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

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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 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 a 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]. Recentstudies have estimated the incidence of AKI in hospital-lized 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 attrib-utes 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]

GFR (ml/min/1.73 m2) = K × Height (cm) ÷ 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
	No.	%	No.	%	No.	%		
Age (months)								
Min. – Max.	6.0 – 144.0		6.0 – 144.0		6.0 – 144.0			
Mean ± SD.	21.35 ± 34.19		20.48 ± 32.60		20.97 ± 33.42		Z=0.797	0.426
Median	8.0		6.0		6.0			
Sex								
Male	57	50.9	41	46.6	98	49.0		
Female	55	49.1	47	53.4	102	51.0	χ^2=0.365	0.546
Weight (kg)								
Min. - Max.	5.0 – 73.50		5.0 – 33.50		5.0 – 73.50			
Mean ± SD.	9.25 ± 10.59		8.30 ± 5.41		8.83 ± 8.70		Z=0.632	0.527
Median	6.55		6.10		6.50			
Height (cm)								
Min. - Max.	59.0 – 156.0		59.0 – 143.0		59.0 – 156.0			
Mean ± SD.	72.49 ± 20.76		70.97 ± 18.54		71.82 ± 19.78		Z=0.624	0.533
Median	67.0		61.0		64.0			
BMI (kg/m^2)								
Min. – Max.	10.70 – 33.0		11.75 – 21.94		10.70 – 33.0			
Mean ± SD.	15.46 ± 2.89		15.66 ± 1.86		15.55 ± 2.48		t=0.604	0.547
Median	15.0		15.0		15.0			
Blood pressure								
Normal	13	11.6	38	43.2	51	25.5		
Pre-Hypertension	4	3.6	3	3.4	7	3.5	χ^2_*=26.846	^{MC}p <0.001*
Hypertension	92	82.1	44	50.0	136	68.0		
Hypotension	3	2.7	3	3.4	6	3.0		
Urine output (ml/kg/hr)								
Normal	77	68.8	78	88.6	155	77.5		
Oliguria	26	23.2	4	4.5	30	15.0	χ^2=	^{MC}p
Anuria	3	2.7	0	0.0	3	1.5	17.128*	<0.001*
Polyuria	6	5.4	6	6.8	12	6.0		
Consciousness								
Conscious	69	61.6	75	85.2	144	72.0	χ^2_*=13.638	<0.001*
Disturbed	43	38.4	13	14.8	56	28.0		
Edema	27	24.1	5	5.7	32	16.0	χ^2_*=12.448	<0.001*

χ^2, p: χ^2 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

*:Statistically significant at $p \leq 0.05$

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			
Mean ± SD.	4.0 ± 0.97		3.90 ± 0.81		3.96 ± 0.90		t=0.773	0.440
Median	3.85		3.86		3.85			
WBC								
Min. - Max.	2.70 – 91.0		2.90 – 256.0		2.70 – 256.0			
Mean ± SD.	14.60 ± 15.92		23.53 ± 46.05		18.53 ± 32.99		Z=2.059*	0.039*
Median	11.3		13.0		11.90			
Platelets								
Min - Max.	16.0 - 7610		13.0 - 768.0		13.0 - 768.0			
Mean ± SD.	278.63 ± 196.18		275.99 ± 166.31		277.47 ± 183.20		t= 0.101	0.920
Median	216.0		268.50		231.0			
CRP (mg/dl)								
Positive	69	61.6	59	67.0	128	64.0	χ^2=0.633	0.426
Negative	43	38.4	29	33.0	72	36.0		
GFR (ml/min/1.73m^2)								
Min - Max.	18.0 - 63.0		43.0 - 131.0		18.0 - 131.0			
Mean ± SD.	39.92 ± 11.28		65.68 ± 18.02		51.26 ± 19.42		t=11.723*	<0.001*
Median	39.50		63.50		49.0			
Creatinine (mg/dl)								
Increased	84	75.0	16	18.2	100	50.0	χ^2=63.636*	<0.001*
Normal	28	25.0	72	81.8	100	50.0		
Min - Max.	0.40 - 2.50		0.30 - 1.50		0.30 - 2.50			
Mean ± SD.	0.92 ± 0.47		0.52 ± 0.20		0.74 ± 0.42		Z=8.073*	<0.001*
Median	0.70		0.40		0.68			
Urea (mg/dl)								
Increased	69	61.6	27	30.7	96	48.0	χ^2=18.882*	<0.001*
Normal	43	38.4	61	69.3	104	52.0		
Min - Max.	7.90 - 218.0		6.0 - 99.0		6.0 - 218.0			
Mean ± SD.	51.87 ± 36.61		33.68 ± 20.23		43.87 ± 31.75		Z=4.051*	<0.001*
Median	40.0		31.50		35.0			
Cystatin c (mg/l)								
Increased	92	82.1	6	6.8	98	49.0	χ^2= 111.887*	<0.001*
Normal	20	17.9	82	93.2	102	51.0		
Min - Max.	0.36 - 6.02		0.14 - 1.26		0.14 - 6.02			
Mean ± SD.	1.62 ± 1.05		0.71 ± 0.30		1.22 ± 0.93		Z= 9.321*	<0.001*
Median	1.44		0.66		1.03			

χ^2, p: χ^2 and p values for Chi square test
Z: Z value for Mann Whitney test
t: Student t-test
*: Statistically significant at $p \leq 0.05$

Table 3. Correlation between Cystatin c and different parameters for AKI group and total sample

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

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

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)

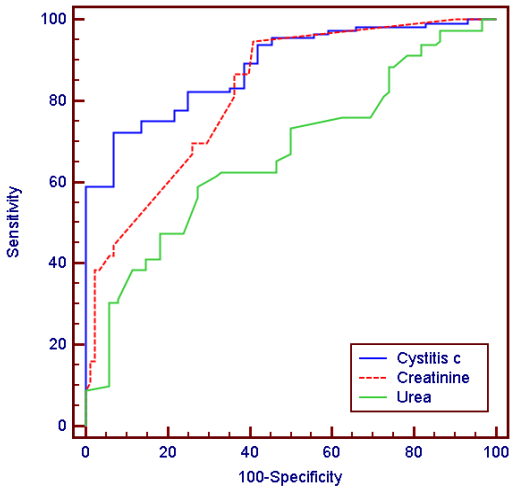

Figure 1. Receiver operating characteristic curve (ROC) curve for cystatin C, creatinine and urea to predict acute kidney injury by P-RIFLE criteria for total sample.

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 anthropo-metric 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 studyin 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 0.57.95%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 [6]. 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 demonst-rated 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.

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