Predictive ability of renal angina index alone or in combination with biomarkers for detection of acute kidney injury in children

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Introduction

Acute kidney injury (AKI), formerly known as ‘acute renal failure,’ is an important clinical entity accounting for about 3–5% of patients admitted to hospitals [1], and 20% in pediatric, 30% in neonatal and 40–60% in cardiac intensive care units [2, 3]. AKI in infants constitutes about 30% of total admitted children [4]. In neonates, sepsis, hypoxic/ischemic injury, hypernatremic dehydration, posterior urethral valves and post-cardiac surgery are predominant etiologies [5–7], while acute gastroenteritis causing hypovolemia, sepsis, hemolytic uremic syndrome, diabetic ketoacidosis, malaria and post-bone marrow or stem cell transplant are common in older infants and children [8–11]. Serum creatinine is not a reliable marker to detect AKI as it rises when about 50% of the glomerular function is decreased and also is affected by height, gender, body mass and hydration status. Management strategy essentially includes correction of fluid and electrolyte imbalance, treatment of underlying conditions, avoidance of nephrotoxic medications and dialytic support, as and when needed. However, it is associated with higher mortality as well as being a potential risk factor for progression to acute kidney disease and residual kidney injury [12]. Therefore, in clinical practice there is a need for early detection, institution of therapeutic measures and prevention of further kidney damage.

Classification of AKI

In 2004, the Acute Dialysis Quality Initiative Group created the first consensus classification by Risk, Injury, Failure, Loss and End stage (RIFLE) criteria [13]. Thereafter, it was modified for use in children as pediatric RIFLE

(pRIFLE) [14]. The Acute Kidney Injury Network (AKIN) criteria were also proposed, expanding the diagnostic criteria to include a ≥ 0.3 mg/dL absolute creatinine rise in a 48-h period [15]. Thereafter, the Kidney Disease Improving Global Outcomes (KDIGO) classification integrated the RIFLE, pRIFLE and AKIN classifications system [16]. Presently, it is the accepted staging system of AKI in infants and older children and also further modified for use in neonates [6]. This categorizes AKI based on an increase in serum creatinine from a previous trough level and decrease in urine output or anuria over a certain time period. The AKI staging is mainly meant for stratifying the severity of AKI from the management point of view and also prognosticating the short-term outcome and future residual kidney damage.

Renal Angina Index

The renal angina index (RAI) was developed by Basu et al. [17] for AKI in children based on the *risk factors* (ICU admission—score 1, solid organ/bone marrow transplant—score 3, ventilation and inotrope use—score 5) and *evidence of kidney injury* (no change in estimated creatinine clearance (eCCl) or fluid overload (FO) $< 5\%$ —score 1, $\downarrow$ eCCl 0–25% or FO $\geq 5\%$ —score 2, $\downarrow$ eCCl 24–49% or FO $\geq 10\%$ —score 4, $\downarrow$ eCCl $\geq 50\%$ or FO $\geq 15\%$ —score 8). It is derived based on the multiplication of scores of two variables (risk strata score and injury score) and ranges between 1 and 40. Subsequently, it was validated in a large cohort of AKI patients ($n = 1590$) admitted in ICUs and RAI of ≥ 8 performed better than rise of serum creatinine from maximum value in first 12 h of ICU admission [odds ratio (OR) 3.21; 95% confidence interval (CI) 2.20–4.67 vs. OR 0.68; and 95% CI 0.49–4.94, respectively] in prediction of severe AKI on day 3 of ICU admission [18]. Sundararaju et al. [19] evaluated utility of RAI (≥ 8) in prediction of severe AKI on day 3 and observed area under the curve (AUC) of 0.82; 95% CI 0.73–0.90 and day 7 AUC of 0.73; and 95% CI 0.62–0.84

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and also found correlation with duration of mechanical ventilation and hospital stay.

Biomarkers in AKI

Biomarkers can be detected in patients with AKI both in plasma and urine. Certain biomarkers like cystatin C, beta2 microglobulin and lysozyme are smaller molecular weight substances that are filtered through the glomerulus and reabsorbed by the proximal tubules, but appear in urine in response to tubular injury. A second group of biomarkers are due to upregulation in renal cells due to kidney injury such as neutrophil gelatinase-associated lipocalin A (NGAL), interleukin-18 (IL-18) and kidney injury molecule 1 (KIM-1). The third group of biomarkers such as N-acetyl-b-D-glucosaminidase (NAG) are expressed by tubular epithelial cells and released into the urine in the setting of AKI [20]. The newer biomarkers like tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are formed and released in urine after kidney tissue injury [21]. Urinary biomarkers have been studied in early detection of AKI; NGAL being the most widely observed and found has an AUC of 0.82 in a meta-analysis including 19 studies covering 2538 patients [22]. In a comparative study of urinary NGAL, NAG and IL-18 in patients with AKI for mortality, NGAL (AUC 0.750, 95% CI 0.580–0.920) and NAG (AUC 0.724, 95% CI 0.541–0.907) had modest values of AUC with sensitivity and specificity of 75% each, while IL-18 had lower values (AUC 0.688, 95% CI 0.511–0.864, sensitivity 62.5% and specificity 70.8%) for prediction. Children requiring dialysis were found to have significantly raised levels of NGAL, NAG and IL-18, and only NGAL level had significant association with duration of hospital stay [23]. However, the combination of RAI and urinary biomarkers may provide better insight and prediction for detection of severe AKI and also correlation with other parameters such as need of kidney replacement therapy (KRT), mechanical ventilation, length of hospital stay and mortality.

Results of Meena et al.'s meta-analysis

Recently, Meena et al. [24] carried out a meta-analysis with the primary objective to investigate the predictive ability of RAI (≥ 8) on day 0 (within 8–12 h) for the development of severe AKI (stages 2 and 3 KDIGO classification or equivalent injury and failure stages of pRIFLE) and secondary outcomes for prediction of any stage of AKI (day 3) and need of KRT. In addition, diagnostic accuracy of a combination of RAI and biomarkers in predicting severe AKI was also analyzed. Other outcome measures were the relationship of

RAI positivity (RAI ≥ 8) with mortality, duration of ICU stay and need of mechanical ventilation.

There were 22 studies (17 prospective, 4 retrospective and 1 mixed) which included 14,001 children. All the studies assessed RAI on day 0 and used a cut-off of ≥ 8 to define RAI positivity. The overall incidence of any stage AKI was 35% (95% CI 22–48) and severe AKI of 15% (95% CI 10–20). Eighteen studies, which included 5847 patients, had reported primary outcome with summary sensitivity of 0.86 (95% CI 0.77–0.92), specificity of 0.77 (95% CI 0.68–0.83), and AUC of 0.88 (95% CI 0.85–0.91) for prediction of severe AKI on day 3; diagnostic odds ratio was 21 (95% CI 12–37). Regarding prediction of any stage of AKI on day 3 of hospitalization, RAI positivity on day 0 had summary sensitivity and specificity of 0.79 (95% CI 0.62–0.90) and 0.81 (95% CI 0.64–0.91), respectively, with AUC of 0.87 (95% CI 0.84–0.90) and OR of 16 (95% CI 5–51). The sensitivity, specificity and AUC of RAI for predicting the need for KRT were 0.82 (95% CI 0.71–0.90), 0.74 (95% CI 0.66–0.81) and 0.85 (95% CI 0.81–0.88), respectively, as reported in 14 studies which included 5521 patients.

A combination of RAI and urinary NGAL showed pooled summary sensitivity, specificity and AUC of 0.76 (95% CI 0.62–0.85), 0.89 (95% CI 0.74–0.96) and 0.87 (95% CI 0.84–0.90), respectively, with diagnostic OR of 24 (13–46) for predicting severe AKI in 4 studies, which included 1523 participants. Thus, there was improvement in specificity with similar AUC for prediction of severe AKI when RAI was combined with urinary NGAL.

Eleven studies (4958 participants) showed that RAI positive (≥ 8) cases had 21.4% mortality as compared to 4.5% in those who were RAI negative. Further, children with RAI ≥ 8 on day 0 are at increased risk for mortality during the hospital stay (OR 5.5; 95% CI 3.0–10.1, $I^2 = 82\%$), had significantly longer duration of ICU stay (mean difference: 1.6 days; 95% CI 0.2–3.0, $I^2 = 84\%$) and also required mechanical ventilation for a longer duration (mean difference: 2.1 days; 95% CI 0.23–4.0, $I^2 = 92\%$).

The analysis of Meena et al. [24] had major limitations also as there was considerable heterogeneity in the studies analyzed (sensitivity ($I^2 = 94\%$, $p < 0.001$) and specificity ($I^2 = 97.5\%$, $p < 0.001$). However, when neonates and children aged more than 18 years were excluded, then no significant difference in pooled estimates of sensitivity and specificity was observed. In meta-regression, only the study setting (sepsis vs. heterogeneous) was associated with heterogeneity. The group of children with sepsis had summary sensitivity of 0.93 ($\geq 95\%$ CI 0.79–0.98, $I^2 = 76\%$) and specificity of 0.58 (95% CI 0.42–0.72, $I^2 = 92\%$) compared with heterogeneous etiologies (summary sensitivity 0.84, 95% CI 0.72–0.91, $I^2 = 94\%$ and specificity 0.81, 95% CI 0.73–0.87, $I^2 = 97\%$).

Overall, positive RAI (≥ 8) had a good predictive ability to identify children at risk of severe AKI on day 3 with moderate certainty and combining RAI with urinary NGAL further improved the predictive ability with low certainty.

Clinical application

Early detection of AKI in critically ill children in an ICU setting is often a challenging situation as diagnosis is mainly based on clinical indications (oliguria/anuria) and/or rise of serum creatinine, which is a late phenomenon. In addition, fluid overload, use of nephrotoxic medications, need of mechanical ventilation and KRT often complicate the condition and contribute to mortality [2, 7, 9]. Therefore, it becomes imperative to apply some other clinical (RAI) and biochemical (urinary/plasma) markers for early detection, application of preventive measures and institution of an early KRT, as and when needed.

The RAI (≥ 8) has been validated in prediction for severe AKI [18, 19], need of KRT, mechanical ventilation and relationship with duration of hospital stay [19]. In addition, a higher RAI threshold (≥ 12 or ≥ 20) has been found to be more useful than RAI of ≥ 8 [19]. Recently, Raina et al. [25] reported that predictive ability of RAI for AKI had a pooled sensitivity of 79.21%, specificity of 73.22% and negative predictive value of 94.83%, analyzed in 11,026 participants.

Biomarkers have also been found to be useful in early prediction of AKI. A meta-analysis showed that serum cystatin C had the highest value of prediction for detection of AKI in children, especially in the first 24 h by considering a cut-off point between 0.4 and 1.0 mg/L [26]. In addition, urinary NGAL, and NAG have modest prediction for mortality and NGAL has significant association with duration of hospital stay also [23].

Thus, individually RAI or biomarker (NGAL or cystatin C) has modest prediction in early detection of AKI. Therefore, attempts have been made to combine RAI and biomarkers to improve the predictive ability. In one study, maximum sensitivity (92.3%), specificity (97.5%) and accuracy of 96.2% were found by combining RAI and urinary cystatin C for detection of AKI in critically ill children [27]. However, in the present meta-analysis by Meena et al. [24], combination of urinary NGAL with RAI positivity was found to have better specificity of prediction of severe AKI. Individually plasma NGAL has been found to have lower predictive ability than urinary NGAL and RAI, but in combination with RAI, they have better prediction for severe AKI [28]. Basu et al. [29] studied discrimination of plasma NGAL, matrix metalloproteinase-8 (MMP-8) and neutrophil elastase-2 (Ela-2), determined individually and in combination with the RAI for severe AKI in children with sepsis. The inclusion of a biomarker with RAI showed net reclassification

improvement of 0.512, 0.428 and 0.545 for NGAL, MMP-8 and Ela-2, respectively ($p < 0.03$ for all), and the authors concluded that incorporation of AKI biomarkers into the RAI improves the discrimination for severe AKI. Considering the utility of RAI and biomarkers, the Acute Disease Quality Initiative recommended that in high-risk patients a combination of biomarkers along with clinical information should be used to improve the diagnostic accuracy of AKI and assists in the management of patients of AKI [30]. Therefore, use of RAI in combination with a biomarker such as NGAL can be employed to predict development of severe AKI and appropriate preventive measures can be undertaken as a management strategy in patients with AKI in the ICU set-up.

Conclusion

Application of RAI of ≥ 8 on the first day of hospitalization in critically ill children had modest prediction of severe AKI on day 3 and requirement of KRT. Combination of urinary NGAL further improves its specificity. Therefore, under the constraints of presently used parameters such as serum creatinine for detection of AKI, utility of a combination of RAI and urinary NGAL is a forward step in its application for prediction of severe AKI in critically ill children.

Data Availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest Author declares no competing interests.

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