Usefulness of Urinary Neutrophil Gelatinase-associated Lipocalin as a Predictor of Acute Kidney Injury in Critically Ill Children

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Abstract

Background: Acute kidney injury (AKI) is common among critically ill children. The current definitions of AKI rely on serum creatinine and urine output, which may not be deranged until late in the course of the illness. There has been a lot of work in search of novel biomarkers to define and predict AKI, and urinary neutrophil gelatinase-associated lipocalin (NGAL) is a promising one. We planned to study the usefulness of urinary NGAL in predicting AKI.

Patients and methods: Children in the age group of 1 month to 18 years admitted to the pediatric intensive care unit (PICU) from September 2016 to December 2017 were enrolled. Children with preexisting kidney disease, urinary tract infection (UTI), postsurgical patients, or children with expected duration of stay <48 hours were excluded. Data regarding demographics, clinical features, and laboratory parameters were collected. Urinary NGAL was sent within 6 hours of admission. Children were classified to have AKI based upon the Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) criteria. Using receiver operating characteristic (ROC) curves, sensitivity, specificity, and area under the curve (AUC) for admission creatinine and urinary NGAL to predict AKI were deduced.

Results: One hundred and thirty children were included. Out of 130 children, 59 (45.4%) developed AKI. Urinary NGAL at admission to the PICU >88.5 ng/mL had a sensitivity of 81.4% and specificity of 83.6% in detecting AKI while its AUC to detect AKI was 0.842 (95% confidence interval (CI) 0.765–0.918). Urinary NGAL predicted AKI in 17 (28.8%) of 59 patients at least 24 hours earlier than serum creatinine. Mortality rates in patients with and without AKI were 18.6 and 2.8%, respectively.

Conclusion: Urinary NGAL has good sensitivity and specificity in detecting AKI and predicts AKI earlier than creatinine in a significant number of patients.

Keywords: Acute kidney injury, Critically ill children, Pediatric acute kidney injury, Urinary neutrophil gelatinase-associated lipocalin.

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Highlights

Urinary NGAL has good sensitivity and specificity in detecting pediatric AKI and helps in predicting AKI in a significant number of children. This may help us in prognostication as well as adopting a more kidney-friendly approach in such children.

Introduction

Acute kidney injury (AKI) affects almost 20–50% of children admitted to the pediatric intensive care units (PICUs).[1,2] Definitions of AKI currently in use are based on changes in serum creatinine and urine output. However, serum creatinine is misleading in that a significant loss of glomerular function would have occurred by the time it rises and it does not give a clear picture till a steady state has been reached.[3] From the clinician's point of view, it would be very useful if there is a marker to diagnose AKI early in the course. Validated serum/urinary biomarkers may help in the diagnosis of AKI.[4] Urinary neutrophil gelatinase-associated lipocalin (NGAL) is one of the biomarkers being widely studied. NGAL is a small protein synthesized during myelopoiesis and stored in neutrophil granules. It is also produced by the epithelia of lungs, colon, and kidneys.[5,6] *De novo* synthesis of NGAL by renal tubular cells is increased with kidney injury.[7] After kidney injury, NGAL produced by other parts of the body is not adequately reabsorbed by the renal tubular cells.[8] Both these factors lead to increased levels of NGAL in urine after kidney injury.

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NGAL has been stated to be promising in predicting AKI and has a high potential to become a point of care test for AKI.[9] Urinary NGAL is more advantageous than plasma NGAL because plasma NGAL can also be elevated during conditions like systemic infection, inflammation, and malignancy, confounding the picture.[10] On the contrary, the utility of NGAL in predicting AKI in critically ill children has been questioned as it has been found to be elevated in other acute and chronic inflammatory conditions common in the intensive care unit (ICU).[11] It is also debated to be a better predictor of hospital mortality than AKI.[12] Furthermore, it has been stated that large multicenter studies are needed to validate the usage of

NGAL.[13] The utility of urinary NGAL in AKI not being clear and the nonavailability of clear cutoff prompted us to plan a study to see the utility of urinary NGAL in predicting AKI in critically ill children.

Materials and Methods

The present study with the model of validation of a diagnostic test was conducted in the tertiary care PICU of a children's hospital in south India from September 2016 to December 2017. All children aged 1 month to 18 years admitted to the PICU were screened for inclusion. Children admitted to the PICU for postoperative care and those with known kidney disease, urinary tract infection, or with expected PICU stay of less than 48 hours were excluded. Blood and urine samples of all children enrolled in the study were collected within 6 hours of admission, after obtaining consent. Estimated creatinine clearance was calculated with the modified Schwartz formula.[14] After admission, creatinine and other investigations were repeated as required by the patient's clinical condition. Patients were categorized into various stages of AKI based on Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) criteria.[15] If the child had serum creatinine measured during the past 3 months, that was taken as the baseline creatinine value. Otherwise, the lowest serum creatinine value during the current admission was taken as the baseline value. According to pRIFLE criteria, at least two creatinine values are required to document changes in estimated creatinine clearance. Normal values of serum creatinine vary with age. Urinary NGAL can be a good predictor of AKI if a patient with normal serum creatinine but elevated NGAL at admission subsequently develops AKI. In view of creatinine values varying with age and muscle mass, we considered any value of creatinine greater than 0.5 mg/dL at admission as elevated. We assumed that urinary NGAL can be considered to predict AKI earlier than serum creatinine if serum creatinine at admission was less than 0.5 mg/dL and urinary NGAL was higher than the cutoff value.

Pediatric Risk of Mortality Score III (PRISM III) scoring was done for all children.[16] Data regarding demographics, clinical features, and laboratory parameters were collected. Data regarding the clinical diagnosis, shock, ventilator and inotrope requirement, multiorgan dysfunction syndrome, requirement of kidney replacement therapy (KRT), and outcome were also collected. Patients were divided into two groups—Group A included those with AKI, whereas Group B included those without AKI. After collection of data, kidney disease improving global outcomes (KDIGO) and acute kidney injury network (AKIN) staging[17,18] were also done for the patients. Serum creatinine was estimated by Jaffe's method and standardization was done with calibration traceable to SRM 967 produced by the National Institute of standards and technology (NIST). Urinary NGAL measurement was done using Human NGAL ELISA kit (KIT 036, Bioporto Diagnostics, Hellerup, Denmark). Urine samples were stored at −80°C until analysis.

This study was approved by the hospital Institutional Review Board.

Statistical Analysis

Based on previously collected data, the prevalence of AKI in our PICU is around 40%. Assuming the sensitivity of urinary NGAL in diagnosing AKI to be 95% and precision to be 10%, we needed approximately 50 patients with AKI as a sample size to test the validity of NGAL as a diagnostic test. Qualitative data were analyzed by Chi-square test/Fisher's exact test, whereas quantitative data were analyzed by Student's "*t*" test and Kruskal–Wallis test, whichever was appropriate. Urinary NGAL, admission creatinine, and PRISM III score were evaluated as a marker/predictor for AKI by comparing the AUC of their respective ROC curves. Based on the ROC curve, a cutoff value for urinary NGAL with reasonable sensitivity and specificity for AKI was deduced. Statistical analysis was performed using SPSS 21 (IBM). The flow of the study and the inclusion of the children proceeded as depicted in the (Flowchart 1).

Results

A total of 130 children were recruited during the study period, out of which 72 were males. The median age of the study population was 48 months (1–216). Among the 130 patients, 31 (23.8%) were due to systemic infections/sepsis, 20 (15.4%) were due to respiratory illness, 19 (14.6%) were due to CNS illness, 16 (12.3%) were due to gastrointestinal illness, 11 (8.5%) were due to hematological illness, 21 (16.2%) belong to the miscellaneous group, and 6 (4.6%) were due to kidney issues.

Flowchart 1: Flow of the study

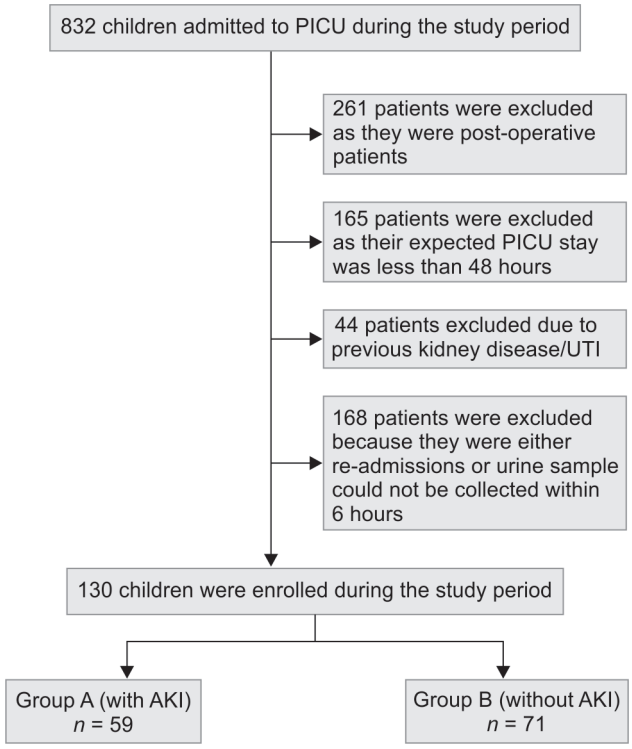

Table 1: Comparison of AUC by ROC curve for various parameters to predict/diagnose AKI

	AUC by ROC curve[a] (95% CI)
Admission creatinine	0.668 (0.572–0.764)
Urinary NGAL[b]	0.842 (0.765–0.918)
PRISM III[c]	0.733 (0.645–0.820)

The value of ROC is given with the 95% CI enclosed within the brackets and shows that urinary NGAL has the highest AUC to predict/diagnose AKI among the three. [a]Area under the curve (AUC) by receiver operatingcharacteristic (ROC) curve; [b]Urinary neutrophil gelatinase-associated lipocalin (NGAL); [c]Pediatric risk of mortality score III (PRISM III)

Of the 130 children, 59 (45.4%) developed AKI. Among the children with AKI, only 8 (13.6%) had oliguria during the PICU stay. Age and sex distribution were not different between those with and without AKI (Table 2). PRISM III score was significantly higher in the group with AKI than those without AKI (p <0.001). AKI did not differ significantly from the system of the primary illness (p = 0.57). AKI was significantly higher in the group with inotrope requirement (p <0.001) and multiorgan dysfunction (p <0.001). AKI did not differ significantly among those who received diuretics and those who did not (p = 0.341).

Among the patients with AKI, 37.3% of patients fell into "Risk" category and 23.7% were in "Injury" category, whereas 39% were in "Failure" category. Using only the urine output criterion of pRIFLE, two were in the "Risk" stage, while three children each were in the "Injury" and "Failure" stages of AKI. AKI rates diagnosed by pRIFLE, AKIN, and KDIGO criteria in this population were similar (Table 3). Eleven out of 59 children with AKI (18.6%) required KRT. Intermittent hemodialysis (HD) was the commonest mode of KRT used in our study population with nine patients, whereas peritoneal dialysis was done in two patients and sustained low-efficiency dialysis (SLED) was done for one patient. Mortality rates in patients with and without AKI were 18.6 and 2.8%, respectively (p = 0.03).

Urinary NGAL values at admission were significantly higher in the patients who had or subsequently developed AKI when compared to patients who did not develop AKI (583 ± 423 ng/mL and 85 ± 163 ng/mL respectively, p <0.0001). Area under the curve (AUC) for urinary NGAL to detect AKI by ROC curve was 0.842(95% CI 0.765–0.918) (Table 1). The ROC curves for admission creatinine and urinary NGAL to detect AKI are given in Figures 1 and 2.

Urinary NGAL at admission to the PICU >88.5 ng/mL had a sensitivity of 81.4% and specificity of 83.6% in detecting AKI. Taking this cutoff, urinary NGAL predicted AKI in 17 (28.8%) of 59 patients at least 24 hours earlier than serum creatinine. Urinary NGAL values of children with AKI who required KRT (596 ± 425 ng/mL) were not significantly different from those who did not require KRT (584 ± 427ng/mL, p = 0.93). The value of urinary NGAL did not differ with the various stages of the pRIFLE criteria, indicating that it did not correlate with the severity of AKI. Urinary NGAL values were significantly higher (p <0.01) among the nonsurvivors (620.9 ± 459) than the survivors (278.8 ± 376).

Table 2: Comparison and demographic, risk factors and outcome variables between the two groups—AKI (n = 59) and non-AKI (n = 71) (p value <0.05 was taken as significant)

	Group A AKI (n = 59)	*Group B Non-AKI (n = 71)*	*p value*
Sex—males (%)	31 (52.5%)	41 (57.7%)	0.552[a]
Age in months (Min–Max)	65 (1–192)	58 (1–216)	0.333[b]
PRISM III score (Min–Max)	8 (0–23)	5 (0–16)	<0.0001[b]
Shock at admission (%)	18 (30.5%)	19 (26.8%)	0.637[a]
MODS[d] (%)	24 (40.6%)	7 (9.9%)	<0.001[a]
Inotropes (%)	25 (42.4%)	12 (16.9%)	0.001[a]
Ventilation (%)	32 (54.2%)	32 (45.1%)	0.298[a]
Diuretic use (%)	22 (37.3%)	23 (32.4%)	0.56[a]
Length of PICU stay (Min–Max)	9 (2–44)	9 (2–45)	0.711[b]
Mortality (%)	11 (18.6%)	2 (2.8%)	0.03[c]

[a]Analyzed by Chi-square test; [b]Analyzed by Kruskal–Wallis test; [c]Analyzed by Fisher's exact test; [d]Multiorgan dysfunction syndrome

Table 3: Comparison of AKIN, pRIFLE, and KDIGO criteria for diagnosing AKI–pRIFLE criteria picked up more number of patients in our study

	Number of patients with AKI (%)
pRIFLE criteria[a]	59 (45.4%)
AKIN criteria[b]	54 (41.5%)
KDIGO criteria[c]	54 (41.5%)

[a]Pediatric (R) risk; (I) injury; (F) failure; (L) loss; (E) end stage renal disease—pRIFLE criteria; [b]Acute kidney injury network—AKIN criteria; [c]Kidney disease improving global outcomes criteria—KDIGO criteria

Discussion

Urinary NGAL had a sensitivity of 81.4% and specificity of 83.6% in diagnosing AKI when the cutoff value for diagnosing AKI was taken as NGAL >88.5 ng/mL, with an AUC of 0.842. Urinary NGAL has been shown to have AUC at least greater than 0.75 to diagnose AKI in many other studies.[19–22] Though these studies have heterogeneities in the age group of the recruited children, different definitions and severity of AKI, and the disease process, it appears that they

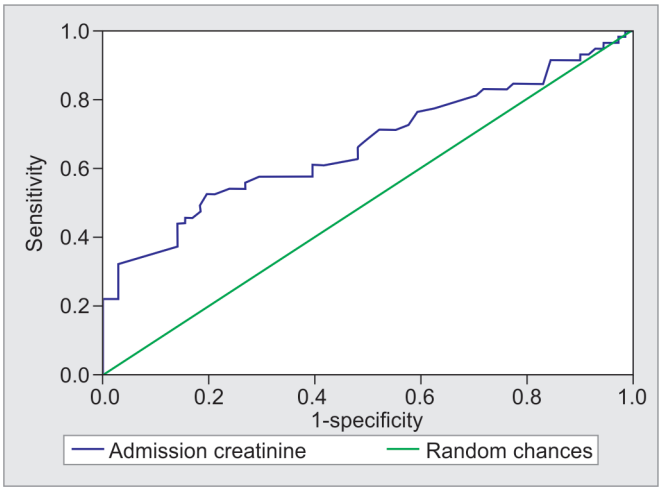

Fig. 1: ROC curve—admission creatinine for AKI

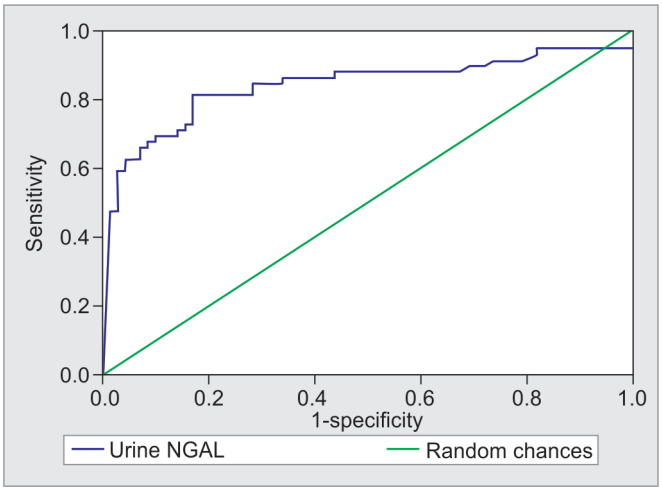

Fig. 2: ROC curve—urinary NGAL for AKI

give a clear signal that urinary NGAL has a good scope in the early diagnosis of AKI. There has been a huge variation in the cutoff values of urinary NGAL for the detection of AKI in various studies ranging from 50 to 223 ng/mL and all these studies had reasonable sensitivity and specificity to detect AKI in their population.[20–22] This signifies that a larger population study involving multiple centers and a uniform definition for AKI would give a better idea of the cutoff value.

The value of urinary NGAL was higher than 88.5 ng/mL even before elevation of serum creatinine in nearly 30% of the patients with AKI. Multiple previous studies have shown that urinary NGAL rises before serum creatinine, giving an early indication that the kidney has been injured.[20,23–26] Zapitelli et al. showed that urinary NGAL predicts AKI before serum creatinine in mechanically ventilated children.[27] An early indicator of AKI can help reduce further damage by instituting measures such as avoidance of nephrotoxic medications and optimizing fluid balance.[28,29] Zwiesr et al. and Kari et al. found in their respective studies that urinary NGAL predicted AKI in at least 80% of their population.[20,22] The predictive value urinary NGAL for AKI in our study was less in comparison with the previous studies. One possible explanation for this could be that children in our population AKI had already set in causing elevation in creatinine by the time of their presentation leading to underestimation of the predictive utility of urinary NGAL in AKI.

Children who are seriously ill have a higher chance of developing AKI, as reflected by the higher PRISM III score and incidence of MODS in the AKI group. Children with shock at admission to the PICU did not have more AKI when compared to those without shock. However, those who required inotropes had a higher chance of developing AKI. This could be because children requiring inotropes may be more seriously ill and need interventions or therapies that are nephrotoxic. Devarajan et al. in their study of urinary NGAL among patients who underwent cardiac surgery showed that urinary NGAL predicted dialysis requirement that was different from the findings of our study.[23] This could be due to two reasons. The first one is that cardiopulmonary bypass is a single-point injury but for a patient in a general ICU, injury occurs at multiple points leading to cumulative damage finally ending in dialysis and the second one is that we analyzed urinary NGAL only at admission but if we measured serial values, that may have shown an association with dialysis requirement. NGAL is generally reabsorbed by the renal tubules and after the kidney injury reached a point beyond which it cannot handle, the excretion in urine would increase to much higher levels.

Among various criteria used to define AKI, pRIFLE appears to be more sensitive than KDIGO or AKIN. This is in agreement with the study done by Sutherland.[30]

Our study is not free of limitations. We measured serum creatinine according to the clinical demands of the patient and not at fixed intervals. This could have led to missing some patients with milder forms of AKI with biochemical derangement only. Measuring creatinine at regular intervals may have provided a better picture of how early urinary NGAL predicts AKI. In addition, the rate of enrolment of eligible patients into the study was relatively low. Data on the nutritional status of the children and gestational age were not collected and could have influenced the serum creatinine values. A larger study will give a better idea about the sensitivity, specificity, and cutoff value of urinary NGAL for predicting AKI.

Conclusion

Urinary NGAL has good sensitivity and specificity to diagnose AKI and predicts AKI earlier than serum creatinine in a significant number of critically ill children. If confirmed in larger cohorts, it can be a very useful early warning, allowing treatment modification to mitigate the risk of worsening AKI.

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