline and an increase from day 1 to 2 was associated with reduced mortality. Lastly, the distance between patients' homes and SUH was not associated with outcomes.

The Global Snapshot study of the 0by25 initiative of the ISN aims to prevent and eradicate all avoidable death from AKI by 2025 [5, 22] and called for simple-to-use, preferably noninvasive diagnostic tools, to detect kidney diseases in low resource settings [14]. Since AKI in developing countries is common due to diseases such as diar-

rhea, infections, or pregnancy-related complications [22, 5], timely diagnosis may facilitate early treatment (e.g., by oral rehydration) and thus increase the odds of recovery. In our study, sepsis was the major cause of pAKI, accounting for 36 cases (44.5%). These data corroborate reports of the 0by25 initiative Global Snapshot study [22] and others [23, 24].

Our research advances the understanding of pAKI diagnosis and classification across all age groups. We compared 3 pAKI classifications, including the Neonatal-KDIGO and the Neonatal RIFLE classifications, which use both SCr and UO in their definitions [25, 26]. Almost all our patients had the highest degree of AKI when diagnosed based on criteria using SCr (particularly in neonates), whereas UO showed some variation in diagnosed severity. This can be explained by the fact that up to 60% of neonatal pAKI is non-oliguric [27] and criteria are deliberately very sensitive in this population.

While substantial research is required into the operational details of kidney care delivery in the sub-Saharan region, we have no doubt that there is a substantial un-

Fig. 2. Map of Sudan.

Table 4. Test results of SUN, BUN, and SCr in patients at all the observational days

Day of admission	Count, <i>n</i>	SUN, mg/dL, mean ± SD	BUN, mg/dL, mean ± SD	SCr, mg/dL, mean ± SD
Day 1	79	79.7±13.9	126.2±45.5	7.0±2.6
Day 2	81	69.5±18.3	106.4±41.0	5.8±2.6
Day 3	81	54.4±25.0	80.5±31.6	4.7±2.4
Day 4	66	41.2±24.9	64.7±25.9	3.8±2.2
Day 5	48	25.9±16.0	45.7±21.6	2.9±2.0
Day 6	32	18.5±9.5	32.6±15.8	1.6±1.1
Day 7	29	16.0±6.1	26.8±9.4	1.1±0.6

BUN, blood urea nitrogen; SUN, saliva urea nitrogen; SCr, serum creatinine.

met need for heightened awareness, timely diagnosis and proper follow-up of kidney patients. Based on our data SUN dipsticks can be seen as a reliable POC tool for timely AKI diagnosis, thus allowing early therapy, recovery of kidney function and improved patient outcomes. Ac-

counting for repeated within-patient measurements, the agreement between SUN and BUN throughout the study was good, irrespective of treatment modalities (Fig. 4). We also observed the already well-known underestimation of BUN by SUN (Fig. 5). Our study corroborates

Fig. 3. Incidence proportion of pAKI according to 3 definitions (based on [a] SCr and [b] UO): 1. pRIFLE, 2. AKIN (since similar with KDIGO based on UO not displayed), KDIGO. AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcomes; UO, urine output; pRIFLE, pediatric Risk, Injury, Failure, Loss of kidney function, and end-stage kidney disease.

Fig. 4. Trends of SUN (**a**) and BUN (**b**) during all observation days. Individual lines were generated for all available patient data during all observation days using linear models, bold line was computed using a linear mixed effects model. SUN, saliva urea nitrogen; BUN, blood urea nitrogen.

earlier ones (Table 1) and supports the use of SUN dipstick as a POC diagnostic tool of kidney function [14–19, 28].

Unlike in our previous Malawi study in adults, SUN was not predictive of mortality. We believe that SUN and

other biochemical markers are less predictive in neonates and young children since pAKI is non-oliguric in >60% of neonates (32, 34). To further evaluate these relationships, we studied medium-term outcomes from pAKI at various stages and levels of retention parameters. There

Fig. 5. Trends of SCr during all observation days. Individual lines were generated for all available patient data during all observation days using linear models and bold lines depict (a) all patients and (b) for different age groups (1. Blue represents neonates [age <120

days], 2. Green represents infants [age between 120 and 365 days] and 3. Red represents toddlers and older children). SCr, serum creatinine.

are only a few studies, mainly in pediatric intensive care unit patients, which have compared the incidence and mortality of AKI using pRIFLE and AKIN criteria. Sutherland et al. [27] compared AKI incidence and mortality in hospitalized children according to pRIFLE, AKIN, and KDIGO definitions based on SCr changes; UO criteria were not used. The authors concluded that all 3 definitions demonstrated excellent inter-stage agreement from 76.7 to 92.5%. However, the lack of a significant association with biomarker-based criteria but significant associations with those based on UO emphasizes the high sensitivity of the criteria. A particularly vulnerable population choosing a sensitive threshold is a positive and useful measure of approaching every child with maximal benefit in mind.

The predictive ability of SUN has been evaluated in several studies in adults. Given the relatively late decrease in UO in the children, biochemical markers generally are of lesser value. However, one may think of algorithms that would utilize them in conjunction with UO in future studies. Overall, a higher sensitivity of all criteria seems in this particularly vulnerable population of great value and thus should be considered.

While Sudan is a vast country, all its 7 pediatric nephrologists practice in Khartoum state. Consequently, some patients need to travel from far afield from home or primary and secondary care facilities to the SUP pediatric nephrology unit. Of note, there were no substantive dif-

ferences in AKI classification based on distance. However, patients who resided >200 km from SUH showed a non-significantly trend to present with stage 3 based on pRIFLE UO criteria.

Strengths and Limitations

Our study has several strengths; it involved children across a wide age range and used SCr and UO to identify pAKI stages. Doing so for the first time enabled a completely standardized diagnostic criterion for pAKI. Importantly, all patients had SCr, BUN, and UO measured on admission.

The study also has some limitations. First, it was performed in a single tertiary center, so patients were severely ill and needed aggressive treatment; this may have resulted in a non-generalizable estimate of pAKI incidence and outcomes. Multicenter studies that use a global definition pAKI in large and diverse populations are warranted to further elucidate the dynamics of pAKI and test generalizable pAKI definitions.

Conclusions

Identification of AKI in neonates and children is complicated for both nephrologist and neonatologist because the renal blood flow and physiology of newborns and infants is different from adults. Diagnosis using different criteria differs in triage and staging. SUN reflects BUN

Fig. 6. SUN as a function of BUN at all observational days. SUN, saliva urea nitrogen; BUN, blood urea nitrogen.

Table 5. Median BUN at different levels of SUN

SUN test pad number (SUN range, mg/dL)	n count	BUN, mg/dL, median (25th–75th) quartile
1 (5–14)	51	34 (23–43)
2 (15–24)	62	36.7 (26.5–46.5)
3 (25–34)	49	52 (42–66.8)
4 (35–54)	45	73 (57–82)
5 (55–74)	90	83 (72.5–98.75)
6 (≥75)	119	126 (94.0–150)

BUN, blood urea nitrogen; SUN, saliva urea nitrogen; SCr, serum creatinine.

particularly at higher BUN levels and allows monitoring treatment responses. Despite the lack of predictive qualities of SUN (but notably also BUN and creatinine) to predict AKI severity, CKD and mortality, SUN measured by dipstick can be used to identify, screen, and monitor pediatric patients with severe AKI in a low-resource setting.

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Statement of Ethics

The study complied with the guidelines for human studies and was conducted in accordance with the Declaration of Helsinki. Subjects (or their parents or guardians) have given their written informed consent.

Disclosure Statement

P.K. holds stock options in Fresenius Medical Care. All other authors have no relevant financial disclosures. V.C.-S. was an ISN fellow and received scholarship from the Brazilian Government (CAPES) during part of the time when the study was conducted. R.P.-F. received a scholarship from the Brazilian Council for Research Support (CNPq). All other authors have no financial interests to declare.

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Author Contributions

R.H.H., V.C.-S., N.W.L., P.K., R.P.-F., and J.G.R.: conceptualization; R.H.H. and V.C.-S.: data curation; R.H.H., V.C.-S., and J.G.R.: formal analysis; R.H.H., V.C.-S., R.E., N.W.L., R.E., E.M.A., Y.B., A.B., Amna A., Asmaa A., M.B.A., P.K., N.W.L., R.P.-F., and J.G.R.: investigation; R.H.H., P.K., V.C.-S., J.G.R., R.P.-F., and N.W.L.: methodology; R.H.H., V.C.-S., R.P.-F., P.K., and J.G.R.: project administration; R.H.H., V.C.-S., R.E., N.W.L., R.A.E., E.M.A., Y.B., A.B., Amna A., Asmaa A., M.B.A., P.K., N.W.L., R.P.-F., and J.G.R.: writing and review. All authors revised the manuscript, provided input in their area of expertise and consented to submission.

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