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Early Detection of Severe Acute Kidney Injury by Urinary Neutrophil Gelatinase Associated Lipocalin in Critically Ill Children

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Abstract

Background: *Acute Kidney Injury (AKI) is independently associated with worsened morbidity and increased mortality in critically ill children in the Pediatric Intensive Care Unit (PICU). Till date Serum Creatinine (S.Cr) is the gold standard for AKI detection. Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) is revealed as a promising novel biomarker for the early detection of kidney damage. The study is aimed to evaluate the ability of uNGAL for early detection of severe AKI in critically ill children.*

Materials and methods: *This prospective observational study included 90 pediatric ICU (PICU) patients aged 1 month to 12 years from December 2020 to November 2021.Urine was collected for uNGAL on admission (Day 0). Blood samples were collected on Day 0 (D0), Day 3 (D3) and Day 7 (D7) for serum creatinine (S.Cr). AKI was defined and staged according to Kidney Disease Improving Global Outcomes 2012 criteria.*

Results: *Among 90 children, 26 (28.9%) develop severe AKI on D3. The median uNGAL level was 182.9 ng/ml in children with severe AKI compared to 44.3 ng/ml in those without severe AKI. The AUC for the D0 uNGALto predict D3 severe AKI was 0.945 (CI 0.867–1.0). The best cutoff point for uNGAL was 102.70 ng/ml, with a sensitivity of 96.15% and specificity of 98.44% for D3 severe AKI. D0uNGAL had no significant correlation with D0S. Crbut had a significant positive correlation with D3 and D7 S.Cr.*

Conclusion: *Urinary NGAL is an useful early AKI marker to detect the development of severe AKI in critically ill children of PICU.*

Key words: Acute Kidney Injury (AKI); Pediatric Intensive Care Unit (PICU); Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL)

INTRODUCTION

AKI is a serious and common complication in critical care.Severe AKI occurs in one-quarter of children and young adults during the first seven days after ICU admission.[1] Severe AKI is associated with long hospital stay including ICU, need for mechanical ventilation with mortality between 8 to 89% and 60% survivors may develop proteinuria, hypertension, reduced GFR.[2-6] Severe AKI conferred an incremental risk ofdeath by day 28.[1] Thus, it is very important to identify the onset of renal damage as early as possible and apply preventive measures and adequate treatment to avoid adverse outcomes and improve outcomes.[7]

Nowadays, pediatric AKI is diagnosed and staged by using Kidney Disease: Improving Global Outcomes (KDIGO 2012) criteria.[8] However, this relies on urine output and changes in serum creatinine measurement that occur in the late stages of AKI. Creatinine starts to rise only after two days when 50% of the renal function has

been lost. AKI occurs due to other diseases rather than renal diseases and severe AKI develops as a consequence of the main disease.[9-11]This impedes early detection and the establishment of preventative measures as there is a lag time of several hours from injury to a rise in creatinine, resulting in a 'sub-clinical' phase of AKI, which may be more amenable to treatment.[12]

One of the suggested approaches to improve the early detection of severe AKI is the measurement of novel renal biomarkers. Novel AKI biomarkers such as kidney injury molecule-1, plasma Neutrophil Gelatinase-Associated Lipocalin (pNGAL), urinary NGAL (uNGAL) interleukin-18 and serum cystatin C (s-Cys-C) have been proposed and investigated as a marker of early detection of kidney damage.[13] Leucocytes, the loop of Henle and collecting ducts are the primary sources of NGAL in the body. It is expressed by tubular epithelial cells in response to injury and tubulointerstitial damage, frequently occurring during kidney disease progression. uNGAL is a good predictor of renal injury before detectable changes in eGFR in critically ill children. Its level correlates well with disease severity and is an independent predictive biomarker of mortality.[14]

uNGAL is a noninvasive, cost-effective, kit based, easily done in any standard lab, and a rapid result is available. There was a scarcity of studies on uNGAL to detect early severe AKI in the pediatric age group, except for neonates in Bangladesh.[15] In this context, to fill this knowledge gap, this study was aimed to evaluate the performance of uNGAL in the early detection of severe AKI in critically ill children of PICU. The study findings may help in the early diagnosis and treatment of severe AKI.

MATERIALS AND METHODS

This is aa prospective observational study in the PICU of Chittagong Medical College Hospital, Chattogram, Bangladesh, from December 2020 to November 2021. The study protocol was approved by the ethical and review committee of Chittagong Medical College (CMC/PG/2020/656, Dated:12/10/2020). Verbal and written informed consent was obtained from the caregivers of the patients.

Pediatric patients one month to 12 years of age, admitted to PICU for at least 72hours, were included in the study. Known CKD patients, patients on dialysis, uncorrected congenital heart disease, congenital anomalies of the kidney and urinary tract, and children whose parents or guardians refused to participate in the study were excluded.

Demographic characteristics for all children were recorded, and complete history was taken from parents or caregivers. Five ml of urine for NGAL measurement were collected on day 0. Samples were immediately stored in an icebox and transported to the laboratory. The samples were centrifuged at 1,500×g, 4°C for 15 min to remove debris and stored in labelled polypropylene tubes at 20 C for later measurement. Samples were then tested using the Invitrogen Human NGAL ELISA Kit (BMS2202) LOT: 234524-003 in one batch at the end of data collection. Blood samples for serum creatinine were collected on day 0 (D0), day 3(D3) and day 7(D7) by creatinine Jaffe gen.2 assay. The primary outcome was the presence of severe AKI on day 3 (D3-AKI). D0, D3 and D7 were considered the first 12 hours of PICU admission, 72 to 96 hours and 168 to 192 hours after PICU admission respectively. AKI staging was done according to KDIGO 2012 criteria and AKI stage ≥2 was regarded as severe AKI, considering serum creatinine as a variable, not urine output as information regarding urine output is not reliable always.

Data were analyzed with SPSS version 23.0 (IBM SPSS Inc., USA) and presented it as the frequency with percentage or as median with interquartile ranges. The Chi-square test and Mann-Whitney U test were used to compare qualitative and quantitative data, respectively, between the two groups. AUC was calculated with 95% CI. Best cutoff point was identified with 95% CI for D0 uNGAL with the Youden index, and calculated sensitivity and specificity using the cutoff point. Pearson correlation coefficients were used to examine the relationship between serum creatinine and uNGAL. Statistical significances were defined as $p < 0.05$ and CIs were set at a 95% level.

RESULTS

Ninety children were included in the study and 26 children developed severe AKI on D3. Males were predominant and the median age at admission was 8.0 months. The most common reasons for admission were bronchopneumonia and Meningoencephalitis.There was no significant difference in the median age, sex, height, weight, comorbidity, GCS and primary diseases between children with and without severe AKI. D0 serum creatinine was significantly lower in severe AKI group compared to no AKI. This significant difference persisted till day 3 and day 7. Median value of uNGAL was significantly higher in patients with severe AKI compared with those without severe AKI (Table I).

Table I Day 0 characteristics of the critically ill children (n=90)

Variables	Total (n=90)	Severe AKI on day 3		p value
		Present (n=26)	Absent (n=64)	
Age, in months	8.0 (2.0-48.0)	12.0 (5.6-64.5)	8.0 (2.0-48.0)	0.167†
Gender				
Male	51 (56.7)	13 (25.5)	38 (74.5)	0.416*
Female	39 (43.3)	13 (33.3)	26 (66.7)	
Diagnosis				
Bronchopneumonia	36 (40.0)	7 (26.9)	29 (45.3)	0.222*
Meningoencephalitis	17 (18.9)	5 (19.2)	12 (18.8)	
Others	37 (41.1)	14 (53.8)	23 (35.9)	
Comorbidity				
Absent	46 (51.1)	13 (28.3)	33 (71.7)	0.223*
Present	44 (48.9)	13 (29.5)	31 (70.5)	
Height/length, cm	66.5 (55.0-90.5)	69.5 (59.8-103.3)	64.0 (55.0-90.0)	0.361†
Weight, kg	6.5 (4.2-12.3)	7.9 (5.0-13.3)	5.8 (4.1-12.0)	0.236†
GCS	15 (10-15)	15 (10-15)	15 (10-15)	0.891†
D0 S. creatinine, mg/dl	0.5 (0.4-0.6)	0.4 (0.3-0.4)	0.5 (0.4-0.6)	<0.001†
D3 S. creatinine, mg/dl	0.6(0.4-0.8)	0.9 (0.8-1.0)	0.5 (0.4-0.6)	<0.001†
D7 S. creatinine, mg/dl	0.6 (0.4-0.6)	0.6 (0.6-0.6)	0.5 (0.4-0.6)	0.043†
uNGALng/ml	56.7 (33.8-126.9)	182.9 (132.9-322.3)	44.29 (26.5-61.4)	<0.001†

Data were presented as frequency (%) or median (Interquartile range). † Mann Whitney-U test. *Chi-square test.

The AUC (95% CI) for D0 uNGAL for detection of D3 severe AKI was 0.945 (0.867-1.0), with a best cutoff value 102.70 ng/ml (Figure 1).

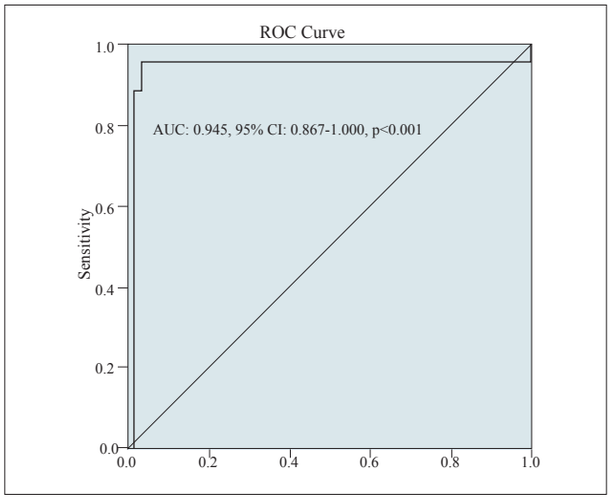

Figure 1 ROC curves of uNGALin detectingD0 severe AKI in PICU

The cut-off value of 102.70 ng/ml uNGAL had sensitivity of 96.15% with specificity 98.44%, PPV 96.15%, NPV 98.44%, accuracy 97.78% (Table II)

Table II Diagnostic accuracy of Day 0 uNGAL to detect AKI on day 3 following admission in PICU

Day 0 uNGAL level	Severe AKI on day 3	
	Present (n=26)	Absent (n=64)
≥102.70 ng/ml	25	1
<102.70 ng/ml	1	63
Accuracy parameters	Value	95% CI
Sensitivity	96.15%	80.36% to 99.90%
Specificity	98.44%	91.60% to 99.96%
Positive Predictive Value	96.15%	78.12% to 99.43%
Negative Predictive Value	98.44%	90.21% to 99.77%
Overall Diagnostic Accuracy	97.78%	92.20% to 99.73%

CI: Confidence Interval.

Table III Correlation between D0 uNGAL and serum creatinine on D0, D3 and D7

Serum creatinine	Correlation coefficient (r)	p value
Day 0	-0.095	0.336
Day 3	0.668	<0.001
Day 7	0.398	0.002

No significant correlation between D0 uNGAL level and D0 serum creatinine was observed. Serum creatinine on D3 and D7 had a significant positive correlation with the D0 uNGAL (Table III).

DISCUSSION

The current study revealed a 28.9% incidence of severe AKI. The incidence of AKI ranged between 15.83% to 49% in previous studies.[12,16,17] These differences in the incidence rates of AKI might be attributed to the small sample size, inclusion criteria, study setting, and the definition of AKI used.

Age, gender and diagnosis on Day 0 did not differ between patients with severe AKI and those without severe AKI in the current study which was in agreement to the study ofMcGalliard et al.[12] In contrast, younger age was found to have independent association with day 3 severe AKI byBasu et al.but Louzada et al. showed, higher prevalence of AKI in older children.[18,19] This variation can be explained by the different characteristics of the pediatric populations admitted to the various intensive care centers.

In the present study median value of uNGAL was significantly higher in patients with severe AKI compared with those without AKI (182.85 ng/ml vs 44.29 ng/ml, p=<0.001). It was similar to the study of McGalliard et al. (Median uNGAL level 186.0ng/ml vs3 0.9 ng/ml). [12]

In the study of Zwierset al. uNGAL measured within 0 to 6 hours following admission had a reasonable ability (AUC = 0.815) to identify children meeting severe AKI criteria within 48 hours. In the current study, it was found that the AUC was 0.945 for the ability to detect severe AKI.[20] A recent systematic review and meta-analysis demonstrated that uNGAL had an AUC of 0.94.[21] However, in these studies, NGAL was measured 2–6 hours after surgery and predominantly in ICU admissions after cardiopulmonary bypass or contrast-induced nephropathy. In another clinically heterogenous population, day1 uNGAL demonstrated only fair diagnostic accuracy (AUC = 0.75).[12] Subclinical AKI also can be diagnosed by uNGAL.[22]

The optimal uNGAL cutoff value in this study was found (102.70ng/ml) lower than for adults (247 ng/ml) for the detection of renal failure and also lower than the reported cutoff value (126 ng/ml) and (>150 ng/ml) in the pediatric population.[23,20,24] With a cutoff value of 102.70 ng/ml, the sensitivity, specificity, PPV, NPV and diagnostic accuracy were 96.15%, 98.44%, 96.15%, 98.44% and 97.78%, respectively. uNGAL cutoff value 126 ng/ml had sensitivity and specificity for detecting AKI were 75% and 84%, respectively.[20]deGeus et al. found the cutoff value of 247 ng/ml with sensitivity of 89% and specificity of 70% for prediction of renal failure in adult patients.[23]

Day 0 serum creatinine was significantly lower in the AKI group compared to the no AKI group. This significant difference persisted till day 3 and day 7. The present study failed to establish any significant correlation between Day 0 uNGAL and serum creatinine on Day 0. However, on Day 3 and Day 7, there was a significant positive correlation between Day 0 uNGAL and serum creatinine of that day. In a small

study by Gavrilovici et al. found a negative relationship between uNGAL and day 1 CrCl. No significant relationship was found between uNGAL and CrCl from day 3 and concluded that uNGALas a good marker of renal injury, but not a good predictor for AKI.[25]

LIMITATIONS

Patients were collected from a single public tertiary hospital. Variations in times when blood and urine samples were collected after admission may also mean that peak concentrations were missed. The study did not evaluate the temporal pattern of changes in uNGAL with the time following admission.

CONCLUSION

In this study, we found that uNGAL measured with a commercially available immunoassay had an excellent accuracy for detecting day 3 severe AKI in critically ill children which may help in promptly instituting reno-protective interventions. It will decrease the use of very expensive and complicated renal supportive therapy like RRT. This will decrease morbidity and mortality related to severe AKI.

RECOMMENDATION

The study findings support the clinical usefulness of uNGAL for detecting AKI in critically ill children. However, the validity of the present finding is emphasized by conducting a multicenter, large prospective study with random sampling.

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DISCLOSURE

The authors declared no conflicts of interest. this work.

REFERENCES

1. Kaddourah, A.Basu RK, Bagshaw SM, Goldstein SL, AWARE investigators. Epidemiology of acute kidney injury in critically ill children and young adults. New England Journal of Medicine. 2017;376(1):11-20.
2. BresolinN,Carlos S, Hallal A, Toporovski J, Fernandes V, Goes J, et al.Prognosis for children with acute kidney injury in the intensive care unit, Pediatric Nephrology.2009; 24(3):537-544.
3. Otukesh H, Hoseini R, Hooman N, Chalian M, Chalian H, Tabarroki A.Prognosis of acute renal failure in children. Pediatric Nephrology.2006; 21(12);1873-1878.
4. De Zan F, Amigoni A, Pozzato R, Pettenazzo A, Murer L, Videl E et al. Acute kidney injury in critically ill children: A retrospective analysis of risk factors. Blood Purification.2020;49(1-2):1-7.
5. Sutherland SM, Ji J, Sheikhi FH, Widen E, Tian L, Alexander SR, et al. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. Clinical journal of the American Society of Nephrology. 2013;8(10):1661-1669.
6. Cho M.H.Pediatric acute kidney injury: focusing on diagnosis and management. Childhood Kidney Diseases.2020;24(1):19-26.
7. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney international supplements. 2012;2(1):1-138.
8. Selewski DT, Cornell TT, Heung M, Troost JP, Ehrmann BJ, Lombel RM, et al. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. Intensive care medicine. 2014;40(10):1481-1488.
9. Bailey D, Phan V, Litalien C, Ducruet T,Merouani A, Lacroix J, et al. Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study.Pediatric Critical Care Medicine.2007; 8(1):29-35.
10. Al-Ismaili Z, Palijan A, Zappitelli M. Biomarkers of acute kidney injury in children: discovery, evaluation, and clinical application. Pediatric Nephrology. 2011;26(1):29-40.
11. Shahrin L. Sarmin M, Rahman AS, Hasnat W, Mamun GM, Shaima SN. et al.Clinical and laboratory characteristics of acute kidney injury in infants with diarrhea: A cross-sectional study in Bangladesh. Journal of International Medical Research.2020; 48(1):1-10.
12. McGalliard RJ, McWilliam SJ, Maguire S, Jones CA, Jennings RJ, Siner S, et al. Identifying critically ill children at high risk of acute kidney injury and renal replacement therapy. PloS one. 2020;15(10):e0240360.
13. Fitzgerald JC, Basu R, Akcan-Arikan A, Izquierdo LM, Olave BE, Hassinger AB, et al. Acute kidney injury in pediatric severe sepsis, an independent risk factor for death and new disability. Critical care medicine. 2016;44(12):2241-2250.
14. Dobiliene D, Rudaitis S, Kevalas R, Masalskiene J. A prognostic value of early urinary biomarkers NGAL and IL-18 in critically ill children: A 10-year literature review. Signa vitae: journal for intesive care and emergency medicine. 2018;14(2):14-19.
15. Hossain M, Biswas M, Islam MS, Ullah M, Sultana N, Hadi FMA, et al. Diagnostic value of urinary neutrophil gelatinase-associated lipocalin in detecting acute kidney injuryin asphyxiated term neonates. The Journal of Chittagong Medical College Teachers Association. 2022;33(1):173-177.
16. Luna SA, Sultana J, Yusuf MA, Uddin GM, Rahman MH, Roy RR. Diagnostic Validity of Serum Cystatin C for Detection of Acute Kidney Injury in Children. Bangladesh Journal of Infectious Diseases. 2020;7(2):44-48.
17. McCaffrey J, Coupes B, Chaloner C, Webb NJA, Barber R, Lennon R. Towards a biomarker panel for the assessment of AKI in children receiving intensive care. Pediatric Nephrology. 2015;30(10):1861-1871.
18. Basu, R.K. Wang Y, Wong H, Chawla LS, Wheeler DS, Goldstein SL. Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. Clinical Journal of the American Society of Nephrology.2014; 9(4):654-662.
19. Louzada CF, Ferreira AR. Evaluation of the prevalence and factors associated with acute kidney injury in a pediatric intensive care unit. 2021;97(4):426-432.
20. Zwiers AJ, de Wildt SN, Rosmalen JV, de Rijke YB, Buijs EA, Tibboel D, et al. Urinary neutrophil gelatinase-associated lipocalin identifies critically ill young children with acute kidney injury following intensive care admission: A prospective cohort study. Critical Care. 2015;19(1):181.
21. Filho LT, Grande AJ, Colonetti T, Della ÉS, da Rosa MI. Accuracy of neutrophil gelatinase-associated lipocalin for acute kidney injury diagnosis in children: Systematic review and meta-analysis. Pediatric nephrology. 2017;32(10):1979-1988.
22. Nehus E, Kaddourah A, Bennett M, Pyles O, Devarajan P. Subclinical kidney injury in children receiving nonsteroidal anti-inflammatory drugs after cardiac surgery. The Journal of pediatrics. 2017;189:175-180.
23. deGeus HR, Bakker J, Lesaffre EM, Le Noble JL. Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. American journal of respiratory and critical care medicine. 2011;183(7):907-914.
24. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, Group NM. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: A systematic review and meta-analysis. American journal of kidney diseases. 2009;54(6):1012-1024.
25. Gavrilovici C,Dusa CP,Mihai CT,Spoial a E.-L,Stârcea IM, Iliescu-Halitchi CO, et al. uNGAL Predictive Value for Serum Creatinine Decrease in Critically Ill Children. Healthcare. 2022; 10: 1575.