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# Cystatin C as a biomarker of acute kidney injury in a group of critically ill children in a pediatric intensive care unit

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**ABSTRACT**

**Introduction:** Acute kidney injury (AKI) is known to be one of the major complications of critically ill children and accounts for a 30%-90% mortality of such patients. Early identification of such patients can significantly influence their mortality and morbidity.
**Objectives:** Serum creatinine levels are not a good marker of early renal dysfunction. Numerous novel biomarkers have been proposed for the detection of AKI. In this study we sought to evaluate the ability of serum creatinine and serum cystatin C levels in the early detection of AKI.
**Patients and Methods:** In this prospective study, serum cystatin C and creatinine levels were serially measured in a group of critically ill children older than 6 months, admitted to the intensive care unit of a tertiary care children hospital.
**Results:** Around 54 patients were evaluated in this study. About 13 of them developed AKI. Serum cystatin C levels significantly changed over time in these patients. Changes in cystatin C levels were more prominent in patients with AKI in comparison with patients with normal renal function or those at risk for kidney injury. Rate of serum cystatin C elevation was more rapid than serum creatinine elevation in patients with AKI ($p<0.05$) and thus serum cystatin C levels can detect kidney injury earlier.
**Conclusion:** Serum cystatin C is applicable as a good biomarker of renal function in early stages of kidney injury. Hence, we can use serum cystatin C for the early detection of AKI in patients more accurately.

*Implication for health policy/practice/research/medical education:*
To find the ability of serum creatinine and serum cystatin C levels in the early detection of AKI, we demonstrated that both serum cystatin C and serum creatinine raised in patients with AKI however cystatin C increased earlier.
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## Introduction

Acute kidney injury (AKI) is a condition that is frequently seen in critically ill children in the pediatric intensive care units (PICUs) and is associated with poor clinical outcomes (1,2). It is defined as a sudden cessation of kidney function and is sometimes associated with catastrophic life-threatening consequences in children admitted to PICUs (3). Critically ill pediatric patients are prone to this condition and its incidence has been reported between 18%-52% in such patients (4). RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) and AKIN (Acute Kidney Injury Network) criteria have been proposed to

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diagnose AKI (5-7). In 2012 these two classifications were combined in the KDIGO guideline for diagnosing AKI (8). Serum creatinine is used to detect and to stage AKI in these guidelines although its limitations are well-known. Serum creatinine can be influenced by non-renal factors such as muscle mass, liver function and dietary creatinine intake, medications, gender and age. Rise in serum creatinine may be delayed for days after renal injury. According to these limitations, researchers have proposed a number of novel biomarkers for the early detection of AKI in recent years (9,10). One of these biomarkers is serum cystatin C which seems to be a useful marker for the early detection of AKI (11). Numerous studies have shown that serum cystatin C acts as a good glomerular filtration rate (GFR) marker (12-14). Cystatin C is a proteinase inhibitor that is constantly produced by nucleated cells in the body and is freely filtered by the glomerulus and is entirely reabsorbed in the proximal tubule (15,16). Recent investigations have proposed that serum cystatin C is a better marker of AKI (15,17-19).

## Objectives

We conducted this study to compare between serum creatinine and serum cystatin C in identifying critically ill children with AKI.

## Patients and Methods

### *Study population*

This was a prospective study. It was conducted in PICU of Dr Sheikh's pediatric hospital in 2014. The hospital is affiliated to Mashhad University of Medical Sciences and is the only pediatric tertiary care hospital in east of Iran. All critically ill children were older than 6 months when admitted PICU. Exclusion criteria were: age younger than 6 months, those with chronic kidney problems and patients whose parents were not willing to take part in the study.

### *Laboratory assessments*

Serum cystatin C (using human cystatin C ELISA kit) and creatinine (using Jaffe colorimetric method) were measured on admission to PICU. They were rechecked every 48 hours for 3 times. Then each serum cystatin C and creatinine measurement was compared with GFR of patients to see which marker was able to show the onset of AKI earlier?

### *Ethical issues*

1) The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained from the parents of children and 3) the research was approved by the ethical committee of faculty of medicine of Mashhad University of Medical Sciences (Grant #910431).

### *Data analysis*

All data was coded and analyzed using SPSS 21. Descriptive studies were used for the calculation of mean and standard deviations (SDs). Chi-square test was used for association between parameters. We also used ROC curves for comparing different measured predictors and to assess sensitivity and specificity levels and *P* value below 0.05 was assumed to be significant ($P<0.05$).

## Results

Fifty-four critically ill children older than 6 months who were admitted in the PICU, entered the study. Mean age of patients was 4.09 ± 3.98 years (minimum; 6 months and maximum was 15 years old). Male gender was predominant (70.4%, n = 38).

Mean height was 91.8 ± 23.3 cm and mean weight was 13.15 ± 7.29 kg. Demographic data of patients are shown in Table 1.

Around 26 patients did not survive and six of them died during the first 3 days of PICU admission, which were excluded from the study. The other 20 patients, died after the fifth day (last sampling for creatinine and cystatin C). On fifth day of the study, 38 patients (70.3%) experienced AKI according to RIFLE criteria (risk 43.7%, injury 27% and failure 8.3%).

Table 2 shows changes in creatinine and cystatin C over time.

Analysis of variance (ANOVA) shows that cystatin C had a significant change over time in all patients. Additionally cystatin C elevation had a significant correlation with the stage of AKI ($P<0.001$).

Alterations of cystatin C were most prominent in the patients at the failure stage of AKI.

ROC analysis was performed at each time point to evaluate the usefulness of serum cystatin C for the diagnosis of AKI (Figures 1-3).

In the first day, the AUC for cystatin C and creatinine were 0.93 ($P=0.005$) and 0.67 ($P=0.268$) respectively. The diagram shows that cystatin C had a greater AUC and thus

**Table 1.** Demographic data of patients with AKI

| | Normal | Risk | Injury | Failure | *P* value |
|---|---|---|---|---|---|
| Age (y) | 3.35± 4.06 | 3.58± 4.75 | 4.89± 4.07 | 4.33±3.26 | 0.110 |
| Sex, No. (%) | | | | | 0.989 |
| Male | 6 (66.7) | 14 (66.7) | 9 (69.2) | 3 (75) | |
| Female | 3 (33.3) | 7 (33.3) | 4 (30.8) | 1 (25) | |
| Height (cm) | 25.91± 101.11 | 25.11± 100.48 | 26.82± 88.61 | 15.36± 77 | 0.238 |
| Weight (kg) | 8.03± 14.33 | 8.41± 16.24 | 12.25± 1481 | 0.5± 7.25 | *0.049 |

**Table 2.** Creatinine and cystatin C levels in patients at different stages of AKI

| | Failure | Injury | Risk | Normal |
|---|---|---|---|---|
| First day serum creatinine, mg/dL | 1.13 ± 0.91 | 0.88 ± 0.59 | 0.66 ± 0.27 | 0.38 ± 0.12 |
| Third day creatinine, mg/dL | 1.7 ± 1.27 | 0.96 ± 0.57 | 0.65 ± 0.14 | 0.63 ± 0.12 |
| Fifth day creatinine, mg/dL | 2.47 ± 1.58 | 1.1 ± 0.5 | 0.74 ± 0.16 | 0.55 ± 0.19 |
| First day cystatin c, mg/dL | 2.45 ± 0.67 | 1.46 ± 0.97 | 1.19 ± 0.21 | 1.17 ± 0.13 |
| Third day cystatin c, mg/dL | 0.41± 2.75 | 1.8 ± 0.81 | 1.24 ± 0.23 | 1.16 ± 0.1 |
| Fifth day cystatin c, mg/dL | 0.56± 3.21 | 1.94 ± 0.79 | 1.39 ± 0.26 | 1.27 ± 0.23 |

was better able to identify AKI.

In the third day the AUC for cystatin and creatinine were 0.96 ($P=0.003$) and 0.95 ($P=0.004$) respectively. These findings showed that cystatin C had a greater AUC and therefore had better ability to identify AKI. However AUC of creatinine was very close to that of cystatin C and there was no significant difference between these two entity for diagnosis of AKI ($P>0.05$).

In fifth day, the AUC for both creatinine and cystatin C was 0.96 and thus these two test had the same ability for the diagnosis of AKI at this time point.

## Discussion

In our study 70.3% of the critically ill children experienced AKI which is greater than the reported incidence of AKI in PICU patients (1,20). The greater proportion may be due to the fact that we had a limited number of PICU beds in our center, thus very ill children were admitted in the PICU. This great proportion shows that AKI is an important and prevalent condition in the PICUs and early detection and management of this condition seems mandatory. Currently, serum creatinine is the most commonly used laboratory test for the estimation of kidney function in pediatric patients. However, due to its being influenced by age, gender, muscle mass, diet and administration of drugs, it is not enough sensitive for early detection of changes in GFR (19,21). According of these limitations, numerous studies have focused on new biomarkers for earlier and more reliable detection of AKI (9,10). One such biomarker is cystatin C. In this study we hypothesized that serum cystatin C would detect AKI in critically ill pediatric patients earlier than serum creatinine. Our results demonstrated that both serum cystatin C and serum creatinine raised in patients with AKI; however, cystatin C increased earlier. Our results were similar to previous studies (22-24).

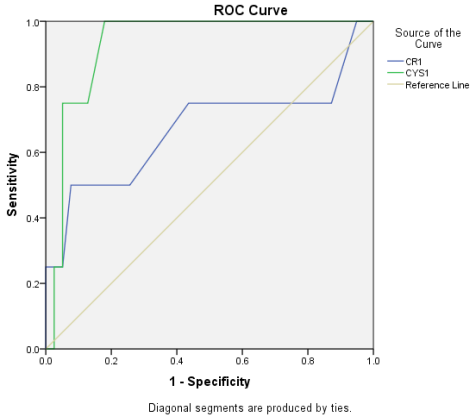


**Figure 1.** ROC analysis of serum cystatin C and creatinine in the first day.

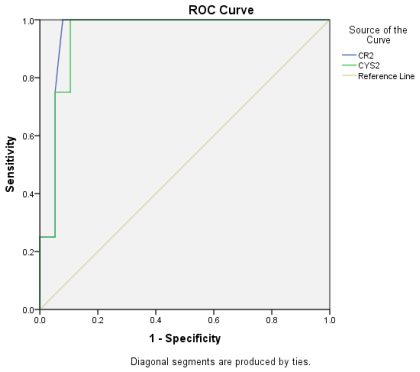


**Figure 2.** ROC analysis of serum cystatin c and creatinine in the second day.

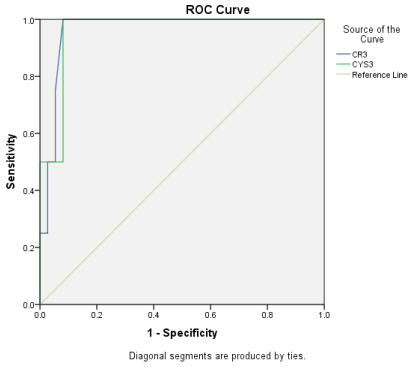


**Figure 3.** ROC analysis of cystatin C and creatinine in the third day following ICU admission.

## Conclusion

In summary serum cystatin C can be used as an early marker of AKI in critically ill pediatric patients. We hope that this study will help to better management of AKI in pediatric patients by institution of early interventions. Also this biomarker may help us identify patients at risk for renal insufficiency like patients with vesicoureteral reflux (25) or those on certain medications with renal complications (26,27) at an earlier stage. Further studies

on these issues seem mandatory.

## Limitations of the study

Our study had some limitations of course. First of all we used serum creatinine for defining AKI. This study conducted with a small sample and the results should be validated by multi- centric studies with larger sample size.

## Authors' contribution

YR and AF; study design, preparation of manuscript, and final revision. ME; study design, manuscript edition, and final revision. SB and SR; data gathering, data interpretation, and manuscript preparation. YR and AA; data interpretation, manuscript preparation, and final revision. YR; data gathering and manuscript preparation.

## Conflicts of interest

The authors declared no competing interests.

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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