Original Article

Renal Angina Index-Clinical Tool to Predict Acute Kidney Injury in Patients Admitted in Pediatric Intensive Care Unit: A Prospective Study

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DOI:10.37821/ruhsjhs.8.2.2023.589

ABSTRACT

Introduction: Acute kidney injury (AKI) is an important risk factor associated with a high incidence of morbidity and mortality in critically ill children. Therapy for AKI is limited by the inability to reliably diagnose AKI in early stages. The renal angina index (RAI) may be a good clinical score to predict AKI in these children. The study aimed to predict development of subsequent AKI in children admitted in PICU using RAI score.

Methodology: A prospective observational study was conducted in PICU including 280 children between one month to 18 years of age with no history of previous or existing kidney diseases. RAI was assessed on day 0 (within 8 to 12 hours of PICU admission) and positivity was defined as RAI score ≥8. On day 3, serum creatinine was performed and glomerular filtration rate (eGFR) was calculated using the Schwartz formula. RAI positivity correlated with the presence/absence of AKI on day 3. Duration of PICU stay, need of dialysis, need of inotropic support, duration of mechanical ventilation, and final out come were also studied in relation to RAI score.

Results: Out of 280 patients, 58 (20.7%) had RAI score >8 (RAI +ve) on day 0. Out of these 58 RAI positive patients, 38 patients (65.51%) developed AKI on day 3 as compared to only 19 (8.56%) patients out of 222 in RAI negative group ($p<0.001$). The mean duration of mechanical ventilation was 72.02 ± 83.45 hours and 9.10 ± 25.64 hours in the RAI positive and negative groups, respectively ($p<0.001$). The mean duration of hospitals stay in the RAI positive group was 6.95 ± 4.33 days when compared to 4.11 ± 1.64 days in the RAI negative group. Mortality was significantly high in the RAI positive group (22.41%) compared to RAI negative group (8.56%).

Conclusion: Renal angina index is a simple and effective clinical tool to predict AKI in critically ill pediatric patients. It could be of great importance in the future, especially in developing countries where costly bio-markers or diagnostic tools for detection of AKI are scarce or not available in all settings.

Keywords: Acute kidney injury, Pediatric intensive care unit, Renal angina index.

INTRODUCTION

Acute kidney injury (AKI), defined as an abrupt decline in renal function within 48 hours is a common complication among critically ill hospitalized children with a rising incidence. Period prevalence of acute renal failure had been reported from 1.5 % to 24 % depending on the population studied and criteria used.[1] AKI leads to increased risk of mortality, duration of mechanical ventilation, and hospital stay among critically ill children.[2,3] The risk of mortality is even higher at around 50% among children with AKI requiring dialysis.[4] AKI survivors are also at risk for chronic kidney disease (CKD) progression.[5] Primarily due to the lag in the rise of serum creatinine, the diagnosis of AKI is often delayed, which creates a significant barrier to effective early intervention.[6,7] Due to this reason, renal angina index (a product of risk factors and renal injury) was conceptualized.[8]

Goldstein et al[9] proposed the empiric clinical model of renal angina to identify which critically ill patients would be at the greatest risk of AKI. Using patient risk factors and early signs of injury, the renal angina model aims to delineate patients at high risk for development of subsequent severe AKI (AKI beyond the period of functional injury) versus those at low risk. Fluid administration beyond the correction of hypovolemia is associated with increased morbidity, a longer hospital stays, and mortality.[10] Renal angina index is also intended

to enrich potential clinical studies of biomarkers by limiting their use to those most likely to have persistent AKI. The present study was done to assess the renal angina index in critically ill children and its role in predicting acute kidney injury.

METHODS

It was a prospective observational study, conducted in the PICU of the Department of Pediatrics, SMS Medical College, Jaipur. Prior approval was obtained from the institutional ethics committee. All children between the age of one month to 18 years who had at least 72 hours of PICU stay were included in the study. Previously known cases of kidney disease were excluded. After obtaining informed consent, relevant clinical examination, and laboratory parameters, pediatric risk of mortality (PRISM II)[11] score was applied and recorded. In patients where baseline creatinine was not available, an assumed glomerular filtration rate (GFR) of 120 ml/min./1.73 m^2 was used. For renal dysfunction, kidney disease improving global outcomes staging (KDIGO) was used.[12]

Renal angina index was calculated within 8-12 hours of the admission in PICU and serum creatinine was measured again at 72 hours (3 days). Risk factors were assigned a score: 1, 3, or 5 (where 1 denotes the lowest risk and 5 denotes the highest risk). The injury score was assigned on the basis of fluid overload percentage and estimated glomerular filtration rate (eGFR) reduction. Percentage fluid overload (FO%) was calculated by the formula: [Fluid in (ml) – Fluid out (ml)] ÷ Patient weight (gm) × 100).[13] eGFR based on estimated creatinine clearance (eCrCl) was calculated by the Schwartz equation[14] for the determination of RAI.

Renal angina index (range 1 to 40) was calculated by multiplication of the risk score and injury scores (FO% score or GFR score, whichever of the two were worse). The index RAI ≥8 was considered renal angina positive (RA positive) and A<8 as renal angina negative (RA negative)[15] (Table 1).

The primary outcome was the presence of AKI on day 3 (Day 3-AKI). Secondary outcomes were the need of dialysis, use of inotropes, need and duration of mechanical ventilation, length of stay (LOS), and mortality. Continuous data were summarized using descriptive statistics (mean ± standard deviation). Statistical differences between the mean values were compared using Student's t-test. Categorical variables were summarized using frequency and proportion and were compared by chi-squared or Fisher's exact tests. Acute RAI cut-off of ≥8 was used to define renal angina fulfillment [ANG (+)] and this cut-off was used for operative characteristics. Area under the curve (AUC) values and Youden's index were calculated for different variables for comparing performance. In all analyses, a p-value <0.05 was considered statistically significant. SPSS version 26 was used for statistical analysis.

RESULTS

The baseline characteristics of the enrolled children and their outcomes have been compared between the groups of positive and negative RAI on day 0 in tables 2 and 3 respectively.

Table 3 depicts the total 280 patients enrolled; 57 (20.3%) patients developed AKI. 36 (12.86%) patients on day 3 had severe AKI. The incidence of AKI on day 3 was significantly higher in RA-positive patients (32/58 (55.17%) v/s 4/222 (1.8%) in RA-negative group (p <0. 001). Out of 36 patients with severe AKI on day 3, 32 (88. 88%) were in RA positive group. RAI positivity (RAI ≥8) predicted day 3 severe AKI with an AUC of 0.931 (95% confidence interval (CI) = 0.874 ± 0.988). Renal angina positivity had a high negative predictive value (NPV) of 98.25%, with

Table 1: Components of the renal angina index (RAI)

Patient type	Risk level	Score
Sepsis or ICU admit	Moderate	1
Diabetes or stem-cell transplant	High	3
Ventilation and inotropic support	Very high	5
Injury level		
Decrease in estimated CrCl	% FO	Score
No Change	<5	1
0-24.99	5-9.99	2
25-50	10-14.99	4
≥50	15	8

ICU: intensive care unit, eCrCl: estimated creatinine clearance, %FO: percentage fluid over load

Table 2: Baseline characteristic of enrolled children

Parameter	Overall	RA positive	RA negative	p value
Number (%)	280	58 (20.71 %)	222 (79.29%)	
Age (years)	5.18 ±4.33	4.52 ± 4.39	5.34 ± 4.31	0.080
Gender (Male: Female)	1.52:1	2.05:1	1.41:1	0.292
Weight (kg)	15.88 ± 8.62	14.15 ± 9.44	16.33 ± 8.35	0.200
Height (cm)	97.59 ± 28.53	93.81 ± 34.52	98.58 ± 26.72	0.080
BSA (m^2)	0.650 ± 0.288	0.602 ± 0.292	0.663 ± 0.286	0.155
PRISM II	9.18 ± 4.95	14.53 ± 7.02	7.76 ± 2.91	<0.001*
Etiological diagnosis, n (%)				
CNS	87 (31.07%)	34 (58.62%)	53 (23.87%)	0.013
CVS	76 (27.14%)	10 (17.24%)	66 (29.72%)	0.082
Gastrointestinal	58 (20.71%)	10 (17.24%)	48 (21.62%)	0.582
Pulmonary	20 (7.14%)	02 (3.45%)	18 (8.1 %)	0.347
Sepsis	30 (10.71%)	2 (3.45%)	28 (12.6%)	0.077
Surgical/trauma	9 (3.21%)	0 (0%)	9 (4.05%)	0.254
Fluid overload % on day 0	2.72 ± 3.92%	6.47 ± 6.0%	1.74 ± 2.33%	<0.001*
% Fall in eCrCl from baseline on day 0	13.69 ± 15.47%	25.61 ± 25.05%	10.57 ± 9.66%	<0.001*

BSA: body surface area, CNS: central nervous system, CVS: cardiovasular system, eCrCl: estimated creatinine clearance, PRISM II: Pediatric risk of mortality II, p <0.05: significant, *p < 0.001: highly significant

Table 3: Outcomes analysis of enrolled children

Outcomes	Overall (280)	RA positive (58)	RA negative (222)	p value
Inotropes use, n (%)	39 (13.93%)	33 (56.9%)	6 (2.7%)	<0.001*
Use of mechanical-n (%) ventilation,	37 (13.21%)	30 (51.72%)	7 (3.15%)	<0.001*
Duration of mechanical-ventilation (hours)	22.14 ± 50.95	72.02 ± 83.45	9.10 ± 25.64	<0.001*
AKI stage (on day 3), n (%)				
No AKI	223 (79.64%)	20 (34.48%)	203 (91.44%)	<0.001*
AKI	57 (20.3%)	38 (65.5%)	19 (8.5%)	<0.001*
Stage 1	21 (7.5 %)	6 (10.34%)	15 (6.76%)	<0.001*
Stage 2	7 (2.5 %)	6 (10.34 %)	1 (0.45%)	<0.001*
Stage 3	29 (10.36%)	26 (44.83%)	3 (1.35%)	<0.001*
Severe AKI (> stage2)	36 (12.86%)	32 (55.17%)	4 (1.8%)	<0.001*
Need of dialysis, n (%)	19 (6.79%)	17 (29.31%)	2 (0.9%)	<0.001*
Mortality, n (%)	32 (11.43%)	13 (22.41%)	19 (8.56%)	<0.001*
LOS (days)	4.70 ±1.64	6.95 ±4.33	4.11 ±1.64	<0.001*

AKI: acute kidney injury, LOS: length of stay, p<0.05: statistically significant, *p < 0.001: highly significant

sensitivity, specificity and PPV (positive predictive value) of 88.9%, 92.2% and 62.75% respectively. Patients in RA-positive group had significantly higher mean PRISM II scores (14.53 ± 7.02) compared to RA-negative group (7.76 ± 2.91) (p <0.001). Additionally, patients in RA-positive group had longer duration of mechanical ventilation (mean 72.02 ± 83.45 hours v/s mean 9.10 ± 25.64 hours; p<0.001), PICU stay (mean 6.95±4.33 days v/s mean 4.11 ± 1.64 days; p <0.0 01), need of dialysis (29.31 v/s 0.9%; p-value <0.001) and higher mortality (22.41 v/s 8.56%; p-value <0.001). Of the 19 cases needing renal replacement therapy, 17 were from RA-positive group.

The predictive value for day 3 severe AKI by percentage fluid overload alone using AUC curve was consistently superior when compared to decrease in estimated Cr Cl. % (AUC = 0.863 (95% CI = 0.805 ± 0.920) v/s 0.824 (95% CI = 0.735 ± 0.913). The AUC for RAI for day 3 severe AKI improved when RAI incorporated the worse of the two scores (GFR score / FO score) (AUC = 0.931 (95% CI = 0.874 - 0.988)). RAI out performed PRISM II score for the prediction of day 3 AKI. (Youden© index = 0.587, AUC = 0.818 (CI- 95% = 0.723- 0.914)) (Figure).

DISCUSSION

This hospital-based study showed that a positive RAI on

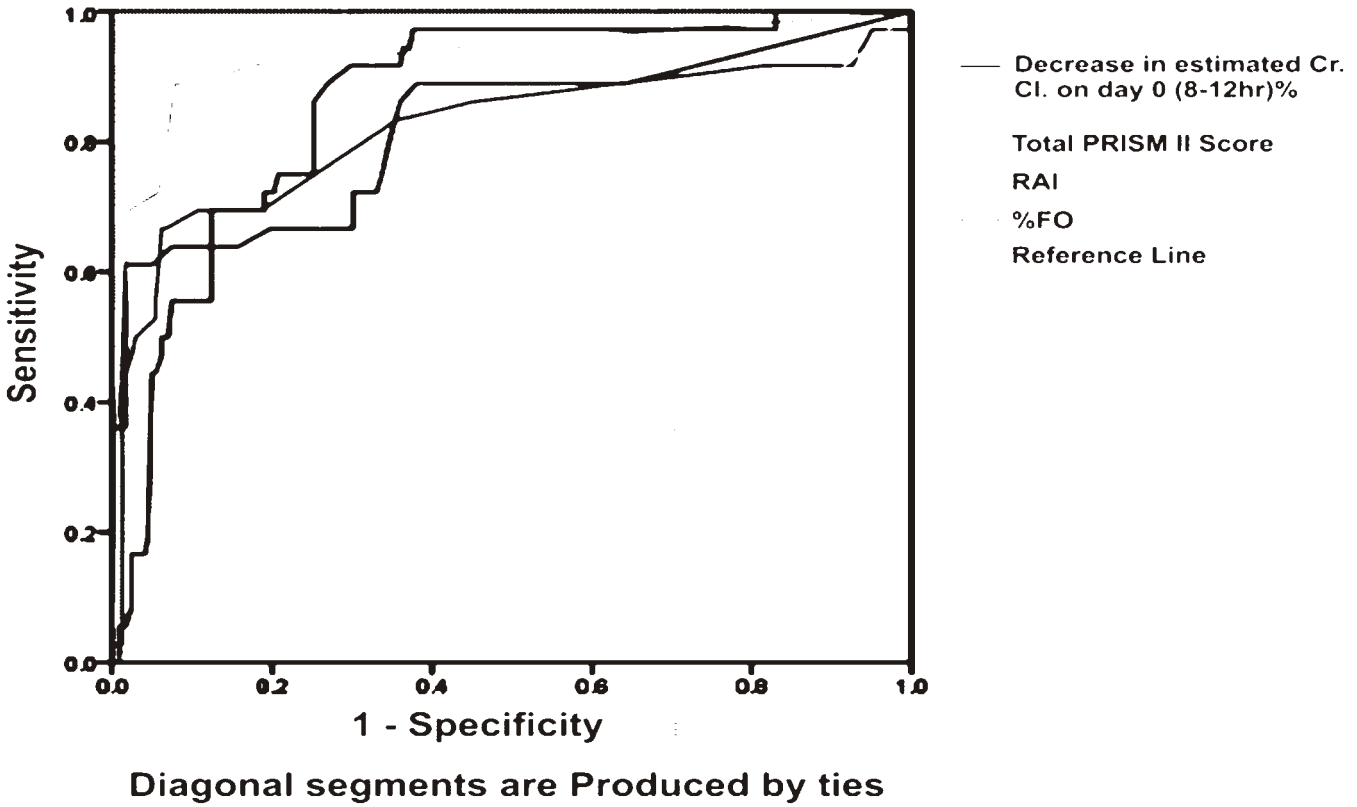

Figure: Receiver operating characteristic curve.

day 0 (8 to 12 hour) after admission in PICU was a strong predictor of AKI on day 3. RAI performed better than percentage fluid over load, decrease in estimated creatinine clearance %, and PRISM II score in predicting AKI. The percentage of children suffering from severe AKI at 72 hours (day 3 AKI) in the present study is indicative of the extent of the AKI burden in the PICU. The concomitant co-morbidities (increased duration of mechanical ventilation, inotropes use, the need of dialysis, and mortality) associated with AKI and RA positivity are clearly evident from the present study.

Our results are in parallel with the results of the AWARE study[15] and other studies.[16,17] Ideally, through a simple calculation of the RAI, a clinician can identify renal angina positivity in any patient on admission and then appropriately allocate the use of an AKI biomarker test to those in whom the test may yield the greatest predictive benefit. Our goal with the validation of the RAI was to use a simple score, which is easily calculable and can be used at the bed side of critically ill patients. Though the previously published prediction scores for organ failure, the severity of illness, or mortality use more rigorous statistical methodologies, these are intended to be used in population analyses, not for single patients. Thus, RAI is simple and has its use in clinical care and in future research. Another important point is that children admitted to the PICU most often do not have clearly identifiable risk factors for AKI. The RAI uses easily identifiable criteria within the first day of PICU admission to predict the highly clinically relevant outcome of subsequent severe AKI. In our setting, there was a high burden of tropical diseases like dengue fever, scrub typhus, malaria, enteric fever causing sepsis, which are a common cause of AKI compared to developed countries.

Limitations: In the present study 37.5% of the patients did not have a baseline creatinine, and we calculated baseline values for these patients based on height and assumed creatinine clearance (120 ml/min/1.73m^2). We did not test any biomarker in RA-positive patients to show that there is an improved diagnostic ability due to non-availability of biomarkers in our set up.

CONCLUSION

Renal angina index (RAI) is a simple and effective clinical tool to determine AKI in critically ill pediatric patients. It could be of great importance in future especially in developing countries where costly biomarkers or diagnostic tools for detection of AKI are scarce or not

available. RAI can be intelligently utilized with more meticulous fluid and blood pressure management, avoiding nephrotoxic drugs and initiating renal replacement therapy in a timely manner in RA-positive patients.

Financial support and sponsorship: Nil

Conflict of interest: None

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