

## Is cystatin C a more reliable marker for estimation of glomerular filtration rate in children with reduced renal function?

Nurdan Yıldız, Salim Çalışkan\*, Levent Kabasakal\*\*, Lale Sever\*, Nil Arısoy\*

Marmara University Medical Faculty, İstanbul, Turkey

\*Cerrahpaşa Medical Faculty Division of Pediatric Nephrology, İstanbul, Turkey

\*\*Cerrahpaşa Medical Faculty Department of Nuclear Medicine, İstanbul, Turkey

### Summary

**Aim:** The aim of this study was to evaluate whether serum cystatin C is superior as a marker of glomerular filtration rate calculation compared to creatinine in children with reduced renal functions.

**Material and Method:** Serum cystatin C, creatinine and <sup>99</sup>Tc-diethylenetriamine penta acetate (DTPA) clearance (GFRDTPA) were measured in 100 children (53 girls, 47 boys; mean age 8.4±5.1). Glomerular filtration rate was calculated by the Schwartz formula. Patients with DTPA clearance which was accepted as the gold standard in the study with a value above 80 ml/dk/1.73m<sup>2</sup> were included in group 1 (n=64) and below 80 ml/dk/1.73m<sup>2</sup> in group 2 (n=36). Receiver-operating characteristics analysis was performed to assess the diagnostic accuracy of variables. Signed informed consents were obtained from the parents in all cases.

**Results:** Serum cystatin C and creatinine were correlated with glomerular filtration rate in group 1 and 2. Diethylenetriamine penta acetate (DTPA) clearance was correlated with glomerular filtration rate in both groups and with cystatin C in group 2. Receiver-operating characteristics analysis showed that the accuracy of cystatin C and glomerular filtration rate was similar. The area under curve values were statistically significant but not different for cystatin C and GFR<sub>Schw</sub>.

**Conclusions:** Serum cystatin C may be a useful variable, but is not superior to glomerular filtration rate calculated by Schwartz formula which is a simple and reliable method to estimate glomerular filtration rate in children with normal and decreased renal functions. (*Turk Arch Ped* 2011; 46: 21-6)

**Key words:** Cystatin C, glomerular filtration rate, renal function, Schwartz formula

### Introduction

Glomerular filtration rate (GFR) is the most significant marker which provides information about renal function. It is of utmost significance that GFR is determined by a reliable method in patients with reduced renal function. Although many methods have been used in determining glomerular filtration rate, the ideal variable has not been found yet. Inulin clearance is accepted to be the golden standard in the measurement of GFR, but it is not widely

used in clinical practice due to difficulty of application and problems in the method of inulin measurement (1). Serum creatinine levels (Cr) and creatinine clearance are the most frequently used variables for GFR measurement. Serum creatinine levels are affected by factors including age, gender, muscle mass and diet. In addition, when renal function is reduced, tubular secretion of creatinine increases and clearance measured by creatinine is increased in these patients (2,3). Therefore, a simple and reliable method which will reflect GFR accurately is still being searched for.

Measurement of GFR with chromium-51-labeled ethylenediaminetetraacetic acid ( $^{51}\text{Cr}$ -EDTA) and technetium-99- diethylene triamine pentaacetic acid ( $^{99\text{m}}\text{Tc}$ -DTPA) is accepted as the golden standard (4,5). These methods are more sensitive in determining minor changes in renal function compared to creatinine and are appropriate for children whose GFR deteriorates slowly.

Studies related to serum cystatin C have shown that it is a better variable compared to creatinine in determining CFR. Cystatin C is a protein with low molecular weight (13 kDa) which inhibits cysteine proteinase. It is excreted freely from the kidneys by glomerular filtration, reabsorbed by proximal tubular cells and metabolized here. In contrast to creatinine, it is not excreted in the tubules and is not affected by age and gender. Because of these properties, cystatin C is recommended to be used in GFR measurement (6-9). However, different results have been reported in studies performed on this subject (10-12). Although cystatin C has been recommended to be used in GFR measurement since 1985, it could not replace creatinine in practice, yet.

In this study, the superiority of serum cystatin C level in GFR measurement over GFR estimation by creatinine and Schwartz Formula was investigated.

## Material and Method

A total of 100 children with normal and reduced renal functions followed up in Ministry of Health Göztepe Education and Research Hospital and Cerrahpaşa Medical Faculty Division of Pediatric Nephrology were included in the study.

Height, weight, serum creatinine, cystatin C levels were measured, GFR was estimated and DTPA clearances ( $\text{GFR}_{\text{DTPA}}$ ) were assessed. The subjects were divided into two groups by  $\text{GFR}_{\text{DTPA}}$ . The first group included the subjects with a  $\text{GFR}_{\text{DTPA}}$  above  $80 \text{ mL/min/1.73m}^2$  and the second group included the subjects who were in the process of chronic renal failure with a  $\text{GFR}_{\text{DTPA}}$  below  $80 \text{ mL/min/1.73m}^2$ .

The subjects' heights were measured in bare feet while standing erect with a stadiometer by the same person and their weights were measured with underclothes on.

Serum creatinine measurements were done by Jaffe method in an autoanalyser (RA-XT) using Bicon diagnostic kit. The GFR's ( $\text{GFR}_{\text{Schw}}$ ) of the patients were calculated with the Formula of Schwartz et al. (13,14) utilizing height and serum creatinine levels. Serum cystatin C levels were measured quantitatively by an autoanalyzer using DAKO Cystatin C Pet Kit and the turbidimetric method.

DTPA clearance was accepted as the golden standard in measurement of glomerular filtration rate. DTPA clearance was measured by plasma clearance method. DTPA labeled with technetium-99 was calculated with the standard method and given to the patients intravenously. 120 and 180 minutes after the injection blood samples of 1-1.5 mL were obtained and GFR was calculated by two plasma sample method described by Blaufox et al. (4,15) or by Ham Pipsz Formula from a single blood sample in patients

in whom two blood samples could not be obtained. The GFR values obtained were adjusted to  $1.73\text{m}^2$ .

## Statistical analysis

Statistical analysis of the data were done using SPSS statistical program. For comparison of the differences between the groups Kruskal Wallis nonparametric analysis of variance and Mann Whitney U test were used. The correlation between the variables were examined using Spearman correlation test. Cystatin C, creatinin and  $\text{GFR}_{\text{Schw}}$  were evaluated by "receiver operation characteristic" (ROC) curve in patients with reduced renal function. The area under the "Receiver operation characteristic" curve (AUC) was calculated using GraphRoc program and the diagnostic values of cystatin C and  $\text{GFR}_{\text{Schw}}$  in reflecting low and normal GFR's were compared.

## Results

53 of the patients were female and 47 were male. Mean age was  $8.4 \pm 5.1$  years (2 months-20.5) and the median age was 8.7 years (interquartile range 7.8). 64 patients were included in group I and 36 patients were included in group II. The average ages of the groups were  $7.9 \pm 4.7$  and  $9.2 \pm 5.1$  years, respectively. Seven children were below the age of one.

Demographic findings, serum cystatin C, creatinine,  $\text{GFR}_{\text{Schw}}$  and  $\text{GFR}_{\text{DTPA}}$  values are shown in Table 1.

In patients with a normal glomerular filtration rate, a strong relation was found between serum creatinine and age, height and body weight ( $r=0.625$ ,  $p=0.000$ ,  $r=0.615$ ,  $p=0.000$  and  $r=0.618$ ,  $p=0.000$ ). A significant relation was found between serum cystatin C and height and body weight ( $r=-0.336$ ,  $p=0.007$  ve  $r=-0.342$ ,  $p=0.006$ ). When the relation of cystatin C with age was examined, a significant relation was found between cystatin C and age in the patients below one year of age ( $r=0.743$ ,  $p=0.035$ ) but not in the patients above one year of age ( $r=0.011$ ,  $p=0.9$ ).

Mean serum cystatin C level was found to be  $1.3 \pm 0.87$  mg/L in girls older than one year of age and  $1.01 \pm 0.40$  mg/L in boys older than one year of age; no significant difference was found by age ( $p>0.05$ ).

**Table 1. Demographic properties and laboratory results of the patients by groups**

	Group 1 $\text{GFR}_{\text{DTPA}} \geq 80$ $\text{ml/min/1.73m}^2$ (n=64)	Group 2 $\text{GFR}_{\text{DTPA}} < 80$ $\text{ml/min/1.73m}^2$ (n=36)
Age (Years)	$7.9 \pm 4.7$	$9.2 \pm 5.1$
Height (cm)	$120.8 \pm 30.2$	$118.4 \pm 34.1$
Body weight (kg)	$28.4 \pm 16.4$	$26.5 \pm 16.3$
Cystatin C (mg/L)	$1.25 \pm 0.9$	$2.3 \pm 1.4$
Creatinine (mg/dl)	$0.64 \pm 0.5$	$1.84 \pm 1.7$
$\text{GFR}_{\text{DTPA}}$	$121 \pm 35.9$	$45.9 \pm 24$
$\text{GFR}_{\text{Schw}}$	$122.4 \pm 33.9$	$63.2 \pm 38.2$

In children with normal renal function, a statistical correlation could not be found between serum cystatin C and creatinine and  $GFR_{DTPA}$ , but a statistical correlation was found with  $GFR_{Schw}$  (Table 2).

When the relation between cystatin C and creatinine was examined, a statistically significant relation was found in both groups, but this relation was weak in the group with normal renal function ( $r=0.38$ ) and strong in the group with reduced renal function ( $r=0.7$ ) (Table 2).

In patients with reduced renal function ( $GFR_{DTPA}<80$  ml/min/1.73m<sup>2</sup>) a strong relation was found between  $GFR_{DTPA}$  and serum cystatin C, creatinine and  $GFR_{Schw}$  ( $r=-0.78$ ,  $r= -0.77$  and  $r= 0.70$ ;  $p<0.001$ ). There was no significant difference between the coefficients of the three variables. A significant relation was found between  $GFR_{Schw}$  and serum cystatin C and creatinine in both groups (Table 2).

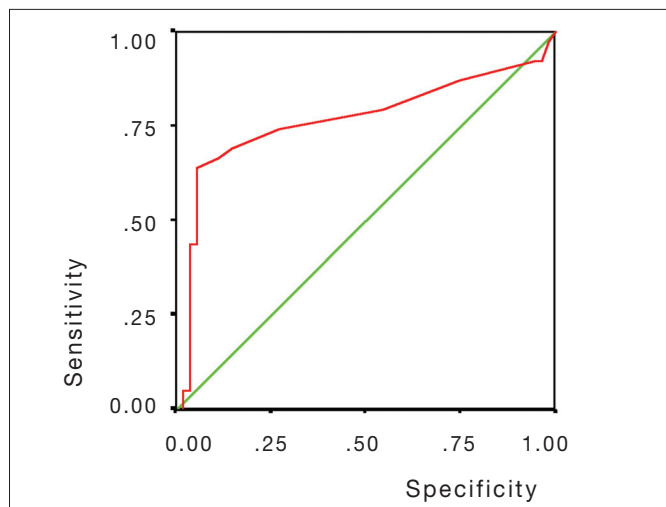
To determine the diagnostic value of cystatin C, creatinine and  $GFR_{Schw}$  in reflecting low and normal GFR values, ROC analysis was performed in both groups. ROC curves are shown in Figure 1, 2 and 3. AUC was found to be  $0.753\pm 0.058$  (mean $\pm$ SD) for cystatin C,  $0.769\pm 0.056$  for creatinine and  $0.877\pm 0.036$  for  $GFR_{Schw}$ . The area values of all three variables were found to be statistically significant (Table 3). In ROC curves, the best AUC value belonged to  $GFR_{Schw}$ . However, no significant difference was observed between the AUC values of the variables.

**Table 2. Relation of creatinine, cystatin C and  $GFR_{Schw}$  values with  $GFR_{DTPA}$**

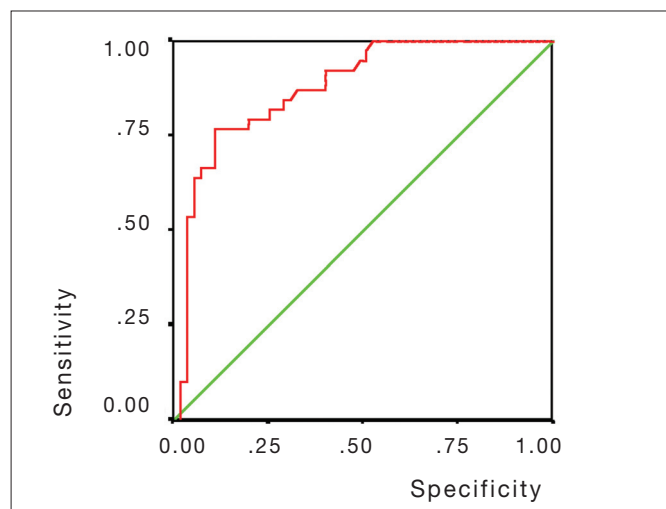
	$GFR_{DTPA}\geq 80$ ml/min/1.73 m <sup>2</sup>	$GFR_{DTPA}<80$ ml/min/1.73 m <sup>2</sup>
	r (p)	r (p)
$GFR_{Schw}$ -Cystatin C	-0.359 (0.004)*	-0.734 (0.000)*
$GFR_{Schw}$ -creatinine	-0.629 (0.000)*	-0.867 (0.000)*
$GFR_{Schw}$ - $GFR_{DTPA}$	0.353 (0.006)*	0.701 (0.000)*
$GFR_{DTPA}$ -Cystatin C	0.091 (0.493)	-0.782 (0.000)*
$GFR_{DTPA}$ -creatinine	-0.126 (0.343)	-0.766 (0.000)*
Sistatin C-creatinine	0.389 (0.002)*	0.727 (0.000)*

**Table 3. Evaluation of diagnostic efficiencies of the variable by ROC analysis**

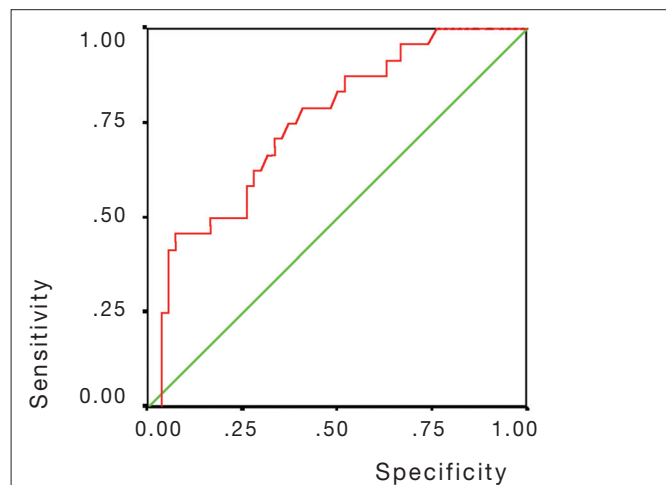
Variable	AUC	Standard error	P	95% confidence interval
Cystatin C	.753	.058	.000	0.639 - 0.866
$GFR_{Schw}$	.877	.036	.000	0.806 - 0.948
Creatinine	.769	.056	.000	0.658 - 0.879



**Figure 1. ROC analysis results for serum creatinine in conditions where  $GFR_{DTPA}$  is normal or reduced**



**Figure 2. ROC analysis results for  $GFR_{Schw}$  in conditions where  $GFR_{DTPA}$  is normal or reduced**



**Figure 3. ROC analysis results for cystatin C in conditions where  $GFR_{DTPA}$  is normal or reduced**

Cystatin C was not superior to  $GFR_{Schw}$  in determining renal function disorder in either group. When the cut-off value was considered to be 1.34 for cystatin C in ROC analysis, the sensitivity was found to be 50% and the specificity was found to be 25%. The cut-off value displaying 90% sensitivity for  $GFR_{Schw}$  was found to be 116.6 ml/min/1.73 m<sup>2</sup> (Table 4). The lowest detectable cystatin C level was 0.37 with a sensitivity of 100% and a specificity of 96%.

## Discussion

Serum creatinine levels and  $GFR_{Schw}$  are the most commonly used variables for monitoring of renal function. It is known that serum creatinine is not an ideal indicator for determining GFR, since it is affected by factors including age, muscle mass, nutrition and inflammation and is reabsorbed and excreted by the tubules (2).  $GFR_{Schw}$  which was calculated by Schwartz et al.(16) using height and serum creatinine values has been proposed to be not sensitive enough. Radionuclide methods are accepted as standard for GFR measurement, but they are not preferred especially in the follow up of patients with reduced renal function and in renal transplant patients considering technical difficulties and exposure to radioactive material (4,5). Therefore, an ideal method for GFR measurement is still being searched for.

Cystatin C which is a low molecular weight protein has been reported to reflect GFR better compared to creatinine and creatinine clearance. It is recommended to be used for GFR measurement as a more sensitive method, since it has a constant production rate, is filtered by the glomerules, is not reabsorbed or excreted by the tubules and is not affected by factors including age, gender and nutrition (7,17). With the development of the automatic immunoturbidimetric method cystatin C can be determined easily, rapidly and reliably and reference values have been determined (18,19).

The major advantage of cystatin C is the fact that it is not affected by age and gender. The levels of cystatin C reach adult values at one year of age and stay constant (18,20). Therefore, reference values by age are not needed. In our study, it was found that cystatin C levels were not affected by age and gender substantially in patients older than one year of age as observed in the studies in the literature.

It has long been investigated if cystatin C has a superiority in determining CFR. While there are studies reporting that cystatin C may be a good indicator in determining GFR, other studies have reported that it has no superiority over creatinine (19, 21-28). Therefore, cystatin C is being used for monitoring renal function in clinical practice, though it has not replaced creatinine in use (23,24).

In our study, no statistically significant relation was found between cystatin C and creatinine and  $GFR_{DTPA}$  in children with normal renal function. A significant relation was found between  $GFR_{Schw}$  and  $GFR_{DTPA}$  in this group. According to these results, we can say that  $GFR_{Schw}$  reflects the changes in GFR better compared to cystatin C and creatinine in children with normal renal function.

Newmann and Musap (19,29) found that cystatin C was a more sensitive variable compared to creatinine in their studies performed using radionuclide methods in adults. Jung and Andersen (8,30) showed that serum cystatin C value was more sensitive compared to creatinine in their studies performed in a patient group composed of children and adults.

Different results have been reported in studies performed in children. There are studies reporting that serum cystatin C level reflects the changes in GFR better and is a good option in determining GFR. Stickle et al.(11) found a better relation between serum creatinine and inulin clearance compared to cystatin C. In contrast to these studies, other investigators defended that there was no significant difference between serum cystatin C and serum creatinine. Filler and Bökenkamp (25,31) reported that cystatin C was a significant variable, but had no superiority over serum creatinine and could not replace known clearance methods. Similarly, it was concluded that cystatin C could be used reliably in children with spina bifida, but was not different from  $GFR_{DTPA}$  and  $GFR_{Sch}$  (32).

According to the results of our study, serum cystatin C, creatinine and  $GFR_{Sch}$  showed a well and similar relation with  $GFR_{DTPA}$  in patients with GFR below 80 ml/dak/1.73 m<sup>2</sup>. Thus, serum cystatin C was not found to have a superiority over creatinine and  $GFR_{Sch}$ . Since determination of a relation between variables will not fully reflect that that variable is a reliable and adequate indicator for GFR measurement, data were evaluated with ROC analysis. When diagnostic efficiencies were compared by ROC analysis, AUC was found to be statistically significant for cystatin C, creatinine and  $GFR_{Sch}$  in a similar way. These results show that cystatin C is a significant variable in determining GFR, but is not different statistically from creatinine and  $GFR_{Sch}$ . For a cut-off value of 1,34 for cystatin C the sensitivity was found to be 50% and the specificity was found to be 25%. Contradictory results have been reported in studies evaluating the reliability of cystatin C in determining GFR and the cut-off values of cystatin C. This was attributed to the patient group selected, the laboratory method used and the differences in calibration devices (18,27).

Cystatin C and creatinine showed a weak correlation in patients with a glomerular filtration rate above 80

**Table 4. Diagnostic properties of cystatin C and  $GFR_{Schw}$  according to the given cut-off value**

Variable	Cut-off value	Sensitivity	Specificity
Cystatin C (mg/L)	1.34	50%	25%
	0.37	100%	
$GFR_{Schw}$ (ml/dak/1.73 m <sup>2</sup> )	80	66%	90%
	116.6	90%	60%

mL/dak/1.73 m<sup>2</sup>. This correlation may be attributed to the fact that cystatin C does not vary by age, but creatinine increases as the age gets older.

In recent years, some of the studies showing that cystatin C is more sensitive in determining renal dysfunction have been performed in patients with acute renal damage. It has been reported that cystatin C increases before creatinine in renal dysfunction due to acute renal damage and is a more sensitive and earlier marker for early diagnosis compared to creatinine (33,34). As observed in our patient group, increases in creatinine do not display sudden changes during follow up of patients with chronic renal failure which is different from acute renal failure.

Although cystatin C is appropriate for GFR measurement, since it is filtrated from the glomerules freely and is not reabsorbed or excreted from the tubules, its serum levels are affected by drugs. In adult kidney transplant recipients, cystatin C levels have been reported to be increased in a dose-dependent fashion in steroid use (35). In addition, cystatin C levels are known to be affected by systemic inflammatory conditions atherosclerosis and hypertension, presence of thyroid dysfunction and tumor (36-39). These interactions should be considered in clinical practice.

Consequently, serum cystatin C is an endogeneous substance which can be reliably used as an option for GFR measurement in patients with reduced renal function. Its serum level is not affected by age and gender. No significant difference was found between cystatin C and creatinin and GFR<sub>Schw</sub> for GFR measurement. Therefore, cystatin C has no superiority over GFR<sub>Schw</sub> in clinical practice. In children with normal and reduced renal function, GFR<sub>Schw</sub> is a simple and adequate method in monitoring GFR.

**Conflict of interest: None declared**

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