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Original Research Article

Cystatin C- an early marker indicative of renal dysfunction in critically ill children: a prospective cohort study

Hawwa M.S. Siddiqua[1], Mathew John[2], V. C. Manoj[3], Rati Santhakumar[1]*

[1]Department of Pediatrics, Jubilee Mission Medical College and Research Institute, Thrissur, Kerala, India
[2]Jubilee Centre for Medical Research, Thrissur, Kerala, India
[3]Department of Neonatology, Jubilee Mission Medical College and Research Institute, Thrissur, Kerala, India

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***Correspondence:**
Dr. Rati Santhakumar,
E-mail: dr.ratisanthan@gmail.com

ABSTRACT

Background: Acute kidney injury (AKI) is a sudden onset of kidney failure or kidney damage that happens within a few hours or a few days and can also affect other organs such as brain, heart and the lungs. Hence early diagnosis and intervention is needed to improve the outcome of the children. In these studies this objective was to determine if cystatin C is an early marker indicative of renal dysfunction in critically ill children and to determine if Cystatin C can detect Acute kidney injury earlier than serum creatinine.
Methods: This prospective cohort study was undertaken in PICU at Jubilee Mission Medical College from December 2016- May 2018. Blood samples were collected from 34 critically ill children for serum creatinine estimation at 0,24 and 48 hours of admission and serum and urine were collected for cystatin C estimation at admission. Children were categorized into AKI and NON-AKI based on pRIFLE criteria. Comparison of cystatin C values with serum creatinine was performed and Statistical analysis was done using IBM SPSS version 20.
Results: A total of 34 critically ill children were enrolled in this study, out of which 12 children progressed to AKI during the course of illness according to modified Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) criteria. We found a strong positive correlation between cystatin C at 0 hours and serum creatinine at 48 hours among AKI groups.
Conclusions: Serum and Urine cystatin C are early markers to diagnose AKI in critically ill children. Serum cystatin C is more sensitive than urine cystatin C for the diagnosis of AKI.

Keywords: Acute kidney injury, Cystatin C, Serum creatinine

INTRODUCTION

Acute Renal Failure, now referred to as Acute Kidney Injury (AKI) is common in critically ill children. Pediatric retrospective studies have reported an 8- 54% incidence of AKI in pediatric intensive care units (PICU).[1] AKI is an independent risk factor for mortality in critically ill children. Recent evidence suggested that even early AKI can increase morbidity in the form of length of hospital stay and need for renal replacement therapy and increase the risk for Chronic Kidney Disease (CKD) in the future.[2] Despite treatment, severe AKI is still associated with high mortality, hence early AKI identification and therapeutic intervention can improve the outcome. In current clinical practice, AKI is typically diagnosed by measuring serum creatinine concentrations. Unfortunately, serum creatinine is an unreliable indicator during acute changes in kidney function due to the following reasons.[3]

Serum creatinine concentrations can vary widely with age, gender, muscle mass and may not change until a significant amount of kidney function has already been lost. During acute changes in glomerular filtration, serum

creatinine concentration does not accurately depict kidney function until steady state equilibrium has been reached, which may require several days.[4-8]

In view of all these three disadvantages of serum creatinine, a new biomarker called cystatin C has been established to detect acute kidney injury. Cystatin C is a 13-kDa proteins normally filtered freely and has been proposed as a promising endogenous marker of GFR in both adults and children. It was first described as 'gamma-trace' in 1961 as a trace protein together with other ones (such as beta-trace) in the cerebrospinal fluid and in the urine of patients with renal failure.[9]

In these studies the objectives were to compare serum creatinine and cystatin C in detecting acute kidney injury and to find which one would be a good biomarker to detect acute kidney injury in early stage itself. Studies reflecting the utility of cystatin C as a early biomarker of acute kidney injury in children are very scarce in Kerala. Hence this study was conducted to verify its usefulness in this tertiary care center.

METHODS

This prospective cohort study was carried out in a tertiary care hospital in South India over a period of 18 months from December 2016- May 2018. Thirty four critically ill children admitted in PICU were included in the study after getting an informed consent from the parents. The institutional ethical committee approved the study. Neonates, children with chronic kidney disease, nephrotic syndrome, Diabetes mellitus and hypothyroidism were excluded.

Demographic profile and baseline clinical and lab data were recorded in a Performa. Urine output was monitored in ml/Kg /h and computed at 8,16 and 24hours.Blood was collected for serum creatinine at 0,24 and 48 hours of admission and serum cystatin C and urine was collected for urinary cystatin C at admission .Creatinine clearance was estimated by modified schwartz equation and children were categorized according to modified Pediatric Risk, Injury, Failure, Loss, End Stage Renal Disease (pRIFLE) criteria. Serum creatinine estimation was done by auto analyser and Cystatin C (serum and urine) estimation was done using ELISA technique using kit based protocol.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 20. Chi square test for association was used to determine whether there was relationship between categorical variable and AKI. Pearson correlation was performed to find the correlation between cystatin c and serum creatinine. Receiver Operating Curve (ROC) analysis was performed to interpret the sensitivity and specificity of cystatin c and to determine the best cut off value of cystatin c concentrations.

RESULTS

A total of 34 critically ill children were enrolled in this study, comprising 18 males and 16 females. Out of which 12 children progressed to AKI according to modified pRIFLE criteria and they were categorized as follows: Risk category (n=7), Injury (n=4) and Failure (n=1).The most common cause of AKI were snake envenomation (viper),dengue hemorrhagic shock and acute diarrheal disease with shock. Majority of children were under 2 years of age with a minimum age of 1 year and maximum age of 9 years. The distribution percentage was 35.5% for AKI and 64.7% for NON-AKI.

Table 1: Comparison of serum cystatin C, urine cystatin C, serum creatinine and creatinine clearance.

Variables	AKI		NON-AKI		p value
	Mean	SD	Mean	SD	
Serum cystatin c at 0 hour(mg/L)	1.470	0.554	0.565	0.205	<0.001
Urine cystatin c at 0 hour(mg/L)	0.823	0.585	0.313	0.167	<0.001
Creatinine clearance%	49.750	20.673	107.482	26.626	<0.001
Serum creatinine at 0 hours(mg/dl)	0.717	0.0835	0.477	0.0752	<0.001
Serum creatinine at 24 hours(mg/dl)	1.008	0.2503	0.495	0.1327	<0.001
Serum creatinine at 48 hours(mg/dl)	1.392	0.5885	0.500	0.2070	<0.001

Table 2: Association of cystatin C and AKI.

Cystatin C	Cut off	Cases				p value
		AKI		NON AKI		
		n=12	%	n=22	%	
Serum cystatin C	> 0.85(13)	12	92.3	1	7.7	<0.001
	≤ 0.85(21)	0	0.0	21	100.0	
Urine cystatin C	>0.48(12)	10	83.3	2	16.7	<0.001
	<0.48(22)	2	9.1	20	90.9	

A comparative study of serum cystatin C, urine cystatin C and serum creatinine revealed that both urine and serum cystatin C markers appeared earlier than serum creatinine and helped in detecting kidney damage at an early stage (Table 1).

Table 2 shows that 12 children had serum cystatin C concentration more than the cut off value obtained by ROC analysis (>0.85 mg/L) with a p value (<0.001). This signifies that these 12 children were high risk candidates to develop AKI. Ten children had urine cystatin C concentration more than the cut off value obtained by ROC analysis (>0.48 mg/L) with a p value (<0.001). Thus it is evident that these 10 children were high risk candidates to develop AKI.

Sensitivity and Specificity was performed by ROC analysis and showed that seum cystatin C was more sensitive in detecting AKI when compared to urine cystatin C (Figure 1 and 2).

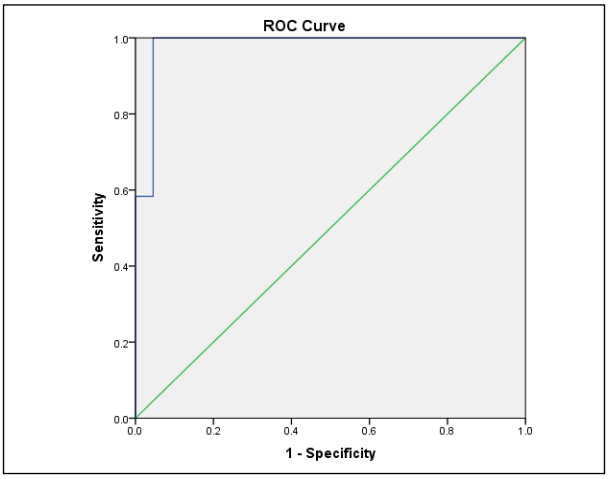

Figure 1: Receiver operating curve(roc) -serum cystatin C.

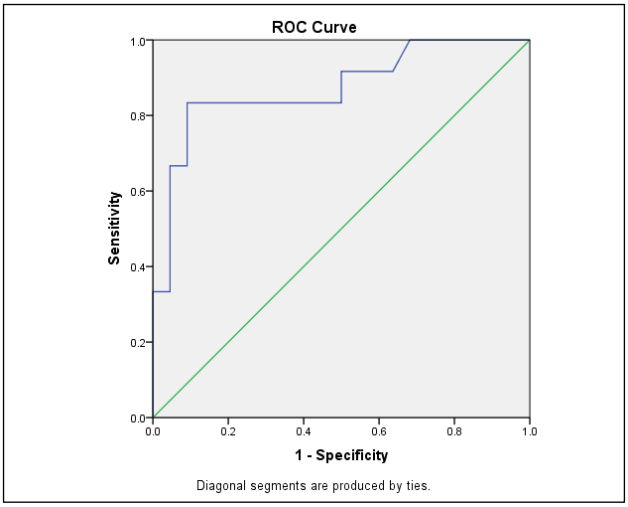

Figure 2: Receiver operating curve(roc) -urine cystatin C.

In AKI the cut off value of serum cystatin c was found to be 0.85 mg/L with AUC (Area under curve) of 0.981.There was almost a perfect Kappa agreement between serum cystatin c and AKI which was shown to be 0.937.The sensitivity of the test was found to be 100% and specificity of 95.5. Positive Predictive Value and Negative Predictive Value was 92.3% and 100% with a accuracy of 97.05 %.

In AKI the cut off value of urine cystatin c was found to be 0.48 mg/L with Area under curve of 0.873 .There was a substantial Kappa agreement between urine cystatin c and AKI which was shown to be 0.742.The Sensitivity of the test was found to be 83.3% and specificity of 90%.Positive Predictive Value and Negative Predictive Value was 83.3% and 90.9% with a accuracy of 88.2%.

DISCUSSION

In this study out of 34 critically ill children 12 children (35.5%) developed AKI and in these cases cystatin C appeared earlier than serum creatinine. These, findings were similar to those of other cohort studies of children admitted to PICU. A study conducted by Shweta Naik et al, included 252 critically ill children out of which 103 children (40.9%) developed AKI.[10] A prospective observational study conducted by Jose David Herrero et al, included 25 critically ill children in PICU, and the study concluded that serum cystatin C and beta 2 microglobin as easy and useful markers better than serum creatinine to detect AKI in critically ill children.[11]

In this study ROC analysis of serum cystatin C showed a cut off value of 0.85mg/L with sensitivity and specificity of 100 % and 95.5% respectively and the urine cyatatin C cut off was found to be 0.48 mg/L with sensitivity and specificity of 83.3%and 90.9% respectively. Hence, this study revealed that serum cystatin C is more sensitive when compared to urine cystatin C. This study can be compared to a similar study conducted by Bokenkamp A et al, which included 184 children, in whom serum cystatin C and serum creatinine were estimated to detect AKI and correlation analysis between the two was done and concluded that cystatin C had a positive reflection of renal function in children and was also independent of age, gender, height, and body composition. The study also found that a cut off cystatin C concentration of 1.39 mg/L had 90% sensitivity and 86% specificity for detecting abnormal GFR.[12]

Cystatin C was considered to be completely reabsorbed and catabolized in the proximal tubule and concentrations of cystatin C in urine may reflect renal tubular injury and impairment. Studies show that cystatin C as an early biomarker of acute kidney injury. A study evaluated 85 critically ill children at high risk to develop AKI of which 44 patients developed AKI and found that cystatin C was significantly preceded that of serum creatinine and the study also concluded that cystatin C increased already by more than 50% at 1 and 1.5±0.6 days earlier compared to

serum creatinine.[13] This study also showed similar findings.

Studies revealed that cystatin C had an advantage over serum creatinine in pediatric population because of the low muscle mass in children, which leads to very low serum creatinine value so that it would be difficult to accurately detect small changes in GFR with serum creatinine in children less than 2 years of age.[14,15] This observation is very relevant in this study as majority of children in this study was under 2 years of age.

This study has a few limitations. First it was a small size study group hence the results should be validated by multi- centric studies with larger sample size. Second, this was a short time study of AKI in critically ill children and hence we did not follow up children to determine the decline, increase or normalization of cystatin C in comparison with creatinine regarding improvement of AKI or deterioration.

CONCLUSION

Authors conclude that cystatin C is a good biomarker to detect acute kidney injury at a early stage in a PICU setting. Once kidney dysfunction is detected by cystatin C, further deterioration can be halted by adjusting the drug dosage, proper fluid and electrolyte management and accurate treatment.

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REFERENCES

1. Krishnamurthy S, Mondal N, Narayanan P, Biswal N, Srinivasan S, Soundravally R. Incidence and etiology of acute kidney injury in southern India. Indian J Pediatr. 2013;80(3):183-9.
2. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, Liu KD, Mehta RL, Pannu N, Van Biesen W, Vanholder R. Acute kidney injury: an increasing global concern. Lancet. 2013;382(9887):170-9.
3. Shemesh O, Golbetz H, KRIss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. Kidney Int. 1985;28(5):830-8.
4. Schrier RW. Editor. Diseases of the kidney and urinary tract. Lippincott Williams & Wilkins; 2007.
5. Akcay A, Turkmen K, Lee D, Edelstein CL. Update on the diagnosis and management of acute kidney injury. Int J Nephrol Renovasc Dis. 2010;3:129.
6. Seikaly MG, Browne R, Bajaj G, Arant Jr BS. Limitations to body length/serum creatinine ratio as an estimate of glomerular filtration in children. Pediatr Nephrol. 1996;10(6):709-11.
7. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem. 1992;38(10):1933-53.
8. Lawson N, Lang T, Broughton A, Prinsloo P, Turner C, Marenah C. Creatinine assays: time for action?. Ann Clin Biochem. 2002;39(6):599-602.
9. Grubb A, Löfberg H. Human gamma-trace, a basic microprotein: amino acid sequence and presence in the adenohypophysis. Proc Natl Acad Sci U S A. 1982;79(9):3024-7.
10. 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(3):129.
11. Herrero-Morín JD, Málaga S, Fernández N, Rey C, Diéguez MÁ, Solís G, et al. Cystatin C and beta2-microglobulin: markers of glomerular filtration in critically ill children. Crit Care. 2007;11(3):R59.
12. Bökenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C-a new marker of glomerular filtration rate in children independent of age and height. Pediatrics. 1998;101(5):875-81.
13. Herget-Rosenthal S, Marggraf G, Hüsing J, Göring F, Pietruck F, Janssen O, et al. Early detection of acute renal failure by serum cystatin C. Kidney International. 2004 Sep 1;66(3):1115-22.
14. Randers E, Krue S, Erlandsen EJ, Danielsen H, Hansen LG. Reference interval for serum cystatin C in children. Clinical Chem. 1999;45(10):1856-8.
15. Filler G, Witt I, Priem F, Ehrich JH, Jung K. Are cystatin C and β2-microglobulin better markers than serum creatinine for prediction of a normal glomerular filtration rate in pediatric subjects?. Clin Chem. 1997;43(6):1077-8.

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