COMMENTARY

Early Diagnosis of Pediatric Acute Kidney Injury: An Achievable Goal?

Rekha Solomon

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Acute kidney injury (AKI) may be seen in 27–73%[1,2] of admissions to pediatric intensive care unit (PICU). Acute kidney injury is associated with mortality of 3–63%[1,3] as well as morbidity and increase in health care costs. Universal criteria such as Kidney Disease: Improving Global Outcomes (KDIGO, 2012), pediatric Risk, Injury, Failure, Loss, End-stage Renal Disease (pRIFLE, 2007), and Acute Kidney Injury Network (AKIN, 2008) criteria use serum creatinine and urine output for diagnosis and staging of AKI. Serum creatinine has been considered the gold standard for the measurement of glomerular filtration rate (GFR). However, glomerular filtration and serum creatinine do not have a linear relationship. Serum creatinine does not rise until 40–50% of baseline glomerular filtration has been lost and has poor sensitivity when there are acute changes in GFR. Serum creatinine level is also affected by multiple factors other than glomerular function. Similarly, urine output as a marker for AKI is confounded by factors, such as volume status, diuretics, and urinary obstruction.

Over the last 20 years, there has been increasing interest in renal biomarkers. These biomarkers may pick up damage prior to worsening of function and may provide an opportunity for intervention. They could also potentially help in clarifying the location of the injury, pathophysiology, cause, and prognosis. Renal biomarkers can be categorized as markers of:

- Tubular injury or stress (e.g., neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), Dickkopf-3 (DKK3), liver-type fatty acid binding protein (L-FABP)).
- Glomerular filtration (urinary cystatin-C).
- Inflammation (interleukin-8).
- Cell cycle arrest (insulin-like growth factor-binding protein-7(IGFBP-7) tissue inhibitor of metalloproteinase 2 (TIMP-2)).

They may also be categorized as stress biomarkers (e.g., Dickkopf-3, [TIMP-2]•[IGFBP7]), damage markers (e.g., NGAL, KIM-1), and functional markers (e.g., cystatin-C).

Renal biomarker research is mostly focused on the following areas: (1) recognition of patients at risk of AKI out of those undergoing planned interventions such as cardiac surgery or intravenous contrast, (2) early recognition of AKI in critically ill patients for prognosis and guiding therapy, (3) choosing the correct time to start as well as stop renal replacement therapy, and (4) to predict recovery or progression to chronic kidney disease.[4]

In this context, Ismail et al.[5] performed a case-control study to look at the utility of urinary TIMP-2 x IGFBP7 in early diagnosis of AKI in children admitted to the PICU over an 8-month period.

Department of PICU, Bai Jerbai Wadia Hospital for Children, Mumbai, Maharashtra, India

Corresponding Author: Rekha Solomon, Department of PICU, Bai Jerbai Wadia Hospital for Children, Mumbai, Maharashtra, India, Phone: +91 9820957669, e-mail: rekhasolomon1@gmail.com

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They studied 72 children admitted to PICU as well as 40 healthy children. Serum creatinine and urinary [TIMP-2]•[IGFBP7] were collected in the first 24 hours. Insulin-like growth factor-binding protein-7 (IGFBP-7) and tissue inhibitor of metalloproteinase 2 (TIMP-2) are markers of cell cycle arrest to prevent cell division of damaged cells. AKI was diagnosed as per p-RIFLE criteria. The authors have not mentioned how many children were admitted to the PICU during this time period, or how many were excluded and why.

Acute kidney injury developed in 45 of 72 patients on day 1 (26 with risk, 18 with injury, and 1 with failure). Renal function of 9 patients further worsened during their stay, with risk in 22, injury in 24, and failure in 6. The commonest causes for AKI were sepsis (38.5%) followed by hemodynamic instability and dehydration (17%). Urinary [TIMP-2]•[IGFBP7] levels were significantly higher in the failure stage [median 0.48, IQR 0.42–0.58 $(ng/mL)^2/1000$] as compared with injury [median 0.22, IQR 0.19–0.28 $(ng/mL)^2/1000$] or risk stage [median 0.16, IQR 0.13–0.21, $(ng/mL)^2/1000$] ($p = 0.001$). Urinary [TIMP-2]•[IGFBP7] had an area under ROC curve of 0.71 (sensitivity 56%, specificity 76.4%) with a cut-off point 0.2 $(ng/mL)^2/1000$. Area under the ROC of > 0.75 indicates good discriminative power of a test. The biomarker level was significantly higher in children receiving inotropes {0.25 ± 0.17 (ng/mL)/1000, $n = 35$} compared with those not receiving inotropes {0.17 ± 0.06 (ng/mL)/1000, $n = 35$, $p < 0.001$, $n = 40$}. Similarly, children receiving mechanical ventilation had higher biomarker levels ($p < 0.02$). The children with AKI had a significantly higher SOFA score and 30 day mortality. The authors have not mentioned how many children needed renal replacement therapy.

While the current study shows that the cell cycle arrest biomarkers may show utility in the diagnosis of the failure stage of AKI when creatinine is already elevated, there is insufficient evidence of its utility in the risk or injury stage of AKI. Studies in adults have shown urinary [TIMP-2]•[IGFBP7] to have area under ROC curve 0.8 to 0.89 for predicting AKI with a cut-off value of 0.3 $(ng/mL)^2/1000$.[6–8] There is however limited data in children. Cut-off values in various studies range from 0.2 to 2 $(ng/mL)^2/1000$. There is similarly wide variation in the population studied (critically ill children,[9] post-cardiac surgery,[10–12] post-nephrotoxin),[13] outcome measure (AKI occurrence,[10–13] mortality,[9] need for renal replacement therapy),[9] and dilution (i.e., with or without normalization for urinary creatinine).

Dong et al.[11] studied sequential levels of multiple biomarkers postcardiopulmonary bypass in 150 children to evaluate their accuracy in detecting AKI. Urine [TIMP-2]•[IGFBP7] levels were negligible at 2 hours, peaked at 12 hours, and declined to less than half the peak value by 24 hours. They found that NGAL was the best test at 2 and 6 hours. At 12 hours, NGAL along with IL-18, and TIMP2 was superior to NGAL alone; the area under ROC curve was 0.973 vs 0.938.

In a heterogeneous population of critically ill children, there may be wide variation in the etiology, site of injury, and timing and duration of the insult, suggesting that a single biomarker such as urine [TIMP-2]•[IGFBP7] may not be sufficient to predict early AKI in this group. In addition, cost and accessibility of the test may be a limiting factor, especially in low- and middle-income countries. The marker may be helpful in specific patient groups exposed to a single planned intervention such as cardiac surgery or nephrotoxin exposure.

Bedside risk stratification tools such as the Renal Angina Index and Frusemide stress test with or without renal biomarkers are being studied for early detection and/or type of renal injury. It is hoped that this will in future help in specific targeted therapy.

Assessment of AKI risk by renal angina index (RAI) may identify patients who are likely to develop severe AKI within 3 days of PICU admission. Renal angina index is a product of AKI risk and signs of injury with a maximum value of 40 and a cut-off value of ≥8. Acute kidney injury risk factors that are scored include ICU admission, solid organ or stem cell transplant, and need for mechanical ventilation or vasoactive support. A recent meta-analysis on the utility of RAI looked at 11 studies with 3,701 children of whom 752 had AKI. Sensitivity of RAI in the prediction of AKI was 0.85 (95% CI: 0.74–0.92) and specificity 0.79 (95% CI: 0.69–0.89). The area under the ROC curve of was 0.88 [95% confidence interval (CI): 0.85–0.91].[14]

It is important to remember that AKI is a dynamic process and has variable phenotype depending on creatinine, urine output, biomarkers, fluid overload, renal functional reserve, timing and duration of risk factors, and diuretic response. Combining clinical data with damage and functional biomarkers may help in delineating phenotype, severity, and mechanism[15] and potentially aid in targeted therapy in the future.

The question is how early diagnosis of AKI would change management. As of now there is no magic panacea. The interventions currently advised in early AKI comprise optimal volume and hemodynamic status along with avoidance of nephrotoxins. These are part of the standard of care of any critically ill child. Additionally, where known, reversible causative factors such as abdominal compartment syndrome, bladder outlet obstruction, and fluid overload should be treated followed by nephrology consultation and consideration for renal replacement therapy.

In summary, a single renal biomarker such as urine [TIMP-2]•[IGFBP7] does not currently appear to be superior to serum creatinine and urine output along with clinical data in early diagnosis of AKI in a heterogeneous group of critically ill children. Biomarkers may have a role in early pick-up and targeted treatment of AKI in specific patient groups although currently not in routine clinical practice.

Orcid

Rekha Solomon https://orcid.org/0000-0001-8611-9237

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