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Original Research Article

Validation of Renal Angina Index (RAI) to improve the prediction of Acute Kidney Injury (AKI) in critically ill children admitted to paediatric intensive care unit (PICU)

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ABSTRACT

Background: Acute Kidney Injury (AKI) is associated with poor outcome in critically ill children. Reliable prediction of severe AKI may optimize treatment. Here we operationalize the concept of renal angina with Renal Angina Index (RAI). The objective of this study was to validate RAI for prediction of severe AKI on Day 3 of admission.
Methods: A prospective observational study including children 1 month to 12 years admitted to PICU at ICH and RC, Madurai over 6 months. Clinical data, urine output (ml/kg/hour), serial S. creatinine values were collected. Renal angina positive was defined as RAI score ≥8.
Results: Overall incidence of AKI was 27.8%. Day 0 RAI ≥8 was 42.9% of which 56.1% developed day 3 AKI. RAI ≤8 had high NPV of 93% for Day 3 AKI. Renal angina concept using RAI predicts subsequent severe AKI. RAI provides clinically feasible and applicable methodology to identify critically ill children at risk of severe AKI lasting beyond functional injury. RAI may potentially reduce capricious AKI biomarker use.
Conclusions: The use of renal angina to stratify patients for enrollment in biomarker or therapy trials may create the uniformity required to properly analyze AKI in pediatric population. We believe that renal angina is a clinical adjunct that will lead to the optimization of AKI biomarker performance across the wide-ranging heterogeneity that exists across the general pediatric PICU population. RAI may potentially reduce capricious AKI biomarker use by identifying patients in whom further testing would be most beneficial.

Keywords: AKI, PICU, Renal angina

INTRODUCTION

Acute Kidney Injury (AKI) describes the clinical syndrome formerly called Acute Renal Failure (ARF), characterized by a reversible increase in the blood concentration of creatinine and nitrogenous waste products and by the inability of kidneys to maintain fluid and electrolyte homeostasis. Acute kidney injury is associated with poor outcome in critically ill children which ranges from 10-80% with increasing severity of illness.[1]

Despite increasing awareness of the prevalence and significance of AKI, effective therapies for this condition are lacking. This, at least in part, results from a failure to recognize AKI before a significant degree of renal damage has already occurred. The inability to diagnose AKI expeditiously follows from the fact that the currently

accepted definitions of AKI rely on changes in serum creatinine (SCr) and urine output.[2]

Increasing AKI severity, characterized by serum creatinine (SCr) and urine output (UOP) based stratifications of AKI, is associated with increased mortality in adults and children. Even small increase in SCr (0.3 mg/dl) reflect significant kidney damage and are associated with poor patient outcome.[3,4] The well-recognized limitations of SCr for real-time accurate AKI diagnosis have prevented timely therapeutic interventions.[5]

Extensive research has targeted the discovery of biomarkers to disclose AKI prior to elevations in serum creatinine. Till date, a number of promising urinary AKI biomarkers have emerged, of which clinical studies indicate that urinary Neutrophil Gelatinase-associated Lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1), Interleukin 18 (IL-18) and Liver-type Fatty Acid Binding Protein (L-FABP) all predict AKI in children following cardiopulmonary bypass where demographic homogeneity, lack of comorbidities, and a known onset and duration of ischemic injury prior to changes in serum creatinine.[6-8]

Demographic heterogeneity likely contributes to the poor discriminatory performance of these biomarkers in non-cardiac pediatric intensive care unit (PICU) patients.

In these situations, the urinary biomarkers are unable to predict the AKI severity, identify children who would require renal replacement therapy (RRT), and predict AKI-associated death.[9-13]

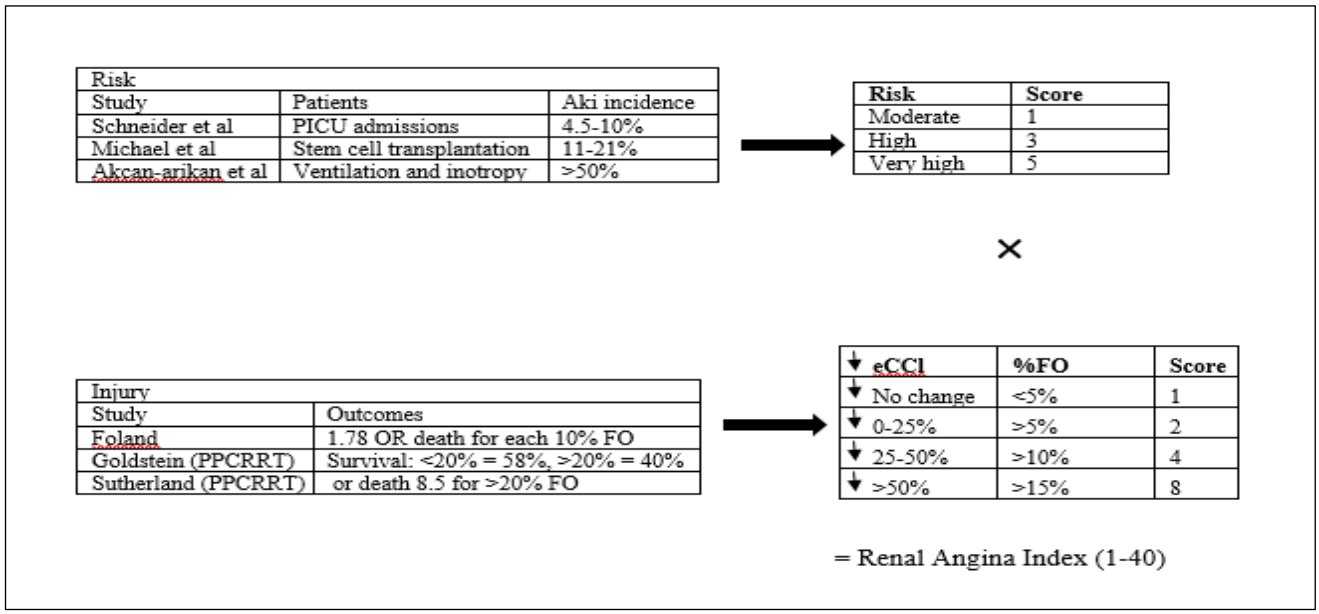

Figure 1: Renal angina model.

We previously found that children with persistent AKI at PICU admission (AKI after 48 hours) were at the highest risk for requiring renal replacement therapy (RRT). Identifying patients at risk for severe and long-lasting AKI in the PICU, and as importantly, identifying patients unlikely to be at risk, is obligatory as risk stratification could allow more judicious AKI biomarker assessment to drive therapeutic intervention, increasing their predictive performance and cost-effectiveness. For any given diagnostic test, the context of that test is a critical component for the interpretation of the results. This context is referred to as pretest probability and forms the basis for the interpretation of any diagnostic test. The value of any diagnostic study without clinical context is minimized.

In the field of acute kidney injury, a multitude of early diagnostic biomarkers have been developed, but utilization in the appropriate context is less well understood and has not been systematized until recently. In order to better operationalize the context and pretest probability assessment for acute kidney injury diagnosis, the renal angina concept was proposed in 2010 for use in both children and adults.[14,15] However, renal angina as a concept is still unfamiliar to most clinicians and the rationale for introducing the term is not obvious. We therefore review the concept and development of renal angina, and the currently available data validating it.

This model comprises of clinical risk factors and clinical evidence, the Renal Angina Index (RAI) of acute kidney

injury that directs biomarker testing, akin to directed assessment of troponin I only in select patients with chest pain. This model seeks a high negative predictive value (NPV) for AKI of not fulfilling renal angina. Unlike other severity of illness scoring systems which merely score existing injury, fulfillment of renal angina aids prediction of severe AKI. Renal angina model is shown in Figure 1.

The aims and objectives of this study were to validate the Renal angina risk stratification model using Renal Angina Index (RAI) for prediction of subsequent severe Acute Kidney Injury (AKI) on Day 3 of admission.

METHODS

The design is a prospective observational study of critically ill children admitted to Pediatric Intensive Care Unit (PICU) at Institute of Child Health and Research Centre, Government Rajaji Hospital, Madurai.

All children within the age group of 1 month to 12 years admitted in the Pediatric Intensive Care Unit with length of stay for at least 48 hours in PICU, at Institute of Child Health and Research Centre, Government Rajaji Hospital, Madurai over a period of 6 months (October 2015 to March 2016) were included in the study after getting consent from parents.

Institutional ethical committee approval was obtained.

PICU admission was based on one or more of the following criteria:

- Impaired level of consciousness (Glasgow coma scale <8)
- Signs suggestive of severe increase in intracranial pressure (e.g., hypertension, bradycardia, papilledema)
- Hypoventilation or respiratory failure (oxygen saturation < 90% or arterial oxygen (PaO_2) <60 mmHg with supplemental oxygen or arterial CO_2 ($PaCO_2$) >60 mmHg
- Uncontrollable or poorly controlled seizures
- Hypotension requiring inotropic support
- Requirement of renal replacement therapy (RRT)
- Fulminant hepatic failure.

Exclusion criteria

- Patients with known chronic kidney disease stage 5 (estimated glomerular filtration rate <15 ml/min/1.73 m^2)
- Post-operative from surgical correction of cyanotic congenital heart disease within 90 days
- Immediately following elective cardiac catheterization.

Data collected includes demographic information, admission diagnoses and co-morbidities, SCr value on the time of admission and repeated every 24 hours. Day 0 denoted the first calendar day of PICU admission. Day 3 included the time period between 72-96 hours after PICU admission. Day 0 data included variables like use of vasopressors/inotrope and use of mechanical ventilation (yes / no) for determination of Renal Angina Index (RAI). Calculated variables for determination of RAI included estimated change in creatinine clearance (eCCl) and % fluid overload. Estimated creatinine clearance was calculated as percent change of daily creatinine from baseline creatinine (using Schwartz formula).

- Baseline creatinine used is lowest consistent serum creatinine 90 days or more prior to admission
- For patients without a prior baseline, an assumed creatinine clearance of 120 ml/min/1.73 m2 is used.[16]

Percent fluid overload on Day 0 was determined by assessing the first 8 hours of admission in the PICU on Day 0.

The time frame of 8 hours was felt to be beyond the generally accepted window of 'early goal-directed therapy' (EGDT) of resuscitation allowing time for some diuresis, and also was sufficiently shorter than an actual full day.[17]

Fluid overload was calculated using the formula:

[(Fluid IN - Fluid OUT) / admission weight in kg] × 100

Acute kidney injury staging was done based on KDIGO guidelines.

Renal angina index calculation

To ascertain fulfillment or absence of renal angina on the day of admission, the renal angina index was calculated as mentioned previously which is given by formula RAI = Risk X Injury. All patients were classified on Day 0 as fulfilling criteria for renal angina (i.e., being ANG (+) versus ANG (-)] using the RAI. An RAI score of ≥8 demonstrated the highest Youden's index and the highest NPV, and thus ANG (+) was defined as an RAI score ≥8.

ANG (+): Renal Angina Index positive

ANG (-): Renal Angina Index negative

Outcome analyzed

The primary outcome was the presence of severe AKI 72 hours after PICU admission (Day 3 AKI), denoted as 'subsequent severe AKI'. Day 3 was chosen because of the following reasons:

- Most PICU patients develop AKI within this time frame; there is enough time to develop the severe or persistent AKI outcome; and

- 3 days surpasses the time frame of what would be considered reversible (or functional) AKI.

Severe AKI was defined by the KDIGO AKI classification stage ≥2: SCr of 200% baseline (a decrease in eCCl of ≥50% from baseline) or ≤0.5 ml/kg/h of UOP for ≥8 hours. We chose KDIGO stage ≥2 as the primary outcome as it is associated with mortality and morbidity in multiple pediatric studies.[18]

The higher of the KDIGO strata (either creatinine clearance or urine output) was used. Secondary outcomes were PICU length of stay, use of RRT, and in-hospital mortality.

RESULTS

All data were entered in Excel 2007 and statistical analysis was performed using the statistical software SPSS 16.

P value was calculated using Chi Square test. Continuous variables were reported as median with interquartile range and compared using the Mann-Whitney test. An RAI cutoff of ≥8 was used to analyze the predictive performance of RAI (sensitivity, specificity, NPV, and PPV).

The cutoff value of ≥8 was chosen on the basis of most superior performance based on Youden's and highest NPV. In all analyses, a P-value <0.05 was considered statistically significant.

Table 1: Demographic and clinical data (n = 133).

Data	Ang (+)	Ang (-)	P value
Total, n (%)	57 (42.9%)	76 (57.1%)	
Moderate risk, n (%)	36 (63.2%)	73 (96%)	
High risk, n (%)	0	0	
Very high risk, n (%)	21 (36.8%)	3 (4%)	
Male, n (%)	35 (61.4%)	42 (55.3%)	
Female, n (%)	22 (38.6%)	34 (44.7%)	
Age in years, median	0.83 (3.69)	5 (7.69)	
Inotrope use, n (%)	18 (31.6%)	3 (3.9%)	0.001
Mechanical ventilation, n (%)	11 (19.3)	3 (3.9%)	0.001
Day 3 AKI, n (%)	32 (56.1%)	5 (6.6%)	0.001
Length of stay (LOS), days, median	6 (5)	4 (2)	0.001
RRT, n (%)	9 (15.8%)	0	0.001
Mortality, n (%)	7 (12.3%)	3 (3.9%)	0.09

Table 2: Comparison of results.

Data	Cincinnati children hospital, sepsis, renal angina derivation study		Montreal children hospital, prospective study on validation of RAI		Present study	
	Ang (+)	**Ang (-)**	**Ang (+)**	**Ang (-)**	**Ang (+)**	**Ang (-)**
N	51 (35%)	93 (65%)	18 (15.3%)	100 (84.7%)	57 (42.9%)	76 (57.1%)
Age, years	5.4 (2, 14)	3.1 (1, 11)	5.9 (0.4,10)	6.0 (0, 12)	0.83 (0.17, 12)	5 (0.17,12)
Male	30 (58.8%)	53 (56.9%)	12 (67.7%)	62 (62%)	35 (61.4%)	42 (55.3%)
D3 AKI	21 (41.2%)	7 (7.5%)	7 (38.9%)	5 (5%)	32 (56.1%)	5 (6.6%)
LOS, days	9 (4,15)	5 (2, 10)	6 (4, 9)	7 (2, 11)	6 (5)	4 (2)
RRT, n%	9 (17.6%)	4 (4.3%)	1 (5.6%)	2 (2%)	9 (15.8%)	0
Mortality	9 (17.6%)	4 (4.3%)	1 (5.6%)	6 (6%)	7 (12.3%)	3 (3.9%)
	Montreal children hospital, retrospective study on validation 2 of RAI		**Cincinnati children hospital, sepsis 2, Renal angina validation 3 study**			
	Ang (+)	**Ang (-)**	**Ang (+)**	**Ang (-)**	**Ang (+)**	**Ang (-)**
N	38 (35.2%)	70 (64.8%)	145 (67.8%)	69 (32.2%)	57 (42.9%)	76 (57.1%)
Age, years	4.5 (0, 10.7)	5.6 (0, 11.7)	1.7 (0.5, 5)	3.8 (1.6, 6.8)	0.83 (0.17, 12)	5 (0.17, 12)
Male	20 (52.6%)	44 (62.9)	94 (44%)	40 (57.9%)	35 (61.4%)	42 (55.3%)
D3 AKI	11 (28.9%)	0	27 (19%)	2 (2.9%)	32 (56.1%)	5 (6.6%)
Los, days	10.1 (3, 17)	12.3 (4, 20)	15 (7, 27)	11 (8, 16)	6 (5)	4 (2)
RRT, n%	3 (7.9%)	0	NA	NA	9 (15.8%)	0
Mortality	1 (2.6%)	3 (4.3%)	23 (16%)	0	7 (12.3%)	3 (3.9%)

Table 3: Performance of the renal angina index for prediction of subsequent severe AKI.

Data	Present study	CCHMC sepsis 1, derivation study	MCH prospective validation study	MCH retrospective validation study	CCHMC sepsis 2, validation study
ANG (+), n%	57 (42.9%)	51 (35%)	18 (15%)	38 (35%)	145 (68%)
Day 3 AKI, n%	37 (27.8%)	28 (19%)	12 (10%)	11 (10%)	29 (13%)
Sensitivity, % (95% CI)	86 (70-95)	75 (55-89)	58 (28-85)	91 (59-100)	93 (76-99)
Specificity, % (95% CI)	74 (64-82)	73 (64-81)	90 (82-95)	71 (61-80)	36 (33-37)
PPV, % (95% CI)	56 (42-69)	40 (27-55)	39 (17-64)	26 (13-43)	18 (15-19)
NPV, % (95% CI)	93 (84-97)	92 (85-97)	95 (89-98)	99 (92-100)	97 (90-99)
AUC, % (95% CI)	0.85 (0.78-0.92)	0.77 (0.68-0.86)	0.74 (0.59-0.88)	0.81 (0.71-0.91)	0.80 (0.75-0.86)

AKI: Acute kidney injury; ANG: Renal angina; AUC; Area under the curve; CCHMC: Cincinnati Children's Hospital; CI: Confidence interval; MCH: Montreal Children's Hospital; NPV: Negative predictive value; PPV: Positive predictive value

A total of 133 children admitted to Pediatric Intensive Care Unit of ICH and RC, GRH, Madurai were studied prospectively over a period of 6 months (October 2015 to March 2016), out of which 77 (57.9%) were boys and 56 (42.1%) were girls. The overall incidence of Acute Kidney Injury in the present study was 27.8% (37 AKI cases out of 133 cases). Out of 37 AKI cases, 20 (54.1%) were boys and 17 (45.9%) were girls. Other demographic parameter are listed in Table 1.

Day 0 (PICU admission day) renal angina positive [ANG (+)] occurred in 57/133 (42.9%) of patients. Among the ANG (+) patients, 32/57 (56.1%) developed Day 3 AKI. renal angina negative [ANG (-)] occurred in 76/133 (57.1%) of patients. Among the ANG (-) patients, 5/76 (6.6%) developed Day 3 AKI. ANG (+) patients had higher day-3 AKI rates, longer PICU length of stay, higher Renal Replacement Therapy (RRT) provision and higher hospital mortality rates. Day 0 Renal Angina Index [ANG (+)] predicted day 3 AKI with a sensitivity of 86.5%, specificity of 74%, positive predictive value of 56% and had a high negative predictive value of 93%(95% Confidence Interval (CI): 84%-97%) with an AUC of 0.85 (95% CI 0.78-0.92). Comparison of results of the present study and various other studies on renal angina validation is given in Table 2 and 3.

DISCUSSION

Renal angina fulfillment identifies children at highest risk of suffering subsequent severe AKI. For a clinician, the ability to predict the presence of severe AKI 3 days in advance carries obvious benefit. The percentage of children suffering from severe AKI at 72 hours (Day-3 AKI) in our study is indicative of the extent of the AKI burden in the PICU. The concomitant comorbidities of ANG (+) associated AKI (increased duration of mechanical ventilation, inotrope use, RRT use, and mortality) are clearly evident from our study.

AKI biomarkers need to demonstrate the appropriate balance of diagnostic performance and cost-effectiveness to gain widespread acceptance leading to implementation at the bedside. Indiscriminate testing for any condition (myocardial infarction, stroke, kidney injury, and so on) in every patient (regardless of size, age, and comorbidities) will render any biomarker virtually useless. Avoidance of such shotgun testing is only possible by providing direction (clinical context) for biomarker use. The context of Renal Angina fulfills this prediction need. Using AKI biomarkers in patients with ANG (+), improves the diagnostic performance of these biomarkers as shown in previous studies.

NPV of our study was 93% which suggests that AKI biomarkers should not be obtained to predict severe AKI in Day 0 ANG (-) children, given the low likelihood of Day-3 AKI. Ideally, through a simple calculation of the RAI, a clinician can identify ANG fulfillment or absence 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. We suggest that renal angina allows biomarker testing to be appropriately directed. Directed use is a logical method that can be used to derive biomarker panels that classify and phenotype AKI types. Such optimization eliminates shotgun use of AKI biomarkers, both cost prohibitive and nonscientific.[19]

Our goal with the validation of the RAI was to use a simple score, which is easily calculable and can be used at the bedside of a critically ill patient. Although published prediction scores for organ failure, 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 thus will enhance 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 (as a preoperative cardiac surgery adult patient may have); the RAI uses easily identifiable criteria within the first day of PICU admission to predict the highly clinically relevant outcome of subsequent severe AKI. Finally, previous studies of adult AKI prediction scores have had extremely large and comprehensive administrative databases available for deriving and validating scores; such databases are nonexistent in the PICU population.

We propose that future research should aim at constructing and validating the use of large, multicenter PICU databases, to enable more refined and rigorous evaluation of AKI risk factors and evidence of injury, which will allow for validation and/or calibration of the RAI score if needed.

Limitations of this study were:

- There seemed to be a paucity of high-risk patients in our study (transplant patients). The apparent higher incidence of AKI in the high-risk group versus the very high-risk group is therefore slightly misleading. Patients with transplants have an increased risk of AKI, and we expect that with future study of renal angina
- We did not test any biomarker in ANG (+) patients to show that there is an improved diagnostic ability due to non-availability of biomarkers in our set up
- In the present study roughly 47% of the patients did not have a baseline creatinine, and we calculated baseline values for these patients based on height and normal creatinine clearance for age. The only effect this manipulation carried on our results was to potentially underestimate the change in eCCl from baseline
- The worse part (either eCCl or FO) was used to stage AKI as in some cases Fluid overload was not known and only eCCl was used to stage AKI according to KDIGO guidelines. (few studies found no significant differences in RAI prediction of AKI when the outcome was based on creatinine or urine output[20]
- We did not test the RAI on ICU admission days other than Day 0 or to predict AKI persistence after ICU Day 3 and acknowledge that the RAI performance may be better or worse than the clinical context we tested.

CONCLUSION

The use of renal angina to stratify patients for enrolment in biomarker or therapy trials may create the uniformity required to properly analyse AKI in paediatric population. We believe that renal angina is a clinical adjunct that will lead to the optimization of AKI biomarker performance across the wide-ranging heterogeneity that exists across the general paediatric PICU population.

RAI may potentially reduce capricious AKI biomarker use by identifying patients in whom further testing would be most beneficial.

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