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Perez MA & Anacleto F. Diagnostic Accuracy of Renal Angina Index in Predicting Acute Kidney Injury in Pediatric Patients with Sepsis: A Philippine Tertiary Hospital Experience

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ORIGINAL ARTICLE

DIAGNOSTIC ACCURACY OF RENAL ANGINA INDEX IN PREDICTING ACUTE KIDNEY INJURY IN PEDIATRIC PATIENTS WITH SEPSIS: A PHILIPPINE TERTIARY HOSPITAL EXPERIENCE

ABSTRACT

Background: The coexistence of acute kidney injury (AKI) in sepsis contributes significantly to morbidity and mortality rates. Traditional diagnostic markers still pose variable limitations in early AKI prediction. The use of renal angina index (RAI) as a clinical predictive tool for AKI is an emerging concept.

Objectives: To determine the diagnostic accuracy of RAI in predicting AKI in patients with sepsis

Methodology: This is a five-year retrospective cohort study conducted at the Philippine General Hospital (PGH). Records of eligible patients with sepsis were reviewed. RAI was calculated based on the composite of risk factors and clinical evidence of injury on day 0 of admission stratifying subjects into two groups: RAI (-) and RAI (+) for those with scores ≥ 8. Prediction of AKI with the RAI was analyzed.

Results: A total of 222 patients were enrolled. The RAI (+) group (score ≥ 8) consisted 95 patients (43%). AKI incidence rate was 40.5 % (90/222) and 87/90 patients (91.6%) were classified in the RAI (+) group. The use of RAI in predicting AKI has a sensitivity of 96.7%, specificity of 94.0%, positive predictive value (PPV) of 91.6%, negative predictive value (NPV) of 97.7%, positive likelihood ratio (LR) of 15.95, negative LR of 0.04 and area under the curve-receiver operating characteristic (AUC-ROC) of 0.953 (95% CI 0.92-0.98).

Conclusions: RAI is a good screening tool in predicting sepsis-associated AKI among pediatric patients. It provides early recognition of AKI and is a practical method which can be used at bedside.

KEYWORDS: *Renal Angina Index, Acute Kidney Injury, Sepsis*

INTRODUCTION

The global pooled incidence rate of pediatric AKI across all clinical settings was 33.7% with a corresponding mortality rate of 13.8% in a meta-analysis by Susantitaphong et. al. in 2013.[1] On the other hand, a study conducted in Korea by Suh et. al. showed that sepsis-associated AKI developed in 57.7% of enrolled pediatric subjects.[2] Despite the availability of accepted definitions, parameters being relied upon for AKI seem to be highly confounded by variability in body mass and sex and by inherent time lag to response to injury.[3,4] Novel urinary biomarkers as promising candidates in the early prediction of injury have emerged. However, studies failed to show their robust efficacy in children especially when used in isolation and outside of the cardiopulmonary bypass population.[5]

The RAI is a composite of an individual's AKI risk and early signs of injury and this is designed to guide the risk stratification of patients for whom the use of AKI biomarker would be most optimal.[6] Risk for AKI as part of the index includes the need for pediatric intensive care unit (PICU) admission, history of transplantation (solid organ or bone marrow), and need for ventilation and inotropic support which correspond to scores of 1, 3 and 5 respectively. On the other hand, clinical signs of injury make use of the degree of change in estimated creatinine clearance (eCCl) or percent of fluid overload (FO). A score of 1 is given for < 5% FO or no change in eCCl, 2 is given for 5-10% FO or less than 25% decrease in eCCl, 4 is given for 10-15% FO or 25-50% decrease in eCCl, and 8 is given for 15% FO or at least 50% decrease in eCCl.[4,6] In a derivation and validation study conducted by Basu and colleagues in 2014, a RAI of at least 8 showed higher AKI rate, longer PICU length of stay, higher renal replacement therapy (RRT) provision and higher hospital mortality rates. Corollary to this, RAI of less than 8 had a high negative predictive value of 92%.[7] RAI utility as a pretest probability assessment tool in AKI appears to have good performance metrics which can improve the efficiency in predicting AKI by biomarkers leading to expedited early therapy.[8,9]

At present, there is still no single diagnostic marker that can accurately predict the occurrence of AKI in critically ill patients, and this poses variable limitations that greatly affect monitoring and the expedited institution of therapy in the affected population. To address this diagnostic challenge in pediatric AKI, the use of RAI as a clinical predictive tool is an emerging concept. This study aims to determine the diagnostic accuracy of RAI in predicting AKI in patients with sepsis and evaluate its utility to clinical practice.

METHODOLOGY

This is a 5-year retrospective cohort study approved by the University of the Philippines Manila Research Ethics Board (UPMREB) Panel at PGH. A list of eligible subjects was obtained from the census files of the different units of the Department of Pediatrics (emergency room, in-patient wards, hematology-oncology unit, neonatal intensive care unit and pediatric intensive care unit) and compiled in a database. Supplemental lists were also obtained from records of the Sections of Infectious and Tropical Diseases and Nephrology as referral services. Charts of these subjects were retrieved from the records section of the institution. The following were the inclusion and exclusion criteria:

Inclusion Criteria

Pediatric patients aged between one month and less than 19 years old admitted at PGH from January 2012 to December 2016 with sepsis or septic shock were included in the study. In the case of patients with multiple admissions in the institution, only the initial admission was considered to eliminate confounders and bias.

Exclusion Criteria

Excluded from the study are the following:

Patients on maintenance RRT (hemodialysis or peritoneal dialysis); patients with preexisting chronic kidney disease with estimated glomerular filtration rate (GFR) of < 15 ml/min/1.73 m^2; patients who underwent kidney transplantation within 90 days of admission; cardiac patients who immediately underwent cardiac catheterization; patients who

underwent surgical corrections requiring cardiopulmonary bypass; and patients who died within the 1st 48 hours of admission

Baseline demographic information, comorbidities, use of any medication prior to admission, clinical signs and symptoms, anthropometric measurements, available values of requested diagnostics, vital signs and admitting diagnosis were recorded. Subsequent results of diagnostic tests during the course of admission were also recorded. Variables including need for inotropic support, mechanical ventilation and daily fluid balance in the first three days of admission were documented. Pediatric Risk for Mortality (PRISM) III was scored based on physiological and clinical variables from the studies of Pollack et al and Tan et al. [10-11] Outcomes which included duration of hospital stay, development of AKI on Day 3 of admission, need for RRT during the course of admission and mortality were recorded. Collected patient information were kept anonymous and confidential by removing identifiers. Only the data necessary for the study were obtained from retrieved charts.

Subjects were classified into two groups based on the calculated RAI defined as the composite of risk factors and clinical signs of injury using FO percentage or change in eCCl. Data used in the composite score were collected on the first calendar day of admission (Day 0) with a minimum of 8 hours stay in the facility. FO percentage was computed as a function of the difference of total fluid input and total fluid output (in liters) divided by the subject's weight on admission, multiplied by 100. Documentation of fluid balance was on a daily basis using the subject's working weight for the first three days. On the other hand, the eCCl was calculated using the modified Schwartz formula defined as the product of 36.5 (constant value) and length or height (in centimeters) divided by the serum creatinine (in µmol/L). The lowest creatinine level of each subject up to three months before the present admission was searched during the review. If no available baseline serum creatinine value was noted, subjects were assigned baseline values of 27 µmol/L for infants < one year old, 44 µmol/L for children one to nine years old and 66 µmol/L for adolescents 10-18 years old based on the mean value of the normal range of serum creatinine by age determined enzymatically by means of either creatininase or creatininase-/creatinase-based assays.[12-13] Corresponding computation of RAI were documented with an RAI score of at least 8 interpreted as fulfillment of the index.[7] Absence or fulfillment of the index were denoted as RAI (-) and RAI (+) respectively.

Sample Size

A priori, four variables which were known risk factors for AKI were included in a comparative prediction model in this study: age, the RAI index, PRISM III scores[10] and the presence of sepsis.[9] Designation of 10 events per variable would yield 40 events (patients developing AKI).[4] Based on the latest meta-analysis of the incidence of AKI across all clinical settings, a 33.7% incidence rate yields an estimate of at least 120 eligible patients for study enrollment.[1]

Statistical Analysis

Data retrieved from each patient were tabulated, and normally-distributed quantitative variables were presented as means and standard deviation with the application of independent t-test for comparison. Non-normally distributed variables were expressed in medians with interquartile ranges and the Mann-Whitney U test was used for comparison. Categorical variables were reported as frequencies and proportions and the Fisher's exact test used for comparison. Accuracy of RAI ≥ 8 in detecting AKI among sepsis patients was computed in terms of its sensitivity, specificity, PPV, NPV, positive and negative LR and AUC-ROC. The association between RAI and AKI among sepsis patients was analyzed using logistic regression. The level of significance was set at 5%.

Primary and Secondary Outcome

The primary outcome of the study is to determine the diagnostic accuracy of RAI in terms of sensitivity, specificity, PPV, NPV, positive and negative LR and AUC-ROC in the prediction of AKI in pediatric patients with sepsis. The secondary outcome is to determine the association between RAI and AKI.

RESULTS

Demographic data and clinical characteristics are shown in Table 1. A total of 222 patients were enrolled and 95 subjects representing approximately 43% of the total population fulfilled the RAI with a score of at least 8. The population was predominantly male (59%) with a median age of two years. The state of nutrition of all subjects in terms of weight for age, length/height for age and weight for length/height was documented with no significant difference between the two groups. Majority of patients (60%) had no known comorbidities. More than 80% of the subjects denied any history of medication use prior to admission. Respiratory, gastrointestinal and neurologic complaints comprised the top three most common reasons for admission with a median presentation time to the hospital of six days.

Table 2 shows a summary of diagnostic results requested and available for both groups. RAI (+) patients have significantly lower values for platelet count (p = < 0.001) and prothrombin time activity (p = 0.025). As expected, the RAI (+) patients had higher BUN (p = <0.001) and creatinine (p = < 0.001) values with a corresponding lower estimated GFR (p = < 0.001) computed using the Modified Schwartz formula. Other variables which showed significant differences between the two groups include calcium values (p = < 0.001), blood pH (p = 0.002), pCO2 (p = 0.002) and bicarbonate levels (p = < 0.001). Results of other variables were comparable between the two groups.

Table 1. Demographic and Clinical Characteristics Stratified by Day 0 Renal Angina Fulfillment

Category	Overall N= 222	RAI (-) n= 127	RAI (+) n= 95	*p* value
Age on Admission (in years)	2 (0.5, 7)	2 (0.5, 5)	3 (0.5, 14)	0.124
Sex				
Male	130 (58.6)	67 (30.2)	63 (28.4)	
Female	92 (41.4)	60 (27.0)	32 (14.4)	0.054
Weight for Age (z-score)				
Normal	99 (44.6)	53 (23.9)	46 (20.7)	
Underweight	123 (55.4)	74 (33.3)	49 (22.1)	0.122
Length/Height for Age (z-score)				
Normal	132 (59.5)	77 (34.7)	55 (24.8)	
Stunted	90 (40.5)	50 (22.5)	40 (18.0)	0.816
Weight for Length/Height (z-score)				
Normal	110 (49.6)	59 (26.6)	51 (23.0)	
Wasted	94 (42.3)	55 (24.8)	39 (17.5)	0.321
Overweight/Obese	18 (8.1)	13 (5.9)	5 (2.2)	
Comorbidities				
None	135 (60.8)	79 (35.6)	56 (25.2)	
Cardiovascular	27 (12.2)	12 (5.4)	15 (6.8)	
Respiratory	4 (1.8)	3 (1.3)	1 (0.5)	
Gastrointestinal	4 (1.8)	2 (0.9)	2 (0.9)	0.827
Hematologic	5 (2.3)	3 (1.3)	2 (0.9)	
Oncologic	6 (2.7)	3 (1.3)	3 (1.3)	
Neurologic	24 (10.8)	15 (6.7)	9 (4.1)	
Others	17 (7.6)	10 (4.5)	7 (3.1)	
Medication Use				
Present	41 (18.5)	19 (8.5)	22 (9.9)	
Absent	181 (81.5)	108 (48.6)	73 (32.9)	0.161
Site of Infection				
Unknown	18 (8.1)	6 (2.7)	12 (5.4)	
Respiratory	122 (55.0)	75 (33.8)	47(21.2)	
Genitourinary Tract	2 (0.9)	0	2 (0.9)	
Gastrointestinal Tract	32 (14.4)	11 (5.0)	21 (9.4)	*0.002**
Skin/Soft Tissue	17 (7.6)	13 (5.9)	4 (1.8)	
Bone	1 (0.5)	1 (0.5)	0	
Central Nervous System	30 (13.5)	21 (9.4)	9 (4.1)	
Time to Present to Hospital (days)	6 (3, 8)	7 (3, 11)	5 (3, 7)	*0.045**
Blood Pressure (percentile)				
< P5	35 (15.8)	7 (3.2)	28 (12.6)	
P5-P95	172 (77.5)	113 (51.0)	59 (26.6)	*< 0.001**
P95	15 (6.7)	7 (3.2)	8 (3.6)	
Baseline Heart Rate				
Bradycardia	1 (0.5)	1 (0.5)	0	
Normal for age	73 (32.9)	37 (16.7)	36 (16.2)	0.245
Tachycardia	148 (66.6)	89 (40.1)	59 (26.6)	
Baseline Respiratory Rate (N=221)				
Bradypnea	2 (0.9)	0	2 (0.9)	
Normal for age	75 (33.9)	43 (19.5)	32 (14.5)	0.317
Tachypnea	144 (65.2)	84 (38.0)	60 (27.0)	
Baseline Temperature (N=214)				
Hypothermia	9 (4.2)	9 (4.2)	0	
Normal	115 (53.7)	66 (30.8)	49 (22.9)	*0.025**
Hyperthermia	90 (42.1)	50 (23.4)	40 (18.7)	
Baseline mental status				
Normal	187 (84.2)	115 (51.8)	72 (32.4)	
Decreased sensorium	35 (15.8)	12 (5.4)	23 (10.4)	*0.005**
Pupillary reflexes				
Reactive	218 (98.2)	127 (57.2)	91 (41.0)	
Non-reactive	4 (1.8)	0	4 (1.8)	*0.032**
Daily Fluid Overload (%)	2.0 (0, 4.8)	1.2 (0, 3.5)	4.0 (0.4, 7.5)	*< 0.001**
Need for Mechanical Ventilation				
Absent	104 (46.8)	80 (36.0)	24 (10.8)	
Present	118 (53.2)	47 (21.2)	71 (32.0)	*<0.001**
Need for Inotropes				
Absent	135 (60.8)	103 (46.4)	32 (14.4)	
Present	87 (39.2)	24 (10.8)	63 (28.4)	*< 0.001**

Data were expressed as n (%) or median (interquartile range). RAI (+) was assigned for index fulfillment (RAI score of ≥ 8). P value compared RAI (-) versus RAI (+) cohorts. Level of significance set at p < 0.05.

Table 2. Laboratory Data on Admission Stratified by Day 0 Renal Angina Fulfillment

Category	Overall N= 222	RAI (-) n= 127	RAI (+) n= 95	*p* value
Hemoglobin (g/L)	109 (93, 124)	107 (93, 125)	110 (92, 124)	0.572
Hematocrit (n= 220)	0.34 (0.29, 0.39)	0.34 (0.29, 0.39)	0.34 (0.3, 0.39)	0.62
White Blood Cell Count (x 10^9/L)	15.2 (10.5, 23.6)	15.1 (10.5, 22.4)	15.3 (10.5, 24.6)	0.457
Platelet Count (x 10^9/L) (N=221)	340 (183, 459)	393.5 (249, 478)	286 (159, 415)	*<0.001**
Prothrombin Time (activity) (N=127)	78 (60, 94)	82 (66, 98)	74 (44, 89)	*0.025**
International normalized ratio (N=127)	1.2 (1.0, 1.4)	1.1 (1.0, 1.3)	1.2 (1.1, 1.7)	0.068
BUN (mmol/L) (N=210)	4.3 (2.5, 8.7)	3.1 (1.9, 4.7)	9.5 (4.4, 22.3)	*< 0.001**
Creatinine (umol/L)	37 (26, 78)	28(22, 36.5	89 (47, 238	*<0.001**
Estimated GFR on admission (ml/min per 1.73 m^2)	80 (39, 112)	105 (82, 126)	35 (12, 60)	*< 0.001**
Sodium (mmol/L) (N=220)	139 (132, 143)	140 (134, 143)	138 (128, 143)	0.087
Potassium (mmol/L) (N= 220)	4.4 ±1.3	4.5 ± 1.0	4.4 ± 1.5	0.885
Chloride (mmol/L) (N=207)	103 (96, 107)	103 (98, 106)	102 (92, 110)	0.819
Total Bilirubin (umol/L) (N=36)	19.4 (7.0, 90.1)	15.5 (7.6, 29.2)	30.9 (6.4,180.1)	0.399
Glucose (mmol/L) (N=140)	4.9 (3.8, 6.5)	4.8 (4.2,6.2	5.4 (3.8,7.1	0.645
Albumin (g/L) (N= 139)	30.6 ± 1.05	31.4 ± 8.4	29.9 ± 8.9	0.319
Calcium (mmol/L) (N=163)	2.2 (2.02, 24	2.3(2.2, 2.5	2.1(1.9, 2.2	*< 0.001**
Blood Culture (N=198)				
No Growth	134 (67.7)	71(35.9)	63 (31.8)	0.975
Gram Positive	29 (14.6)	15 (7.6)	14 (7.1)	
Gram Negative	34(17.2)	19 (9.6)	15 (7.6)	
Fungi	1 (0.5)	1 (0.5)	0	
Blood pH (N=183)	7.42 (7.37, 7.47)	7.44 (7.4, 7.48)	7.4 (7.33, 7.47)	*0.002**
pCO2 (mm Hg) (N=182)	29.2 (23.5, 34.9)	31.6 (25.7, 36.9)	25.9 (21.4,32.2)	*0.002**
pO2 (mm Hg) (N=182)	110 (75, 203)	104 (70, 195)	120 (79, 217)	0.278
Bicarbonate (mmol/L) (N= 183)	19.5 ± 6.2	21.9 ± 4.8	17.1 ± 6.5	*<0.001**

Normally-distributed data were expressed as mean ± standard deviation. Other data were expressed as n (%) or median (interquartile range). RAI (+) was assigned for index fulfillment (RAI score of ≥ 8). P value compared RAI (-) versus RAI (+) cohorts. Level of significance set at p < 0.05.

A summary of clinical outcomes is presented in Table 3. All outcomes showed significant differences between the two groups. The overall incidence of AKI was 40.5% with the RAI (+) group having significantly higher incidence. PRISM III scores were also much higher in the RAI (+) group with a median score of seven. The number of patients needing RRT was also higher in the RAI (+) group. Overall mortality rate was high at 29% and majority belonged to the RAI (+) group. In terms of hospital stay, the RAI (+) group had a shorter duration of stay with a median admitted days of 12 compared to the RAI (-) group of 20 days.

Table 3. Clinical Outcomes Stratified by Day 0 Renal Angina Fulfillment

Category	Overall N= 222	RAI (-) n= 127	RAI (+) n= 95	p value
Length of Hospital Stay (in days)	14 (8, 30)	20 (10, 36)	12 (5,19)	< 0.001*
PRISM III Score	5 (0, 7)	0 (0, 4.5)	7 (5, 10)	< 0.001*
Presence of AKI	90 (40.5)	3 (1.4)	87 (39.2)	< 0.001*
Need for RRT	54 (24.3)	2 (0.9)	52 (23.4)	< 0.001*
Mortality	64 (28.9)	10 (4.5)	54 (24.3)	< 0.001*

Data were expressed as n (%) or median (interquartile range). RAI (+) was assigned for index fulfillment (RAI score of ≥ 8). P value compared RAI (-) versus RAI (+) cohorts. Level of significance set at p < 0.05.

The diagnostic accuracy of RAI is presented in Table 4. AUC-ROC was at 0.953 (95% CI 0.92-0.98). Figure I shows the prediction model and its corresponding AUC- ROC plot.

Table 4. Diagnostic performance of renal angina index in prediction of acute kidney injury

Sensitivity (%)	96.7 (90.6-99.3)
Specificity (%)	94.0 (88.4-97.4)
Positive Predictive Value (%)	91.6 (84.1-96.3)
Negative Predictive Value (%)	97.7 (93.3-99.5)
Positive Likelihood Ratio	15.95 (8.1–31.3)
Negative Likelihood Ratio	0.04 (0.01-0.11)
AUC ROC	0.953 (0.92-0.98)

Data were presented as percentage (95% confidence interval). RAI (+) was assigned for index fulfillment (RAI score of ≥ 8). P value compared RAI (-) versus RAI (+) cohorts. The absolute RAI value (range, 1-40) was used to derive the AUC-ROC which was expressed with 95% confidence interval.

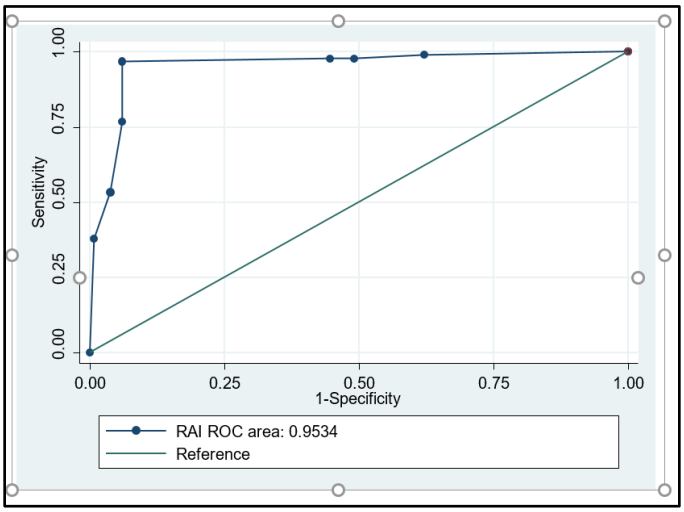

Figure I. AUC-ROC Plot for AKI Prediction Using RAI. The RAI AUC-ROC area was at 0.9534 and showed clear separation of the two distributions

The fulfillment of RAI with a score of at least 8 on day of admission was independently associated with the occurrence of AKI (odds ratio 449.5, p value < 0.001) as presented in Table 5.

Table 5. Logistic Regression of Renal Angina Index for Acute Kidney Injury

	Odds Ratio	95% Confidence Interval	p-value
RAI	449.5	116 - 1742.5	<0.001*

Odds ratio was expressed with 95% confidence interval. Level of significance set at p < 0.05.

DISCUSSION

The burden brought about by the occurrence of AKI remains to be high across all regions of the globe with geographic variations noted between countries and their economies. A published meta-analysis by Susantitaphong et al. in 2013 reported a high AKI incidence rate of 33.7% in the pediatric population encompassing all clinical settings such as critical care, trauma and cardiac surgery.[1] Sepsis and septic shock have been shown as the most significant predictors of AKI in critically ill patients as supported by a study in 2008 by Bagshaw et al.[14] In this present retrospective study, 90 of 222 subjects developed AKI, roughly a rate of 40.5% which was double than the reported incidence of 20% among a pediatric cohort with severe sepsis in a study conducted by Fitzgerald et al. in 2016.[15] This alarmingly high incidence rate was coupled by an overall mortality rate of 28.9%. Early recognition and management of AKI is the most logical way to address its dreaded complications. However, the use of creatinine or clinical symptom such as oliguria as a marker of AKI remains to be a hindrance in achieving this goal since these parameters are often late markers of injury. Unlike other systemic diseases with successful breakthroughs in early diagnosis with the use of biomarkers, available breakthrough diagnostics for AKI provide inconsistent to fair performance. The introduction of the RAI concept paved the way in predicting AKI in vulnerable patients. The use of RAI as a risk-stratification model optimizes the pre-test probability of the disease which will be complemented by novel biomarkers once necessary to have an improved post-test probability of detecting AKI.[4] A composite score of at least 8 signify fulfillment of the index which reflected marked discriminatory utility.

Given that risk tranches and clinical evidence of injury are basic components of the RAI definition, it is not surprising to have a greater number of patients in the RAI (+) group needing inotropes and mechanical ventilation with a concomitant higher percentage of fluid overload and higher values of BUN and creatinine. The negative effect of sepsis is manifested by substantial derangements in other organ systems such as thrombocytopenia (p = < 0.001), lower prothrombin activity (p = 0.025), lower calcium level (p = < 0.001) and lower blood pH, pCO2 and bicarbonate levels (p = < 0.001). These changes which were significantly noted in the RAI (+) group suggest possible risk factors in the development of sepsis-associated AKI. The blood gas parameters reflected the presence of metabolic acidosis combined with respiratory alkalosis supporting the increased need for hemodynamic and ventilatory support in the RAI (+) group. Moreover, the higher AKI incidence reflected poorer clinical outcomes such as increased need for RRT and mortality

thereby suggesting the proposed additive detrimental effect of having both sepsis and the subsequent AKI rather than having sepsis alone. PRISM III scores turned out to be higher in the RAI (+) group supporting its association with higher mortality rate. Several studies have reported that RAI (+) patients had a longer hospital stay. [4,6-7] This is in contrast with what was seen in this study where RAI (-) patients had significantly longer duration of stay compared to RAI (+) subjects with a median of 20 and 12 days respectively. This significant result can be hypothesized to be due to the sicker state of RAI (+) patients, a more complicated and stormier course and earlier demise.

The utility of RAI as a clinical guide is brought about by integration of baseline, contextual and clinical evidence of injury which identifies patients at risk for AKI.[9] Several studies have concluded that RAI is a good screening tool due to its high NPV and acceptable AUC-ROC.[5-7]

In this study, the diagnostic accuracy of RAI tested in pediatric patients with sepsis yielded good results in all parameters for the validation of an assessment tool. The high sensitivity and NPV of RAI further confirm its beneficial role as a screening tool in ruling out AKI and preventing further indiscriminate testing such as use of biomarkers. The high specificity and PPV suggest that RAI can successfully detect those who need further investigation and for whom an AKI biomarker will be most beneficial and cost-effective. With the study's sample size, the utility of RAI as a predictive tool is supported by positive and negative LR. A high positive LR of 15.95 supports AKI consideration while its low negative LR aids in ruling out the possibility of AKI in each subject. The discriminatory nature of RAI is further supported by the high AUC ROC value of 0.953 and a plot showing separation of the two distributions. Inherent validity of the diagnostic tool is therefore appreciated. Logistic regression computation showed a very high odds ratio thus RAI can be considered as an independent risk factor associated with the occurrence of AKI.

There are several potential limitations of this study. First, the study design has inherent restrictions especially in the analysis and data extraction of variables not available upon review of the medical records. Second, being a single-center study, the management of patients can be subject to institutional bias especially in the provision of work-ups and in the use of management algorithms. Lastly, no transplant patients were enrolled since this patient subset is usually referred and followed-up in another tertiary institution. The inclusion of these groups in future studies will refine the RAI stratification and will make comparison between high risk and very high-risk tranches possible.

CONCLUSION

RAI is a good screening tool in the prediction of sepsis-associated AKI in the pediatric population. Its application provides early AKI recognition upon admission. It is a clinically practical and feasible method which can be used at bedside with relatively simple calculations. Its discriminatory utility may reduce arbitrary use of expensive biomarkers providing context to their use. Its pragmatic nature and good performance holds promise to its future integration into clinical practice.

RECOMMENDATION

The call for a larger pediatric population and for prospective studies involving serum and urinary biomarkers in conjunction with RAI stratification of children with sepsis is recommended to aid in targeted and early management of AKI which involves hemodynamic intervention, vigilance in renal monitoring, avoidance of nephrotoxins, aggressive sepsis treatment, and provision of adequate nutrition and target goals for fluid balance.

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