RESEARCH PAPER

# Prediction of Severe Acute Kidney Injury using Renal Angina Index in a Pediatric Intensive Care Unit

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**Objectives:** To determine the proportion of children in a pediatric intensive care unit with a positive Day 0 Renal angina index who develop severe acute kidney injury (AKI) on Day 3; and to compare the predictive ability of the index with that of individual markers of renal injury, for the development of severe acute kidney injury. **Design:** Observational study. **Setting:** Pediatric intensive care unit of a tertiary-care hospital. **Participants:** Consecutive children, 1 month to 12 years, admitted in Level 3 pediatric intensive care unit for a minimum of 8 hours, having weight and intake-output records, were eligible. Children known to have chronic kidney disease or already in stage 2/3 acute kidney injury/dialysis were excluded. **Procedure:** Day 0 Renal angina index was calculated from the product of Risk Group score (Pediatric intensive care admission/Ventilation and inotropy) and Renal Injury score (fluid overload over previous 8 hours or the % fall in estimated creatinine clearance from baseline). Renal angina index ≥8 was considered positive. **Main outcome measure**: The proportion of children with positive Day 0 Renal angina index who develop severe AKI (Kidney Disease Improving Global Outcomes (KDIGO) ≥ Stage 2) on Day 3. **Results:** Of 162 enrolled children (median (IQR) age 10.5 (3,39) months), 86 (53%) had positive Renal angina index. On Day 3, a higher proportion of children with positive index developed severe AKI, compared to negative group (RR 95.5; 95% CI 21.7,420.5; *P*<0.001). Day 0 positive Renal angina index had a sensitivity, specificity, positive predictive value and negative predictive value of 96.9%, 75.5%, 72% and 97.4% respectively, for predicting severe AKI on Day 3. The Receiver Operating Characteristic curve of Day 0 renal angina scores showed AUC of 0.90 (95% CI 0.85, 0.95), better than the AUC obtained from either Day 0 serum creatinine or Day 0 percent fall in estimated creatinine clearance from baseline. **Conclusion**: Day 0 Renal angina index positivity is a promising tool to identify critically ill children with impending severe AKI.

**Keywords:** *Acute renal failure, Creatinine, Management, Outcome*.

There is a pressing need to identify subsets of critically ill children who are at high risk for incurring severe renal injury, which has been shown to have detrimental effects both in short and long term [1-3]. The essential marker by which acute kidney injury (AKI) has been diagnosed for years is serum creatinine, which deceptively remains normal till much of the renal injury has already occurred [4,5]. The diagnostic performance of biomarkers of AKI has been poor when used in a heterogenous population [6,7]. To prevent delayed recognition of AKI, it is imperative to have a composite set of clinical and laboratory parameters, the combined presence of which is likely to predict severe AKI. To this end, a 'Renal Angina Index' (RAI) scoring system has recently been validated in children [8-10].

In this study, we aimed to determine the ability of RAI, calculated on Day 0 of admission of children to an intensive care unit, to predict the occurrence of severe AKI (≥Stage 2 of Kidney Disease Improving Global Outcome (KDIGO) classification) [11,12] on Day 3. We also compared the predictive ability of RAI with other traditional markers of renal injury.

*Accompanying Editorial: Pages 641-42.*

## Methods

This was a prospective observational study, conducted in the pediatric intensive care unit (PICU) of a tertiary care, public hospital from January 2017 to October 2017. Ethical approval was obtained from Institutional Ethics Committee, Maulana Azad Medical College. All consecutive children, 1 month to 12 years of age, admitted in PICU, with at least 8 hours of PICU stay and having documented body-weight and intake-output

records over this duration, were eligible for the study. Known cases of chronic kidney disease, and children already in stage 2 or 3 AKI or on dialysis were excluded.

Considering an incidence of severe AKI (stage 2 and stage 3) in PICU as 10% per year [8], precision of 5%, and alpha error of 0.05, a sample size of 144 was obtained. Expecting an attrition rate of 10%, due to protocol deviation, our final sample size was 160.

After obtaining informed consent, subjects meeting eligibility criteria were enrolled and relevant data including anthropometry, demographic parameters, admission diagnosis, co-morbidities, vital signs, and other clinical and laboratory parameters were recorded. Those who had a PICU stay of less than 3 days were excluded from the study.

Basic investigations like complete hemogram, urea, creatinine, total protein, albumin, sodium, potassium were done on Day 0. Serum creatinine was estimated daily till Day 3, following which it was done as per clinical requirement. The RAI was determined for all enrolled subjects between 8 and 12 hours from the time of PICU admission on Day 0. The Renal angina index was defined as the product of Risk Group Score and Renal Injury Score [8]. Subjects having a RAI score ≥8 on Day 0 were classified as RAI Positive.

Day 0 was defined as the first calendar day of PICU admission, considered after a minimum of 8 hours from the time of PICU admission. Day 3 was defined as the time period between 72 and 96 h after PICU admission. Severe acute kidney injury was defined by the KDIGO AKI classification stage ≥2, that is, serum creatinine of ≥200% above baseline/nadir value or ≤0.5 mL/kg/h of urine output for ≥12 hours [11,12].

Fluid overload on Day 0 was determined by subtracting urine output or any other major extra renal losses over 8-12 hours of admission in PICU from the total fluid intake during this duration, and was expressed as a percentage of bodyweight. The percentage fall in estimated creatinine clearance (eCrCl) was calculated by comparing serum creatinine at enrolment (after minimum 8-12 hours of PICU admission) with the patient's baseline serum creatinine (lowest serum creatinine value documented in the 3 months prior to PICU admission), if available. When baseline serum creatinine was not available, a reference eCrCl as per age standards for GFR was used as a baseline GFR [13].

The primary outcome was the proportion of children in level 3 PICU with Day 0 RAI score ≥8 who develop severe AKI on Day 3 of admission. The secondary outcomes were comparison of the predictive ability of Day 0 RAI with those of serum creatinine and %fall in eCrCl on Day 0; the association of different risk factors, with the development of severe AKI on Day 3.

*Statistical analyses*: Predictive ability of Day 0 RAI score was assessed by calculating sensitivity, specificity, positive predictive value and negative predictive value. Receiver operating characteristic (ROC) curves for Day 0 RAI values, Day 0 serum creatinine and Day 0 percentage fall in eCrCl from baseline were constructed for predicting severe AKI on Day 3. Other possible risk factors associated with the occurrence of severe AKI on Day 3 were also assessed by univariate and multivariate logistic regression. Risk factors associated with mortality were also assessed by univariate and multivariate analyses. The data were analyzed with SPSS version 23. All the results were considered significant at $P<0.05$.

## RESULTS

Out of a total of 293 children admitted in Level 3 of PICU, during the study period, 162 children were enrolled (***Fig.* 1**). ***Table* I** shows the baseline RAI scores; on Day 0, 86/162 (53%) children had a RAI ≥8. The lowest RAI of 1 was seen in 32 (19.8%) children, while 15 (9.3%) had the highest RAI of 40.

The baseline characteristics of the enrolled children and their outcomes have been compared between the groups of Positive and Negative Day 0 RAI in ***Table* II**. Of the 86 children who were RAI positive on Day 0, 62 (72.1%; 95% CI 62.6 %-81.4%) developed severe AKI on Day 3 in contrast to 2/76 (2.6%) children who were RAI negative (RR 95.5; 95% CI 21.7, 420.4; $P$ <0.001). During their entire PICU stay, a total of 66 out of 86 RAI positive children developed severe AKI, the median (IQR) time for this development being 3 (2,4) days.

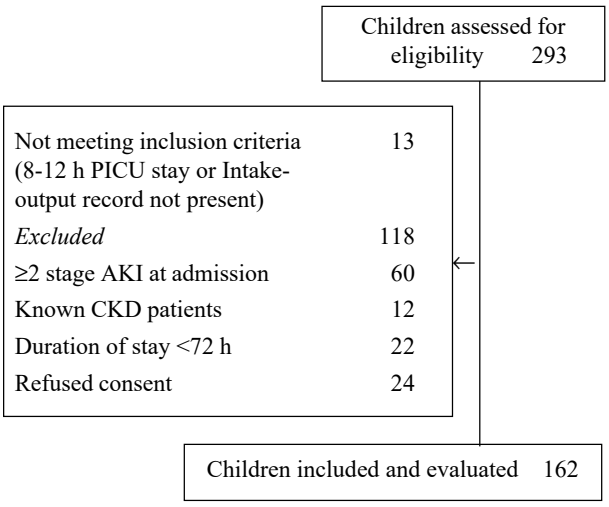


**Fig. 1** *Flow of participants in the study.*

**TABLE I** CLASSIFICATION OF CHILDREN IN PICU AS PER RISK GROUP, RENAL INJURY AND RENAL ANGINA INDEX

| *Renal Angina Index parameter scores* | *n (%)* |
|---|---|
| *Risk Group Scores* | |
| 1 (PICU admission) | 92 (56.8) |
| 3 (Stem cell/solid organ transplantation) | 0 |
| 5 (Mechanical ventilation and use of inotropes) | 70 (43.2) |
| *Highest Renal Injury Scores* | |
| 8 | 41 (25.3) |
| 4 | 46 (28.4) |
| 2 | 33 (20.4) |
| 1 | 42 (25.9) |
| *Renal Angina Index (RAI)* | |
| Positive (>8) | 86 (53%) |
| Negative (<8) | 76 (47%) |

*PICU: Pediatric intensive care unit; Renal angina index: Risk group score x Renal injury score.*

A positive Day 0 RAI was found to have a sensitivity of 96.9%, a specificity of 75.5%, a positive predictive value of 72% and a negative predictive value of 97.4%. A Receiver operating characteristic (ROC) curve was constructed for assessing individual values of Day 0 RAI for predicting severe AKI on Day 3, with an AUC (Area Under the Curve) of 0.90 (95% CI 0.85, 0.95). Serum creatinine at enrolment and Percentage fall in eCrCl from baseline showed AUC (0.68 and 0.73, respectively) much inferior to that of RAI (***Fig.* 2**).

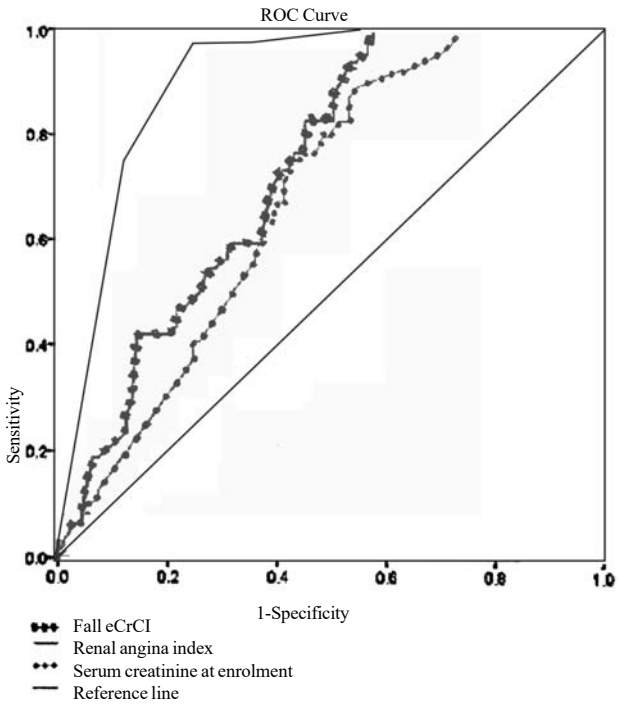


**Fig. 2** *Receiver Operating Characteristic curves for (i) Day 0 Renal angina index, (ii) Day 0 serum creatinine, and (iii) percentage fall in eCrCl from baseline on Day 0 for predicting severe AKI on Day 3.*

Univariate regression analysis done to evaluate the effect of individual parameters showed that use of mechanical ventilation, inotropes, amikacin, hypotension, fall in eCrCl from baseline, mean oxygen saturation during ICU stay and Day 0 positive RAI score were significantly associated with occurrence of severe AKI on Day 3. Multivariate analysis showed that positive Day 0 RAI score was the only parameter which had an independent association with the occurrence of Severe AKI on Day 3 (***Table* III**).

**TABLE II** COMPARISON OF PARAMETERS BETWEEN CHILDREN WITH POSITIVE DAY 0 RAI (RAI ≥8) AND THOSE WITH NEGATIVE RAI

| *Parameters* | *RAI Positive (n=86)* | *RAI Negative (n=76)* |
|---|---|---|
| *Age, mo (*median, IQR*) | 7 (3-24) | 24 (4-60) |
| Gender (*Male:Female*) | 51:35 | 44:32 |
| *Major Diagnostic* group, *n (%)* | | |
| *Respiratory | 65 (76) | 41 (54) |
| CNS | 20 (23) | 16 (21) |
| Gastrointestinal | 14 (16) | 19 (25) |
| Sepsis | 19 (22) | 9 (12) |
| *PRISM 3 score, n(%)* | | |
| <5 | 51 | 49 |
| 5-10 | 21 | 23 |
| 10-20 | 12 | 3 |
| >20 | 2 | 1 |
| *At enrolment*, *n* (%) | | |
| *GCS | 11.5 (2.5) | 12.3 (1.8) |
| #Mechanical ventilation | 61 (71) | 17 (22) |
| #Inotropes | 67 (78) | 24 (32) |
| Fluid overload (% body wt) | 1.3 (1.3) | 2.8 (1.6) |
| $% Fall in eCrCl from baseline | 39.8 (18.8) | 14.6 (18.3) |
| *Maximum AKI stage, n (%)* | | |
| #No AKI | 1 (1.2) | 47 (61.8) |
| Stage 1 | 19 (22.1) | 26 (34.2) |
| #Stage 2 | 51 (59.3) | 2 (26) |
| #Stage 3 | 15 (17.4) | 1 (1.3) |
| #Severe AKI (>Stage2) on Day 3 | 62 (72) | 2 (2.6) |
| †Mortality, *n* (%) | 21 (24) | 6 (8) |

*RAI: Renal angina index; CNS: Central nervous system; GCS: Glasgow Coma Scale; eCrCl: estimated creatinine clearance; AKI: acute kidney injury; PICU: Pediatric intensive care unit; *P<0.005; #P<0.001; $P<0.01; †P=0.005.*

**TABLE III** UNIVARIABLE AND MULTIVARIABLE ANALYSIS EVALUATING ASSOCIATION OF INDIVIDUAL PARAMETERS WITH OCCURRENCE OF SEVERE ACUTE KIDNEY INJURY ON DAY 3

| *Parameters* | *Univariate analysis OR (95% CI); P value* | *Multivariate analysis OR (95% CI); P value* |
|---|---|---|
| Age (mo) | 0.9 (0.9, 1.0); 0.17 | |
| Gender | 1.2 (0.6, 2.2); 0.63 | |
| Sepsis | 1.7 (0.7, 3.8); 0.21 | |
| Mechanical ventilation | 7.8 (3.8, 16.0); <0.001 | 2.2 (0.6, 8.0); 0.25 |
| Use of amikacin | 1.9 (1.0, 3.8); 0.04 | 1.3 (0.5, 3.3); 0.58 |
| Use of inotropes | 6.6 (3.1, 13.9); <0.001 | 1.1 (0.2, 5.3); 0.94 |
| Hypotension | 3.9 (2.0, 7.7); <0.001 | 1.4 (0.4, 4.9); 0.62 |
| Fall in estimated creatinine clearance from baseline | 1.0 (1.0, 1.1); <0.001 | 1.0 (0.97, 1.04); 0.65 |
| Urine output in 8 h prior to enrolment | 1.2 (0.9,1.4); 0.13 | |
| Fluid overload (% of body weight) | 1.1 (0.8, 1.3); 0.57 | |
| Episodes of significant hypoxia | 5.4 (1.7, 17.7); 0.005 | |
| Mean $O_2$ saturation during ICU stay | 0.9 (0.8, 1.0); 0.024 | 0.9 (0.8, 1.0); 0.16 |
| Post-operated case | 0.4 (0.1, 2.1);0.28 | |
| Positive Renal Angina Index score on day 0 | 95.6 (21.7, 420.5); <0.001 | 55.5 (8.9, 333.3); <0.001 |
| PRISM III score ≥10 | 2.7 (0.99, 7.4); 0.53 | |

Of the total of 69 children developing severe AKI (≥ Stage 2) during ICU stay, 49 (71%) children had a complete recovery of renal function and 4 had some improvement. On the other hand, 16 children had persistent severe derangement of renal function and all of them died at a median (IQR) time of 3.5 (2,5) days after admission.

The median (IQR) length of ICU stay for all enrolled subjects was 6 (4,11) days, with no significant difference between those who were RAI Positive or RAI negative [6 (4,13) *vs* 5 (4,9); *P*=0.54].

## DISCUSSION

This hospital-based study showed that a positive RAI at admission was a strong predictor of AKI on day 3. RAI performed better than baseline serum creatinine and percentage fall in eCr/Cl from baseline in predicting AKI.

The study, comprising of children with a similar spectrum of diseases, as observed in other studies in intensive care [8,14-17], had a significantly higher proportion of younger children in the RAI positive group, compared to the RAI negative group, in contrast to the AWARE study [17]. However, other studies found neither demographic parameters nor primary system of involvement to have any significant bearing on renal angina positivity [18,19].

With a total of 91 (56%) children receiving one or more inotropes, and 78 (48%) on mechanical ventilation, at enrolment, our study had a relatively larger proportion (over 50%) of children in PICU showing RAI positivity on Day 0, compared to other reports [8,19]. As reported by others, severity of sickness, reflected in higher PRISM scores, was significantly more common in the RAI positive group [10,18]. However, unlike other studies, development of severe AKI was not influenced by the severity of PRISM scores in our study. The unreliability of the non-specific 'severity of illness' (SOI) scores like PRISM or PIM (Pediatric Index of Mortality) to adequately predict progression of individual organ failure is already a known fact in medical literature [20,21].

In our study, more than 70% of RAI positive developed severe AKI on Day 3; the proportion being higher than those reported by others [18,19]. Basu, *et al*. [8], also concluded that a RAI under 8 had high NPV (92-99%) for Day-3 AKI. However, the predictive ability of RAI in their study was only modest (AUC 0.78-0.81) [8], while another study found an even poorer predictive accuracy of RAI (AUC 0.61-0.82) [22].

Our results are in parallel with the results of the AWARE study [17] and of Basu, *et al.* [8], wherein RAI outperformed other markers of renal injury. Other authors have also provided multivariate analysis showing RAI as an important marker of AKI [22].

Our study has the limitation that while calculating the

**WHAT IS ALREADY KNOWN?**

- Serum creatinine is presently used as a marker of acute kidney injury.

**WHAT THIS STUDY ADDS?**

- A positive Renal Angina Index (≥8) is a superior tool, compared to serum creatinine, to reliably identify critically ill children at high risk for severe acute kidney injury by day 3 of hospital admission.

percentage fall eCrCl on Day 0, we have used age based Western reference standards for GFR as baseline GFR [13]. This may have overestimated the RAI scores, but due to lack of standards available in Indian children, this is the best approximation as of today.

This study shows that RAI, when ≥8 on the first day of hospitalization, reliably identifies those critically ill children who are at higher risk for developing severe AKI on Day 3 of hospitalization. The discriminative accuracy of RAI supersedes that of individual traditional creatinine based renal injury parameters. The independent effect of RAI for predicting severe AKI is maintained even after adjustment for other risk factors. Intensive care practitioners should consider using RAI for risk stratification and prognostication in sick children.

*Contributors*: J: enrolled subjects, collected data, was involved in analysis of data and creation of final draft. KM: conceptualized the study, supervised and monitored the conduct of the study, and was responsible for analysis of data and writing the final manuscript; MK: provided critical inputs Meaning the study, supervised the study and approved the manuscript writing; DS: was responsible for regular guidance and supervision of data collection and approval of final manuscript.

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