

Original Article**Renal angina validation of acute kidney injury in critically ill children****Doaa Youssef¹, Saad Mansour¹, Amal El Shal², Ahmed Osman¹, Yousif Mohamed Yousif¹, Faika Arab¹, Mona Hamed Gehad¹**

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Abstract**Introduction**

Since the initial (renal angina) RA proposal in 2010 and Developing (renal angina index) RAI, increased in prediction of severe (acute kidney injury) AKI at the time of intensive care unit admission. New biomarkers such as Cystatin C has better performance in prediction of sever AKI in critically ill children with different illness.

Aim of the study

To test the hypothesis that combination of Cystatin C in patients with renal angina improves the prediction of AKI.

Patients and methods

In this study 53 critically ill children admitted to the pediatric intensive care unit in our university hospital, Measurement of urine Cystatin C by ELISA kit and in combination with the RAI which is calculated in each critically ill child for severe AKI. Also statistical analysis was done in days (0-3-7).

Results

Cystatin C has a sensitivity of 76.5%, a specificity of 95%, positive predictive value of 83.3% negative predictive value of 92.7% and accuracy of 90.6% regarding prediction of AKI. Combination of both cystatin C and RAI has a sensitivity of 92.3%, a specificity of 97.5%, positive predictive value of 92.3%, and negative predictive value of 97.5% and accuracy of 96.2% regarding prediction of AKI.

Conclusions

This study shows that combination of Cystatin C with RAI improves detection ability of AKI in critically ill children.

Keywords

Acute kidney injury, Cystatin C, critically ill children, renal angina index

Running Title

Renal Angina and acute renal failure

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Introduction

Acute kidney injury (AKI) occurs frequently in critically ill patients and is associated with high rates of morbidity and mortality. In a recent meta-analysis among the 154 studies of over 3.5 million patients during a hospital episode of care, originated from North America, Northern Europe, and Eastern Asia and from high-income countries, the incidence of AKI was 21.6% in adults and 33.7% in children, with mortality rates of 23.9 and 13.8%, respectively [1].

Cystatin C (Cys c) is a low molecular weight (13.4 kDa) cytoplasmic protein, functioning as an inhibitor of various cysteine proteases in the bloodstream. It has emerged as a sensitive measure of renal function. It has also proven to be a better predictor of mortality and cardiovascular events than serum creatinine (sCr)-based estimates in different populations studied (coronary heart disease, acute and chronic heart failure) [2].

CysC has been proposed as a complementary or possibly marker of baseline renal function. Although sCysC measurement is more expensive than SCr, it is implemented in routine renal function measurement of pediatric patients and used to monitor kidney transplant patients [3].

Since the initial renal angina (RA) proposal in 2010, RA has been assessed. A renal angina index (RAI) was developed and validated to operationalize the bedside use of RA. Basu et al., [4]. Cruz et al. [5] assessed the capacity of RA to predict severe AKI. Their results are consistent with the performance of RA in children. They found that RA was strongly associated with the development of AKI, and that the sensitivity was high (92%) with a high negative predictive value (NPV) (99%). The NPV was high (92 to 99%). In addition, they assessed the performance of each of the hazard tranches (HTs). They found the performance to indicate that the HTs perform similarly, and the sensitivity is high with an excellent NPV.

Matsuura et al. [6] evaluated the performance of RAI for predicting patients who were at higher risk of persistent severe AKI in the Asian population. They concluded that the RAI was shown to be effective in predicting persistent AKI in adult patients admitted to ICU from general wards. RAI scoring at ICU admission might be effective for predicting the onset of moderate-to-severe AKI. Incorporation of an AKI biomarker into the RAI might improve prediction of severe AKI.

Aim of the study

The study aim was to validate the combination of RAI and cystatin C level to standard pRIFLE using creatinine and urine output to predict early AKI.

Patients and methods

Technical design:

- Setting of the study: A Prospective cohort study, which was conducted in the Intensive Care Unit (ICU), Pediatric Department, our University Hospitals. The study was done from January 2018 to January 2019.
- Population of the study: 53 critically ill children aged from 3 months to 14 years. From whom we extract the demographic and outcome data. We measured cystatin C for all children on the day of admission.
- Inclusion criteria: Children admitted to the PICU from the ages of 3 months to 14 years, who had a predicted discharge >48 h from PICU admission.
- Exclusion criteria: Children aged <3 months and >14 years.

Patients with history of end-stage renal disease and those immediately following renal transplant.

f) Sample size calculation: Sample size was calculated by Institutional Review Board (IRB). The total number of critically ill children at pediatric department is 500 children per 6 months. The PPV of renal angina index is 62% the sample size is 53 children with EPI-INFO with power 80% and CI 95%.

Operational design: Written informed consent was obtained from all children's parents, the study was approved by the research ethical committee of Faculty of Medicine, our University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The following was done for all patient:

1. Data timing: Data was collected from the first day of PICU admission (Day0) for seven consecutive days until 7 days after admission (Day7). A minimum of 8 h from PICU admission considered Day0.

Cystatin C was assessed admission between 12 and 24 h after the time of PICU admission (Day 1).

Day3 is the time period between 72 and 96 h after PICU admission.

2. Collected variables: Demographic information, admission diagnoses, comorbidities, height, weight, available laboratory values and vital signs were collected at the time of admission. Baseline SCr was established as the lowest creatinine up to 3 months before PICU admission on Day0, If no baseline S.Cr is available in the computer system, a reference estimated creatinine clearance of 120 mL/min/m² was used and a baseline creatinine was imputed using the patient's height in centimeters (Schwartz formula) [(crcl = k*Ht/S.cr) k = 0.45 in infants, k=0.55 in children] [7]. Daily collected variables were assessed at 8:00 am for each patient on Days 0, 3, 7 and included vital signs, laboratory values, nephrotoxin use such as vancomycin or aminoglycosides, vasopressor use, mechanical ventilation support level and total ICU fluid intake and output. Urine output was calculated as mL/kg/h in 8 h blocks using PICU admission weight.

3. Calculated variables and RAI

a. The RIFLE classification (table 1) is including both biochemical measures of renal function and urine output as components of the definition, was done on first 24h.

b. The RAI score was determined between 8 and 12 h from the time of PICU admission on Day0, (figure 1) [4].

Determination of Day 0 - RAI needed the calculation of percent fluid overload (% FO),

% Fluid overload = (total fluid in – total fluid out) / admission body weight x 100 [7].

A RAI ≥8 was considered fulfillment of renal angina. Fulfillment or the absence of renal angina was denote 'RA+' or 'RA-'. Net ICU fluid balance was determined using simple subtraction of total fluid balance during ICU course. Urine output will be calculated as ml/kg/h in 8 h blocks using PICU (admission weight) [4].

4. Urine collection and biomarker analysis: Urine samples were collected from all enrolled patients. Urine was centrifuged and stored in aliquots at -80°C until measurement. Day [1]Cys C values will be used for the purposes of this initial analysis (urine

obtained from Days1-4 when possible). Cystatin C was assayed using a human-specific commercially available enzyme-linked immunosorbent assay [4].

Table 1 RIFLE classification for AKI [8]

Class	GFR	UO
Risk	↑ SCr × 1.5 or ↓ GFR >25%	< 0.5 mL/kg/h × 6 h
Injury	↑ SCr × 2 or ↓ GFR >50%	< 0.5 mL/kg/h × 12 h
Failure	↑ SCr × 3 or ↓ GFR >75% or if baseline SCr ≥353.6 μmol/L (≥4 mg/dL) ↑ SCr >44.2 μmol/L (>0.5 mg/dL)	< 0.3 mL/kg/h × 24 h or anuria × 12 h
Loss of kidney function	Complete loss of kidney function >4 weeks	
End-stage kidney disease	Complete loss of kidney function >3 months	

GFR, glomerular filtration rate; UO, urine output; SCr, serum creatinine

Renal angina index (RAI) = Risk of AKI * Signs of injury

		Risk	Score
RISK		Moderate	1
		High	3
		Very High	5
		X	
INJURY	↓ eCCI	% FO	Score
	No change	<5%	1
	↓ 0-25%	≥5%	2
	↓ 25-50%	≥10%	4
	↓ ≥50%	≥15%	8

Figure1 The renal angina index (RAI).

Patients are stratified depending on their 'risk' of developing acute kidney injury (AKI) and their signs of injury. There are three risk groups: moderate (pediatric intensive care admission), high (prior stem cell transplantation) and very high (ventilation and requirement for either an inotrope or vasopressor). The worse parameter between change in estimated creatinine clearance (eCCI) from baseline and percentage fluid overload (% FO) yields an injury score. The resultant RAI can range from 1 to 40. A cut-off value of ≥8 is used to determine fulfilment for 'renal angina.' [4].

Statistical analysis

Data collected, coded, entered and analyzed using Epi-Info version 6 and application for Windows version 8, throughout history, basic clinical examination, laboratory investigations and outcome measures. Data were then imported into the Social Sciences Statistical Package (SPSS version 20.0) for analysis software. Depending on the type of qualitative data represented by number and percentage, quantitative continuous group represented by mean ± SD, the following tests were used to test differences for meaning, correlation by Pearson's correlation or Spearman's. For significant results, the P value was set at < 0.05 and < 0.001 for highly significant results.

Results

We studied RAI and cystine C level in relation to standard pRIFLE using creatinine and urine output and its association to RAI in pediatric intensive care unit in our University Hospitals in 53 children (34 males and 19 females) admitted to PICU of our University. Out of 53 patients, 25 patients (47.2%) were found to have bronchopneumonia, 3 patients (5.7%) had HUS, 13 patients (24.5%) had dehydration and 12 patients (22.6%) had sepsis.

Our study showed that there were statistically significant differences in serum creatinine and blood urea on D3 and D7. (Table 2). Our study showed that 45 out 53 critically ill patients developed AKI, these 45 patients were divided according to p RIFLE criteria into:

3 (5.7%) at D0 and 7 (13.2%) at D3 as risk, 8 (15.1%) at D0, 5 (9.4%) at D3 and 4 (7.5%) at D7 as injury, and 1 (1.9%) at D0, 8 (15.1%) at D3 and 9 (17%) at D7 as failure. (Table3).

Our study showed that there were statistically a high significant relation between RAI and p RIFLE at day 3 and cystatin C Day₃ was chosen since most PICU patients develop AKI within this timeframe, the time highlights the advantage of biomarkers on the PICU admission day to predict the outcome; in addition, Day₃ is a clinically relevant time frame for AKI management ,Day 3 is also beyond the period of time that AKI may be functional and is more likely to be damage-associated AKI [9] (Table 4).

AUC-ROC values were calculated for each prediction model (RAI and biomarker concentrations used as continuous variables) and compared using DeLong's method, Our study showed that at a cutoff point at of cystatin C ≥ 1.5 has a sensitivity of 76.5%, a specificity of 95%, $P < 0.001$ with an area under the curve (AUC) of 0.800 for Cys C (figure 1)

Cystatin C has a sensitivity of 76.5%, a specificity of 95%, positive predictive value of 83.3%, negative predictive value of 92.7% and accuracy of 90.6% regarding prediction AKI according to p RIFLE criteria. Also, RAI has a sensitivity of 84.6%, a specificity of 97.5%, positive predictive value of 91.7%, negative predictive value of 95.1% and accuracy of 94.3% regarding prediction of AKI. But combination of both cystatin C and RAI has a sensitivity of 92.3%, a specificity of 97.5%, positive predictive value of 92.3%, negative predictive value of 97.5% and accuracy of 96.2% regarding prediction of AKI (Table 5).

Table 2 Changes in serum creatinine and blood urea (mg/dl).

	Serum creatinine (mg/dl) Mean \pm SD (range)	Blood urea (mg/dl) Mean \pm SD (range)	p
D0	1.2 \pm 0.6 (0.6 - 3)	84.3 \pm 57.1 (28 - 172)	
D3	1.5 \pm 1.1 (0.6 - 4.2)	93.1 \pm 65.4 (25 - 180)	< 0.001 (HS)
D7	1.4 \pm 1.3 (0.6 - 4.9)	93.6 \pm 68.7 (24 - 200)	< 0.001 (HS)

Table 3 A category number of AKI according to RIFLE criteria

	Risk		Injury		Failure	
	No	%	No	%	No	%
D0	3	5.7	8	15.1	1	1.9
D3	7	13.2	5	9.4	8	15.1
D7	0	0	4	7.5	9	17

Table 4 Relation between RAI and p RIFLE at D3 and cystatin C.

RAI	P RIFLE				Cystatin C Mean \pm SD (range)	p
	No	Risk	Injury	Failure		
- ve	33	6	2	1	0.9 \pm 0.25 (0.6-1.9)	< 0.001 (HS)
+ve	0	1	3	7	2.5 \pm 0.75	

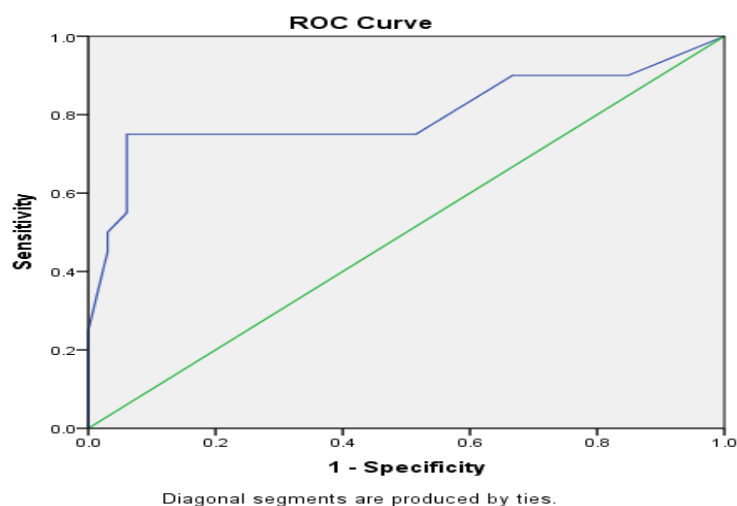


Figure 1 Show area under the receiver operating characteristic (ROC) curve for detecting the cut –off of Cys C.

Table 5 Validity of Cystatin C and RAI in prediction of AKI

	Sensitivity	Specificity	PPV	NPV	Accuracy
Cystatin C	76.5%	95%	83.3%	92.7%	90.6%
RAI	84.6%	97.5%	91.7%	95.1%	94.3%
Both	92.3%	97.5%	92.3%	97.5%	96.2%

Discussion

Acute kidney injury (AKI), formerly known as acute renal failure, continues to represent a very common and potentially devastating problem in critically ill children and adults. The reported incidence of AKI in this population varies greatly due to the lack of a standard consensus definition. We observed in our study that 45 out of 53 critically ill patients (84.91%) developed AKI. While Basu, et al. [10] reported incidence rate of AKI in children admitted to pediatric intensive care units (PICUs) range from 8% and 89%.

Goldstein and Chawla [11] derived and validated the empirical clinical model of renal angina for prediction of subsequent severe AKI. In order to optimize performance, care providers must seek novel ways of directing AKI biomarker use. Incorporation of a positive AKI biomarker test (e.g., a renal troponin) in the novel RAI AKI risk stratification system (kidney pain) heightens the sensitivity and discrimination for a kidney attack. The renal angina index (RAI) is a composite of patient AKI risk and early signs of injury, created to risk stratify patients for whom biomarkers testing would be most optimal. In short, fulfillment of renal angina informs the pretest probability of any AKI diagnostic test.

Improvement of AKI prediction by incorporation of biomarkers into the RAI occurs via correct classification of disease. Each of these urinary biomarkers (NGAL, kidney injury molecule-1, IL-18, and liver-type fatty acid binding protein) added alone and in combination with the clinical model of patient age and CPB duration, improved prediction of AKI development and severity Krawczeski et al., [12].

Our study included 53 children (34 males and 19 females) admitted to PICU of our University. All children included in this study underwent detailed history taking, thorough clinical examination, laboratory investigations, and calculating RAI.

In our study, bronchopneumonia was the most common cause of ICU admission, in addition to various other causes as HUS, dehydration and sepsis accounting for ICU admission. Matsuura et al. [6] evaluated the performance of RAI for predicting patients who were at higher risk of persistent severe AKI in the Asian population. Sepsis was the most common cause of ICU admission, where various other causes, as well as sepsis, accounted for ICU admission.

Our study showed that there were statistically high significant differences in serum creatinine and blood urea at D3 and D7. Our study showed that 45 out of 53 critically ill patients developed AKI, these 45 patients were divided according to RIFLE criteria into: 3 (5.7%) at D0 and 7 (13.2%) at D3 as risk, 8 (15.1%) at D0, 5 (9.4%) at D3 and 4 (7.5%) at D7 as injury, and 1 (1.9%) at D0, 8 (15.1%) at D3 and 9 (17%) at D7 as failure

Zapitelli et al. [13] analyzed a group of 140 children admitted to PICU, AKI developed in 75.7%, with 35.7% being at the risk stage, 22.1% at the injury stage, and only 17.9% at the failure stage. Plotz et al. [14] demonstrated that at the general AKI prevalence 58%, as many as 52% reached the risk stage, 37% the injury stage, and only 11% the failure stage.

According to Washburn et al. [15] in the population of 137 children, AKI was noted in 75.2% of patients, with the risk stage seen in 36.5% of cases, the injury stage in 20.4%, and failure stage only in 18.3%. Kavaz et al. [16] analyzed a group of 189 children admitted to PICU in whom AKI was seen in 35.9% of cases and demonstrated the following prevalence of particular pRIFLE stages: R - 7%, I -18.5%, and F - 9.6%.

In the reports of Bersolin et al. [17] and Hui et al. [18], the analysis included 126 and 140 children respectively. The prevalence of AKI and the prevalence of particular stages was 46% (R: 17.4%, I: 16.7%, F: 11.9%) and 56% (R: 23%, I: 20%, F: 12%), respectively.

Kaddourah et al. [19] found that the overall incidence of AKI in the 4683 critically ill children evaluated was 26.9%, and the incidence of severe AKI (KDIGO Stage 2 or 3) was 11.6%. Diagnosis of severe AKI conferred an increased risk of mortality by an adjusted odds ratio of 1.77, with a mortality rate of 11% versus 2.5% in patients without severe AKI.

The benefit of including multiple criteria (both serum creatinine and urine output) by which to increase sensitivity was also confirmed, as 67.2% of the patients found to have AKI by oliguria would have been missed if using serum creatinine alone. Strikingly, a significant increase in mortality was also observed (7.8% versus 2.9%) when severe AKI threshold (KDIGO Stage 2 or 3) was achieved due to oliguria compared to creatinine.

Our study showed that there were statistically a high significant relation between RAI and creatinine at day 3 and a high significant correlation between RAI and Cystatin C. Menon et al. [20] stated that there was statistically significant increase in serum creatinine and renal angina fulfillment (RAI+).

Our study showed that Cystatin C has a sensitivity of 76.5%, a specificity of 95%, positive predictive value of 83.3%, negative predictive value of 92.7% and accuracy of 90.6% regarding prediction AKI. Also, RAI has a sensitivity of 84.6%, a specificity of 97.5%, positive predictive value of 91.7%, negative predictive value of 95.1% and accuracy of 94.3% regarding prediction of AKI. But combination of both cystatin C and RAI has a sensitivity of 92.3%, a specificity of 97.5%, positive predictive value of 92.3%, negative predictive value of 97.5% and accuracy of 96.2% regarding prediction of AKI

Basu et al. [4] showed that incorporation of AKI biomarkers into the RAI improves discrimination for severe AKI. The RAI optimizes the utility of AKI biomarkers in a heterogeneous, critically ill patient population.

Matsuura et al. [6] showed that the RAI was effective in predicting persistent AKI in adult patients admitted to ICU from general wards. RAI scoring at ICU admission might be effective for predicting onset of moderate-to-severe AKI. Incorporation of an AKI biomarker into the RAI might improve prediction of severe AKI.

Limitations of the study

We have a limitation of number of study population so we recommend larger study size and longer duration of follow up, as large number may reveal more disease that may affect the result.

Conclusion

- ❖ Cystatin C increases in critically ill children with AKI in pediatric ICU.
- ❖ Increase the rate of AKI in critically ill children with RAI+.
- ❖ Incorporation of Cystatin C with RAI enhances the predictive ability of AKI in critically ill children.

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Statements

Ethics approval and consent to participate

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Zagazig

university hospitals and informed written consent was obtained in every case from their legal guardians.

Consent for publication

“Not applicable”

Availability of data and material

Not applicable”

Conflict of interest

The authors declare no conflict of interest.

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