Serum Cystatin C as an Early Indicator for Acute Kidney Injury in Critically Ill Children in Pediatric Intensive Care Units

Authors
Mohsen Taha Elkeiy1, Moftah Mohamed Rabeea1, Ahmed Mohsen Abd Alhakeem1, Ahmed Abdou Ellawah2, Ahmed Raafat Elsalamouny1
1Pediatrics Department, Faculty of Medicine, Al Azhar University, Cairo, Egypt.
2Clinical Pathology Department, Faculty of Medicine, Al Azhar University, Cairo, Egypt
Corresponding Author
Dr Ahmed Raafat Elsalamouny
13, Shaarawy Street, Louran, Alexandria, Egypt.
Email: ahmraafat@hotmail.com, Telephone No: +201222359019

Abstract
Background: Acute kidney injury (AKI) has been associated with high morbidity and mortality rates among critically ill children. Cystatin C is a protease inhibitor, and studies have shown that it is a promising marker for the early diagnosis of AKI. Our goal in this study was to evaluate the accuracy of cystatin C as a marker of AKI in critically ill children.

Subjects and Methods: This cross sectional study was undertaken in the pediatric intensive care unit at Bab El-Sharyea University Hospital. It included 200 critically ill children according to certain inclusion criteria. Serum creatinine and cystatin C levels were measured in all patients within 48 hours of admission. AKI was diagnosed according to the pediatric RIFLE criteria. Receiver operating characteristic (ROC) curve analysis was performed.

Results: In our study, 112 cases (56%) were diagnosed as AKI. The area under the ROC curve for serum cystatin c indicated that it was a good marker for the diagnosis of AKI, with a sensitivity of 93.75%. However, the specificity of serum cystatin C was 57.95%. The optimal cutoff value was 0.749 mg/L. The area under the ROC curve for serum creatinine showed a sensitivity of 86.61% and specificity of 60.23%. The optimal cutoff value for serum creatinine was 0.5 mg/dL.

Conclusion: Serum cystatin is a sensitive marker for the early diagnosis of AKI in critically ill children. It is superior to traditional markers, namely blood urea & serum creatinine.

Keywords: Pediatric, Acute kidney injury, Cystatin C, Creatinine.

INTRODUCTION
Acute kidney injury (AKI) is associated with increased mortality, morbidity, and resource use among hospitalized patients [1]. Recent studies have estimated the incidence of AKI in hospitalized children to range from 9% to 64% [2,3].

Various clinical criteria have emerged with the goal of diagnosing AKI, all of them depend heavily on the serum creatinine level and/or urine output (UOP). However, the use of the serum creatinine level has many drawbacks, including...
variability according to age and sex and dependence on muscle mass[4].
Cystatin C is 13-kDa cysteine protease inhibitor that is produced by all nucleated cells at a constant rate. This compound is freely filtered by the glomeruli and completely catabolized by the proximal tubules with no secretion. These attributes make Cystatin C an ideal marker of GFR[5].
In pediatric clinical studies, cystatin C has shown a high predictive value for diagnosis, and some studies have even shown that it is superior to serum creatinine in the early detection of AKI. [2] Recently, cystatin C has been shown to be a sensitive marker for early AKI diagnosis in children admitted to a pediatric intensive care unit (PICU) [6].

PATIENTS AND METHODS
This study is a cross sectional study, carried out on two hundred children, their ages range was 6-144 months, who were admitted to pediatric intensive care unit, at Bab El-Sharyea University Hospital, suffering from acute critical conditions associated with signs of renal impairment during the period from December 2014 to August 2016. The exclusion criteria included the following: patients who were known to have chronic kidney disease, diabetes mellitus and malnutrition.
All selected cases were subjected to:
1) Thorough history taking.
2) Complete clinical examination, with emphasis on vital signs, anthropometric measurements, urine volume, and complete abdominal examination.
3) Investigations including:
   - CBC, CRP, renal function (blood urea & creatinine).
   - Serum sodium and potassium, arterial blood gases.
   - Imaging study including ultrasonography.
   - Serum cystatin C within the first 48 hours of admission.
   - Estimation of GFR was calculated using the Schwartz formula: [7]

\[
\text{GFR (ml/min/1.73 m²)} = K \times \text{Height (cm)} ÷ \text{Plasma creatinine (mg/dl)}
\]
where \(K\) = constant determined by regression analysis for different ages: for full term infants ≤1 year, \(K = 0.45\), for children aged 2 to 12 years, \(K = 0.55\), and for children above 12 years old, \(K\) for girls 0.55 and for boys 0.70.

The serum creatinine level was measured using the Jaffe kinetic spectrophotometric method. The serum cystatin C level was measured according to the manufacturer’s protocol supplied with the ELISA kit.(BioVendor – Laboratorní medicína a.s. Catalogue. No.: RD191009100, European Union: In vitro diagnostic medical device Rest of the world) Reference values for serum cystatin c differ in many populations. Across different studies, the mean reference interval was between 0.52 and 0.98 mg/L.

Patients were classified to have AKI according to the pediatric RIFLE criteria (R=Risk, I=Injury, F=Failure, L=Loss, E=End stage renal disease)[8].

Ethical Considerations
All procedures were explained to parents or guardians of the participating children and written informed consent was obtained.

Statistical Analysis
The following statistical analyses were performed using IBM SPSS statistics version 20.0:
1. Chi-square test: For categorical variables, to compare between different groups.
2. Fisher’s Exact or Monte Carlo correction: Correction for chi-square when more than 20% of the cells have expected count less than 5.
3. Student t-test: For normally quantitative variables, to compare between two studied groups.
4. Pearson coefficient: To correlate between two normally quantitative variables.
5. Mann Whitney test: For abnormally quantitative variables, to compare between two studied groups.
6. Kruskal Wallis test: For abnormally quantitative variables, to compare between more than two studied groups.

7. Receiver operating characteristic curve (ROC): It is generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test.

8. Sensitivity: The capacity of the test to correctly identify diseased individuals in a population “true positives”.

9. Specificity: The capacity of the test to correctly exclude individuals who are free of the disease “true negatives”.

10. Positive Predictive value (PPV): The probability of the disease being present, among those with positive diagnostic test results.

RESULTS

A total of 200 patients, comprising 98 boys and 102 girls, were recruited for the study. The mean age for AKI occurrence was 21.35 ± 34.19 months, while for non-AKI patients, the mean age was 20.48 ± 32.60 months. Age and gender had no effect on the development of AKI. According to the modified pRIFLE criteria, 112 patients had AKI (56 %), and they were categorized as follows: Risk class, 53 patients (47.3%); Injury class, 21 patients (18.8%); and Failure class, 38 patients (33.9%). Table 1 shows the important clinical characteristics of both groups.

The common presenting symptoms of our cases were, oliguria or anuria (25.9%), disturbed level of consciousness (16.1%), diarrhea and vomiting (13.4%). Results of anthropometric measurements showed that there was no significant difference between AKI and non-AKI cases. Regarding vital signs, we found that AKI group had a significantly higher heart rate, temperature and blood pressure than non AKI group.

In the present study, disturbed conscious level (38.4%) and presence of edema (24.1%) were the most significant clinical findings associated with AKI patients. The most common possible etiology of AKI was sepsis, which occurred in 39 patients (34.8 %), followed by gastroenteritis (13.4%), neurological (11.6%), meningoencephalitis (8.9%), post arrest (8.9%), respiratory (7.1%), renal and cardiac (5.4%) each.

Regarding laboratory investigations, non AKI cases had lower hemoglobin but higher white blood cells level than AKI group. Hyperkalemia and metabolic acidosis were the most significant two biochemical abnormalities in the AKI group. By urine analysis, we found that cases of AKI had a significantly higher prevalence of proteinuria, and a higher urine specific gravity. Table 2 shows the important laboratory parameters of both groups.

By ultrasonography, abnormalities were detected in 17% of cases, which were as follows: Increased echogenicity (5.4%), hydronephrosis/ pyonephrosis (3.6%),ascites (3.6%), free peritoneal fluid collection (3.6%), single kidney (0.9%). In the present study, there was a significant difference between AKI and non-AKI cases regarding the three renal function tests(urea, creatinine and cystatin c).

We found that there was no significant correlation between cystatin C and age, sex and anthropometric measurements, in contrast to creatinine, which was significantly correlated to age and anthropometric measurements.

In our study, we found a significant positive correlation between cystatin c level and both urea and creatinine levels. Moreover, a significant negative correlation was observed between serum Cystatin C and estimated glomerular filtration rate, which was more significant than the correlation between creatinine and estimated glomerular filtration rate. Furthermore, there was a significant progressive rise in serum Cystatin C concentration with worsening of pRIFLE category. (Table 3)
Table 4 summarizes the linear regression analysis for the parameters that affect Cystatin c for AKI group and total sample.

Table 1. Comparison between the two groups according to important clinical characteristics

|                      | AKI (n=112) | Non-AKI (n=88) | Total (n=200) | Test of sig. | p    |
|----------------------|-------------|----------------|---------------|--------------|------|
| **Age (months)**     |             |                |               |              |      |
| Min. – Max.          | 6.0 – 144.0 | 6.0 – 144.0    | 6.0 – 144.0   | Z=0.797      | 0.426|
| Mean ± SD.           | 21.35 ± 34.19 | 20.48 ± 32.60 | 20.97 ± 33.42 |              |      |
| Median               | 8.0         | 6.0            | 6.0           |              |      |
| **Sex**              |             |                |               |              |      |
| Male                 | 57          | 41             | 98            | χ²=0.365     | 0.546|
| Female               | 55          | 47             | 102           |              |      |
| **Weight (kg)**      |             |                |               |              |      |
| Min. - Max.          | 5.0 – 73.50 | 5.0 – 33.50    | 5.0 – 73.50   | Z=0.632      | 0.527|
| Mean ± SD.           | 9.25 ± 10.59| 8.30 ± 5.41    | 8.83 ± 8.70   |              |      |
| Median               | 6.55        | 6.10           | 6.50          |              |      |
| **Height (cm)**      |             |                |               |              |      |
| Min. - Max.          | 59.0 – 156.0| 59.0 – 143.0   | 59.0 – 156.0  | Z=0.624      | 0.533|
| Mean ± SD.           | 72.49 ± 20.76| 70.97 ± 18.54 | 71.82 ± 19.78|              |      |
| Median               | 67.0        | 61.0           | 64.0          |              |      |
| **BMI (kg/m²)**      |             |                |               |              |      |
| Min. – Max.          | 10.70 – 33.0| 11.75 – 21.94  | 10.70 – 33.0  | t=0.604      | 0.547|
| Mean ± SD.           | 15.46 ± 2.89| 15.66 ± 1.86   | 15.55 ± 2.48  |              |      |
| Median               | 15.0        | 15.0           | 15.0          |              |      |
| **Blood pressure**   |             |                |               |              |      |
| Normal               | 13          | 38             | 51            | χ²=26.846    | MC p<0.001*|
| Pre-Hypertension     | 4           | 3              | 7             | 3.5          |      |
| Hypertension         | 92          | 44             | 136           | 68.0         |      |
| Hypotension          | 3           | 3              | 6             | 3.0          |      |
| **Urine output**     |             |                |               |              |      |
| (ml/kg/hr)           |             |                |               |              |      |
| Normal               | 77          | 78             | 155           | χ²=17.128*   | MC p<0.001*|
| Oliguria             | 26          | 4              | 30            | 15.0         |      |
| Anuria               | 3           | 0              | 3             | 1.5          |      |
| Polyuria             | 6           | 6              | 12            | 6.0          |      |
| **Consciousness**    |             |                |               |              |      |
| Conscious            | 69          | 75             | 144           | 72.0         | χ²=13.638* |
| Disturbed            | 43          | 13             | 56            | 28.0         | <0.001*   |
| **Edema**            |             |                |               |              |      |
|                     | 27          | 5              | 32            | 16.0         | χ²=12.448* |

χ², p: χ² and p values for Chi square test
Z: Z value for Mann Whitney test
t: Student t-test
MC: Monte Carlo for Chi square test
Table 2. Comparison between the two groups according to important laboratory parameters

|                      | AKI (n = 112) | Non-AKI (n = 88) | Total (n = 200) | Test of sig. | p      |
|----------------------|---------------|-----------------|-----------------|--------------|--------|
|                      | No.           | %               | No.            | %            | No.   | %    |       |       |
| RBC                  |               |                 |                 |              |       |      |       |       |
| Min. – Max.          | 2.0 – 7.40    | 1.63 – 5.19     | 1.63 – 7.40     | t=0.773      | 0.440 |
| Mean ± SD.           | 4.0 ± 0.97    | 3.90 ± 0.81     | 3.96 ± 0.90     |              |       |      |       |       |
| Median               | 3.85          | 3.86            | 3.85            |              |       |      |       |       |
| WBC                  |               |                 |                 |              |       |      |       |       |
| Min. - Max.          | 2.70 – 91.0   | 2.90 – 256.0    | 2.70 – 256.0    | Z=2.059*     | 0.039*|
| Mean ± SD.           | 14.60 ± 15.92 | 23.53 ± 46.05   | 18.53 ± 32.99   |              |       |      |       |       |
| Median               | 11.3          | 13.0            | 11.90           |              |       |      |       |       |
| Platelets            |               |                 |                 |              |       |      |       |       |
| Min - Max.           | 16.0 - 7610   | 13.0 - 768.0    | 13.0 - 768.0    | t= 0.101     | 0.920 |
| Mean ± SD.           | 278.63 ± 267.99 | 275.99 ± 266.3 | 277.47 ± 231.0  |              |       |      |       |       |
| Median               | 196.18        | 268.50          | 231.0           |              |       |      |       |       |
| CRP (mg/dl)          |               |                 |                 |              |       |      |       |       |
| Positive             | 69            | 61.6            | 59              | χ²=0.633     | 0.426 |
| Negative             | 43            | 38.4            | 29              |              |       |      |       |       |
| GFR (ml/min/1.73m²)  |               |                 |                 |              |       |      |       |       |
| Min - Max.           | 18.0 - 63.0   | 43.0 - 131.0    | 18.0 - 131.0    | t=11.723*    | <0.001*|
| Mean ± SD.           | 39.92 ± 11.28 | 65.68 ± 18.02   | 51.26 ± 19.42   |              |       |      |       |       |
| Median               | 39.50         | 63.50           | 49.0            |              |       |      |       |       |
| Creatinine (mg/dl)   |               |                 |                 |              |       |      |       |       |
| Increased            | 84            | 75.0            | 16              | χ²=63.636    | <0.001*|
| Normal               | 28            | 25.0            | 72              |              |       |      |       |       |
| Min - Max.           | 0.40 - 2.50   | 0.30 - 1.50     | 0.30 - 2.50     | Z=8.073*     | <0.001*|
| Mean ± SD.           | 0.92 ± 0.47   | 0.52 ± 0.20     | 0.74 ± 0.42     |              |       |      |       |       |
| Median               | 0.70          | 0.40            | 0.68            |              |       |      |       |       |
| Urea (mg/dl)         |               |                 |                 |              |       |      |       |       |
| Increased            | 69            | 61.6            | 27              | χ²=18.882*   | <0.001*|
| Normal               | 43            | 38.4            | 61              |              |       |      |       |       |
| Min - Max.           | 7.90 - 218.0  | 6.0 - 99.0      | 6.0 - 218.0     | Z=4.051*     | <0.001*|
| Mean ± SD.           | 51.87 ± 36.61 | 33.68 ± 20.23   | 43.87 ± 31.75   |              |       |      |       |       |
| Median               | 40.0          | 31.50           | 35.0            |              |       |      |       |       |
| Cystatin c (mg/l)    |               |                 |                 |              |       |      |       |       |
| Increased            | 92            | 82.1            | 6               | χ²=111.887    | <0.001*|
| Normal               | 20            | 17.9            | 82              |              |       |      |       |       |
| Min - Max.           | 0.36 - 6.02   | 0.14 - 1.26     | 0.14 - 6.02     | Z= 9.321*    | <0.001*|
| Mean ± SD.           | 1.62 ± 1.05   | 0.71 ± 0.30     | 1.22 ± 0.93     |              |       |      |       |       |
| Median               | 1.44          | 0.66            | 1.03            |              |       |      |       |       |

*χ², p: χ² and p values for Chi square test
Z: Z value for Mann Whitney test
t: Student t-test
*: Statistically significant at p ≤ 0.05
Table 3. Correlation between Cystatin c and different parameters for AKI group and total sample

|                | Cystatin c |
|----------------|------------|
|                | AKI (n=112) | Total Sample (n=200) |
| Age (months)   | -0.118     | -0.072 |
|                | 0.216      | 0.310 |
| Sex            | -0.119     | -0.087 |
|                | 0.212      | 0.219 |
| Weight         | -0.106     | -0.062 |
|                | 0.268      | 0.381 |
| Height         | -0.179     | -0.123 |
|                | 0.059      | 0.082 |
| BMI (kg/m²)    | -0.065     | -0.055 |
|                | 0.498      | 0.439 |
| SBP            | 0.043      | -0.017 |
|                | 0.656      | 0.812 |
| SBP %          | 0.140      | 0.137 |
|                | 0.141      | 0.054 |
| DBP            | 0.142      | 0.068 |
|                | 0.137      | 0.339 |
| DBP %          | 0.187      | 0.184 |
|                | 0.048      | 0.009 |
| Hypertension   | 0.199*     | 0.296* |
|                | 0.036*     | <0.001* |
| level of Consciousness | -0.280* | -0.059 |
|                | 0.003*     | 0.405 |
| RBC            | -0.106     | -0.072 |
|                | 0.269      | 0.315 |
| Hemoglobin     | -0.108     | 0.006 |
|                | 0.259      | 0.934 |
| WBC            | -0.146     | -0.132 |
|                | 0.125      | 0.062 |
| Platelets      | -0.137     | -0.116 |
|                | 0.150      | 0.101 |
| CRP            | 0.173      | 0.071 |
|                | 0.069      | 0.315 |
| Creatinine     | -0.065     | 0.161 |
|                | 0.498      | 0.023 |
| GFR            | -0.665*    | -0.664* |
|                | <0.001*    | <0.001* |
| GFR %          | -0.500*    | -0.609* |
|                | <0.001*    | <0.001* |
| P-RIFLE        | 0.558*     | 0.671* |
|                | <0.001*    | <0.001* |
| Urea           | 0.188*     | 0.243* |
|                | 0.048*     | 0.001* |
| Na⁺            | 0.005      | -0.021 |
|                | 0.961      | 0.769 |
| K⁺             | -0.032     | 0.164* |
|                | 0.739      | 0.020* |

r: Pearson coefficient
*: Statistically significant at p ≤ 0.05

Table 4. Linear regression for the parameters that affecting Cystatin c for total sample (n = 200)

|                | t        | Sig.     | 95% C.I  |
|----------------|----------|----------|----------|
|                |          |          | Lower    | Upper    |
| p-RIFLE        | 12.674   | <0.001*  | 0.540    | 0.739    |
| Creatinine     | 5.233    | <0.001*  | -0.959   | -0.434   |
| Hypertension   | 2.543*   | 0.012*   | 0.064    | 0.508    |
| Urea           | 1.734    | 0.084    | 0.000    | 0.006    |
| K⁺             | 1.512    | 0.132    | -0.143   | 0.019    |

We performed ROC analysis to assess the utility of serum cystatin C for diagnosing AKI. (Figure 1) The analysis revealed that the best cutoff values for serum cystatin C and serum creatinine were 0.749 mg/L and 0.5 mg/dl, respectively. The estimated area under the curve (AUC) for Cystatin C was greater than that of the estimated AUC for SCr. (Table 5)
Figure 1. Receiver operating characteristic curve (ROC) curve for cystatin C, creatinine and urea to predict acute kidney injury by P-RIFLE criteria for total sample.

Table 5 Agreement (sensitivity, specificity and accuracy) for cystatin C, creatinine and urea to predict acute kidney injury by P-RIFLE criteria for total sample.

|            | AUC      | P        | 95% C.I     | Cutoff | Sensitivity | Specificity | PPV  | NPV  |
|------------|----------|----------|-------------|--------|-------------|-------------|------|------|
| Cystatin c | 0.884*   | <0.001*  | 0.832 - 0.925 | >0.749 | 93.75       | 57.95       | 73.9 | 87.9 |
| Creatinine | 0.822*   | <0.001*  | 0.762 - 0.872 | >0.5   | 86.61       | 60.23       | 73.5 | 77.9 |
| Urea       | 0.667*   | <0.001*  | 0.597 - 0.731 | >31    | 73.21       | 50.0        | 65.08| 59.46|

DISCUSSION
In our study, 56 % of the admitted patients were diagnosed with AKI. This incidence is similar to that observed by Herrero-Morin et al[9] and Safdar et al[10], indicating that AKI is a significant and common issue among critically ill children. The incidence was lower in other studies [11], this may be explained by the small sample of our study, as we included only children having symptoms and signs suggestive of renal impairment.
We classified AKI cases into probable prerenal, renal and postrenal cases. This classification was based on clinical data (hydration status, blood pressure, presence of edema), laboratory data (BUN/creatinine ratio, urine specific gravity) and ultrasonography. We found that 79.5% of cases had prerenal AKI, 18.8% had intrinsic AKI, and 1.8% had post renal AKI. A study in Nigeria [12] also reported that prerenal causes of AKI were common than the others. On the other hand, a study in Norway revealed that most cases were renal.[13] This could be explained by the increased incidence of sepsis and dehydration in developing countries than the developed ones.
We found that there was no significant correlation between cystatin C and age, sex and anthropometric measurements, in contrast to creatinine, which was significantly correlated to age and anthropometric measurements.
These results are supported by Franco et al [14] who reported that serum concentrations of cystatin C appear to be unaffected by age, sex, or muscle
mass. Also, Schanz et al[15], who found that BMI has no impact on diagnostic accuracy of cystatin c. This is in contrast to Wang et al[16], who concluded that a graded association between BMI and increased cystatin C level has been observed, however, a multivariable adjusted association was not reported.

We failed to demonstrate a correlation between Cystatin C and CRP levels. On the other hand, Schanz et al[15] found positive correlation of CRP and Cystatin C and that higher Cystatin C levels were found in cases of elevated CRP levels. However, he stated that there was no significant impact of CRP on the diagnostic accuracy of Cystatin C to detect AKI.

A significant negative correlation was observed in our study between serum Cystatin C and estimated glomerular filtration rate, which was more significant than the correlation between creatinine and estimated glomerular filtration rate. Herrero-Morin et al[9] have shown that the serum cystatin C and beta-2 microglobulin levels are more strongly correlated with creatinine clearance than with serum creatinine in children with AKI admitted to an ICU. Furthermore, serum Cystatin C was accurate in stratifying AKI severity according to pRIFLE classification. There was a progressive rise in serum Cystatin C concentration with worsening of pRIFLE category, which is in accordance with a recent study in pediatric patients[17].

Our data showed that the performance of serum Cystatin C to diagnose AKI defined by p-RIFLE criteria was very good and better than creatinine which is better than urea. A serum Cystatin C level of 0.749 mg/L had sensitivity of 93.75% and specificity of 57.95% for detecting AKI. The relatively low specificity of cystatin c for the diagnosis of AKI could be explained by the observation that the serum cystatin C level can be affected by factors such as hyper/hypothyroidism, steroid treatment, growth hormone, and insulin. This finding is similar to those of other cohort studies of children admitted to ICUs. Safdar et al[10] found that at 24 h of admission, the AUC for serum cystatin C was 0.780 (95% CI: 0.634–0.925), with a sensitivity of 83% and a specificity of 50% with cut-off value of 0.645 mg/l. Also, Volpon et al[17] stated that in critically ill children, serum Cystatin C is an early and accurate diagnostic marker of AKI.

Another study has reported that the sensitivity and specificity of serum cystatin C for diagnosing AKI are 73.9% and 78.9%, respectively, using 0.6 mg/l as the cutoff value[17]. Similarly, a study conducted by Lagos-Arevaldo et al[18] on pediatric patients admitted to a PICU has reported that serum cystatin C has more diagnostic accuracy than serum creatinine and a greater predictive value for clinical outcomes.

Other studies have shown contradictory results and have found that cystatin C is a poor marker for AKI diagnosis. A recent study of pediatric patients admitted to an ICU demonstrated that the use of serum cystatin C is not superior to that of serum creatinine for the diagnosis of AKI[19]. This finding is similar to that of a clinical study performed by Royakkers et al[20], who demonstrated that both serum and urine cystatin C are poor markers for the diagnosis of AKI. There is no clear explanation for these conflicting results, but they might reflect the heterogeneity of the populations assessed and differences in the AKI definitions used; another possibility is that different cutoff values for serum creatinine and cystatin c were used to diagnose AKI in these studies.

CONCLUSION

From this study, we can conclude that AKI is common in critically ill children admitted to PICU. Serum cystatin C is a sensitive and accurate marker for diagnosis of AKI in critically ill children if it is measured within the first 48 hours of admission. Our study has several limitations, including the following: 1) it was a single-center study with a relatively small number of patients; 2) the definition of AKI used in this study was based on changes in the eGFR according to the Schwartz formula and using serum creatinine,
which has several drawbacks. 3) We lack data regarding other factors that could affect levels of serum cystatin C, such as steroid therapy, the use of insulin and thyroid function test results. 

We recommend that further prospective multicenter studies are needed, including a big number of patients, for more evaluation of accuracy of cystatin c as a sensitive marker to diagnose AKI.

REFERENCES

1. Watkins SC, Williamson K, Davidson M, Donahue BS. Long-term mortality associated with acute kidney injury in children following congenital cardiac surgery. Paediatr Anaesth 2014;24:919–26.

2. Hassinger AB, Backer CL, Lane JC, Haymond S, Wang D, Wald EL. Predictive power of serum cystatin C to detect acute kidney injury and pediatric modified RIFLE class in children undergoing cardiac surgery. Pediatr Crit Care Med 2012;13:435–40.

3. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. Clin J Am Soc Nephrol 2015;10:554–61.

4. Finney H, Newman DJ, Price CP. Adult reference for serum cystatin C, creatinine and predicted creatinine clearance. Ann Clin Biochem 2000; 37:49–59.

5. Goldstein SL, Zappitelli M. Evaluation and Management of Acute Kidney Injury in Children. In: Avner E, Harmon W, Niaudet P, Yoshikawa N, editors. Pediatric Nephrology, 7th edition. Springer-Verlag Berlin Heidelberg, 2016:2139-67.

6. Ataei N, Bazargani B, Ameli S, Madani A, Javadilarijani F, Moghtaderi M. Early detection of acute kidney injury by serum cystatin C in critically ill children. Pediatr Nephrol 2014;29:133–8.

7. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am 1987; 34: 571–90.

8. Akcan-Arikan A, Zappitelli M, Loftis LL. Modified RIFLE criteria incritically ill children with acute kidney injury. Kidney Int 2007; 71: 1028–35.

9. Herrero-Morin JD, Malaga S, Fernandez N. Cystatin C and β2-microglobulin: markers of glomerular filtration in critically ill children. Crit Care 2007; 11:59.

10. Safdar OY, Shalaby M, Khathlan N, Elattal B, Bin Joubah M, Bukahri E, Saber M, Alahadal A, Aljariry H, Gasim S, Hadadi A, Alqahtani A, Awleyakhan R, Kari JA. Serum cystatin is a useful marker for the diagnosis of acute kidney injury in critically ill children: prospective cohort study. BMC Nephrol 2016;17(1):130.

11. Naik S, Sharma J, Yengkom R, Kalrao V, Mulay A. Acute kidney injury in critically ill children: risk factors and outcomes. Indian J Crit Care Med 2014;18:129–33.

12. Sadeghi-Bojd S, Noori NM, Mohammadi M, Teimouri A. Clinical characteristics and mortality risk prediction in children with acute kidney injury. Nigcr Med J 2015;56(5):327-32.

13. Jenssen GR, Hovland E, Bangstad HJ, Nygård K, Vold L, Bjerre A (2014): The incidence and aetiology of acute kidney injury in children in Norway between 1999 and 2008. Acta Paediatr;103(11):1192-7.

14. Franco M, Nishida SK, Sesso R. GFR Estimated From Cystatin C Versus Creatinine in Children Born Small for Gestational Age. Am J Kidney Dis 2008; 51:925-32.

15. Schanz M1, Pannes D, Dippon J, Wasser C, Alscher MD, Kimmel M. The Influence of Thyroid Function, Inflammation, and Obesity on Risk Prediction of Acute Kidney Injury by Cystatin C in the
Emergency Department. Kidney Blood Press Res 2016;41(5):604-13.

16. Wang GN, Sun K, Hu DL, Wu HH, Wang XZ, Zhang JS. Serum cystatin C levels are associated with coronary artery disease and its severity. Clinical Biochemistry 2014; 47:176–81.

17. Volpon LC, Sugo EK, Carlotti AP. Diagnostic and prognostic value of serum cystatin C in critically ill children with acute kidney injury. Volpon LC1, Sugo EK, Carlotti AP. Pediatr Crit Care Med 2015;16(5):e125-31.

18. Lagos-Arevalo P, Palijan A, Vertullo L (2015): Cystatin C in acute kidney injury diagnosis: early biomarker or alternative to serum creatinine? Pediatr Nephrol;30: 665-76.

19. Hamed HM, El-Sherbini SA, Barakat NA, Farid TM, Rasheed EA. Serum cystatin C is a poor biomarker for diagnosing acute kidney injury in critically-ill children. Indian J Crit Care Med 2013;17(2):92-8.

20. Royakkers AA, Korevaar JC, van Suijlen JD, Hofstra LS, Kuiper MA, Spronk PE. Serum and urine cystatin C are poor biomarkers for acute kidney injury and renal replacement therapy. Intensive Care Med;37:493–501.