Serum Cystatin-C Is Not Superior to Serum Creatinine in Predicting Glomerular Filtration Rate in Cirrhotic Patients

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ABSTRACT

BACKGROUND

Assessment of glomerular filtration rate (GFR) by common creatinine-based methods is potentially inaccurate in patients with cirrhosis. Cirrhotic patients have several underlying conditions that contribute to falsely low serum creatinine concentrations, even in the presence of moderate to severe renal impairment. Therefore creatinine-based methods usually overestimate true GFR in these patients. Cystatin-C is a low molecular weight protein and an endogenous marker of GFR. We compared the accuracy of plasma cystatin-C and creatinine in assessing renal function in cirrhotic patients.

METHODS

We serially enrolled cirrhotic patients with stable renal function admitted in our ward if they met the inclusion criteria and consented to participate. Child-Pugh (CP) score was calculated for all patients. GFR was calculated using serum creatinine, serum cystatin-C, and 99m TC-DTPA clearance with the last one serving as the gold standard. The area under curve (AUC) on receiver-operating characteristic curves (ROC) were used to assess the diagnostic accuracy of each calculated GFR with that measured by DTPA.

RESULTS

Fourty-eight patients were enrolled (32 males, 66.7%). Nine were in class-A, 20 in class-B and 19 in class-C of CP. Cystatin-C did not perform well in predicting the true GFR, while serum creatinine performed relatively accurately at GFR<80ml/min (AUC=0.764, p=0.004). Serum creatinine at a cutoff of 1.4 mg/dl was 20% sensitive & 92% specific and with at a cutoff of 0.9 mg/dl was 77% sensitive & 72% specific for diagnosis of impaired renal function. Cystatin-C could not predict GFR effectively even after stratification for CP score, gender, and BMI. Serum creatinine could predict GFR<65ml/min in females (ROC curve AUC=0.844, p=0.045). In those with BMI>20 kg/m2 a GFR<80 ml/min could also be predicted by serum creatinine (ROC curve AUC=0.739, p=0.034). It also could predict GFR<80ml/min in patients with CP class A & B (ROC curve AUC=0.795, p=0.01), but not in patients with CP class C.

CONCLUSION

Neither serum creatinine nor Cystatin-C are good predictors of GFR in cirrhotic patients, although serum creatinine seems to perform better in selected subgroups.

KEYWORDS
Creatinine; Cystatin-C; Glomerular filtration rate (GFR); Cirrhosis

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INTRODUCTION

Serum creatinine is the most commonly used test to assess glomerular filtration rate (GFR) in clinical practice. Serum creatinine level is affected by several factors other than GFR, including muscle mass, metabolic state of the individual, diet, age, sex, and race.[1] In addition, some creatinine is secreted by renal tubules. All these restrict its use for accurate assessment of GFR. Renal function is a critical index of stability of patients with cirrhosis. Renal dysfunction is associated with poor prognosis in these patients.[2] Cirrhotic patient with renal impairment are given priority on the list of liver transplantation as depicted by inclusion of serum creatinine in the "Model for End Stage Liver Disease (MELD)" formula. However, in these patients, liver dysfunction, muscle wasting and decreased protein intake seriously affect serum creatinine. It has been shown that GFR estimation by serum creatinine can overestimate the true GFR by up to 200%.[2,3] Despite all these, creatinine-based calculation of GFR is still the most commonly used method for evaluation of GFR because of its simplicity and availability.

Cystatin-C (Cys-C) is a cationic nonglycosylated low-molecular-weight (13,359 kd) cysteine-proteinase.[4-5] It is produced by all nucleated cells at a constant rate not affected by changes in diet, gender, age or muscle mass. At least two studies have questioned these beliefs, one showing higher Cys-C levels with male gender, older age, and taller and heavier people,[6] and another showing a correlation of serum Cys-C levels with lean body mass.[7] Scandinavian investigators used serum Cys-C levels (or its reciprocal) to predict GFR in 1985.[8-9] Since then, several studies have assessed the accuracy of serum Cys-C to predict GFR. Most of them have shown good correlation for the reciprocal of Cystatin-C (1/Cys-C) with measured GFR.[10-12] In addition, some studies comparing the area under curve (AUC) of "Receiver Operating Characteristic Curves, (ROC)" for Cys-C and serum creatinine have shown superiority for Cys-C[13-17] in predicting GFR. On the other hand, some investigators failed to detect a significant difference between Cys-C and serum creatinine in cirrhotic patients.[18-22]

Inulin fulfils all criteria for an ideal GFR marker (i.e. stable production rate and circulating levels not affected by other pathological changes, freely filtered at the glomerulus without tubular reabsorption or secretion).[23-24] Therefore, inulin clearance has been considered the reference standard for GFR measurement. More recently, clearance of radioisotope-labeled or nonlabeled trace quantities of chromium 51-EDTA (51Cr-EDTA), technetium 99-diethylenetriamine pentacetic acid (99Tm99m TC-DTPA), iothalamate, or iohexol have shown greater than 97% identity and have been accepted as accurate substitutes for inulin clearance.[25-26] However, all these techniques are labor and time intensive and thus not ideal for clinical practice or large-volume clinical research. Thus, there has been an ongoing search for suitable alternative endogenous markers of GFR.

The aim of this study is to evaluate the diagnostic accuracy of Cys-C and serum creatinine for estimation of GFR as compared to TC-DTPA-based GFR measurement as gold standard in cirrhotic patients.

MATERIALS AND METHODS

Patients with a definite diagnosis of cirrhosis getting admitted in the gastroenterology ward of Shariati Hospital in Tehran were eligible if consented to participate. Those with hepatic encephalopathy or active GI bleeding were excluded. Body mass index (BMI) was calculated for each. All patients needed to have stable renal function (by measuring daily serum creatinine) over three successive days. In patients with ascites, estimated lean body mass was used for calculation of BMI. Fasting serum was obtained to measure creatinine and Cys-C. Serum creatinine was measured on the same day by the Jaffe colorimetric method. An aliquot of serum was kept in refrigerator at -4ºC until Cys-C was measured. Serum Cys-C was measured by particle-enhanced turbidometric immuno-assay (PETIA) using PET kit. The normal range for this assay was 0.63-1.33 for those fifty years and younger and 0.74-1.5 for those older than fifty years. GFR was assessed by clearance of 99m TC-DTPA on the same day. Three

milli-curie of 99mTC-DTPA was infused intravenously as a bolus and blood samples were drawn at two and three hours after infusion.[2] The GFR was calculated using ser Cys-C and creatinine separately and the values were compared with the measured GFR by 99mTC-DTPA clearance. Relationships of Cys-C, serum creatinine, and 99m TC-DTPA clearance were linearized by plotting their reciprocals in a simple regression model. Diagnostic efficiency was calculated from ROC curves.

Results are presented as mean (SD) or median (range). To assess the diagnostic value of each marker, nonparametric ROC curves were generated by plotting the sensitivity versus (1-specificity). Areas under the curves (AUC), 95% confidence intervals (CI), and differences between ROC curves were calculated using Wilcoxon test. SPSS version 15-5 and STATA softwares were used for data analysis. Thereafter we compared ROC curves of Cys-C and serum creatinineby using Pearson correlation coefficients to assess correlation of Cys-C with serum creatinine for estimating the GFR.

RESULTS

Forty-eight patients meeting the inclusion criteria were enrolled serially. Sixteen were females (33.3%). Mean age was 50.5+/-16.2. The Child-Pugh classification of patients was as follows: nine patients (18.8%) Child-A, twenty (41.7%) Child-B and nineteen (39.6%) Child -C. Three females had Child-C (19%), five Child-A and eight Child-B, while sixteen males had Child-C (50%), four Child–A and twelve Child-B. The means of GFR, serum Cys-C, serum creatinine, BMI and age according to different Child stages are shown in table-1.

Thirty-nine patients (81.2%) had various amounts of ascites and eleven patients had hepatic encephalopathy (22.9%).

There was a reverse moderate positive correlation between serum creatinine and GFR (r= -0.28, p=0.05). The serum Cys-C c did not correlate with GFR. There was a weakly positive correlation between serum Cys-C & serum creatinine (r=0.33, p=0.05). Plotting GFR and ROC curves for Cys-C and serum creatinine demonstrated that the AUC of Cys-C was not greater than that of creatinine at a cutoff level of GFR of 90 ml/min (AUC for Cys-C: 0.58, p=0.43;) and AUC for serum creatinine: 0.68, p=0.08, figur1-a).

At a cutoff level of GFR of 80 ml/min, AUC for Cys-C was 0.53 (p=0.725) and for serum creatinine was 0.764, p=0.004 (figure1-b). The AUC of serum creatinine at this level was acceptable and better than that of Cys-C.

The comparison of ROC curves of Cys-C and serum creatinine in different subgroups; male versus female, Child's classes A, B, and C, and in different BMI groups (<20 kg/m^2 and >20 kg/m^2) are demonstrated in figure-2. The serum Cys-C level didnot perform well in any of these subgroups. (figure-3). Table-2 shows the performance of serum creatinine at different levels of GFR measured by 99m TC-DTPA. As shown there, at GFRs of 80-82 ml/min, the serum creatinine performed relatively well (AUC equal to 0.764 and 0.730 respectively with respective p-values of 0.004 and 0.015)(figure-4).

The positive and negative predictive values for serum creatinine are shown in table-3. AUC for serum creatinine for different Child-Pugh classes are shown in table -4.

DISCUSSION

Estimating the area under curve of reciver operating characteristic curves which are made by plotting sensitivity against 1-specificity for any given test, is a useful method for assessing the test's performance and is used widely to show limits of a test's ability to discriminate state of health versus disease.[27-29]

We reviewed the literature assessing the ROC curves for performance of Cys-C with a reference standard.[13-17,20-21,30-35]as well as that comparing performance of Cys-C and serum creatinine with a reference standard.[13-16,20-21,30-35] Subject populations included adults, children, healthy volunteers, and patients with varying degrees of renal impairment caused by a diverse group of conditions. In some studies serum for Cys-C performed better than serum creatinine For predicting GFR.[13-17] while in others Cys-C was not superior to serum creatinine

Table 1: Mean Cys-C, serum creatinine, BMI and age according to Child- Pugh class

Child-Pugh class	Variable	Gender	number	Mean	SD
A	Serum Cystatin-C	Male	4	2.40	0.38
		Female	5	2.08	0.96
	Serum creatinine	Male	4	0.99	0.26
		Female	5	0.90	0.17
	GFR	Male	4	57.68	21.30
		Female	5	74.37	33.29
	BMI	Male	4	23.10	2.69
		Female	5	23.31	5.64
	Age	Male	4	56.75	20.27
		Female	5	37.40	17.30
B	Serum cystatin-C	Male	12	2.43	0.77
		Female	8	1.91	1.05
	Serum creatinine	Male	12	1.31	0.34
		Female	8	0.84	0.26
	GFR	Male	12	56.83	25.71
		Female	8	63.44	32.42
	BMI	Male	12	22.16	2.75
		Female	8	25.10	2.61
	Age	Male	12	56.83	11.32
		Female	8	44.75	16.91
C	Serum cystatin-C	Male	16	1.62	0.96
		Female	3	1.76	1.06
	Serum creatinine	Male	16	1.15	0.47
		Female	3	0.77	0.34
	GFR	Male	16	54.89	32.97
		Female	3	73.58	6.14
	BMI	Male	16	22.82	4.48
		Female	3	22.37	5.26
	Age	Male	16	52.00	15.8
		Female	3	45.67	19.8

Table 2: Performnace of serum creatinine for predicting GFR

	ROC plot AUC	*p*	Sensitivity		Specificity	
			Cr=0.89	Cr=1.40	Cr=0.89	Cr=1.40
GFR=90ml/min	0.648	0.088				
GFR=82 ml/min	0.730	0.015	69%	20%	69%	92%
GFR=80ml/min	0.764	0.004	77%	20%	72%	92%
GFR=70 ml/min	0.728	0.011	69%	22%	63%	94%
GFR=60 ml/min	0.707	0.014	73%	23%	59%	91%

for this purpose.[18-22] We identified five papers addressing this issue in cirrhostics.[2, 10, 36-38] (table-5). In one study looking at 44 cirrhotic patients, the reciprocal of serum Cys-C correlated with inulin clearance (p=0.0001), while that of serum creatinine did not (p=0.0662).[12] Additionally, Cys-C level was

Table 3: Negative and positive predictive values and likelihood ratios for serum creatinine at a GFR of 80ml/min

Creatinine	Sensitivity	Specificity	L.R	P.P.V	N.P.V
1.40mg/dl	20%	92%	2.50	86%	32%
1.19mg/dl	35%	92%	4.37	91%	37%
1.00mg/dl	62%	86%	4.65	91%	48%
0.89mg/dl	77%	72%	2.75	87%	56%

Table 4: ROC curves for serum creatinine at GFR of 80 ml/min for different Child-Pugh classes

Child-Pugh class	AUC	*p*- value
A	0.7	0.320
B	0.8	0.039
C	0.7	0.194

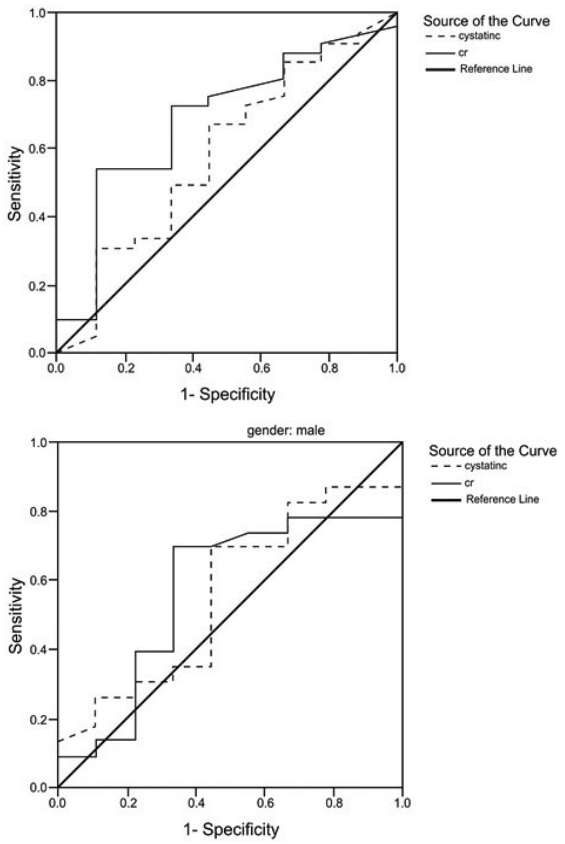

Fig. 1: ROC curves for SCr and CysC when kidney dysfunction is defined at cutofflevel GFR = 90 mL/min.ROC plot for cystatin c waso.58,p=o.43 and for Cr.was0.68,p=0.08 (a) and at cutoff level 80ml/min ROC plot for custatin c waso.53,p=o.725 and for Cr.was0.764,p=0.004(b)
1-a(up)
1-b(down)

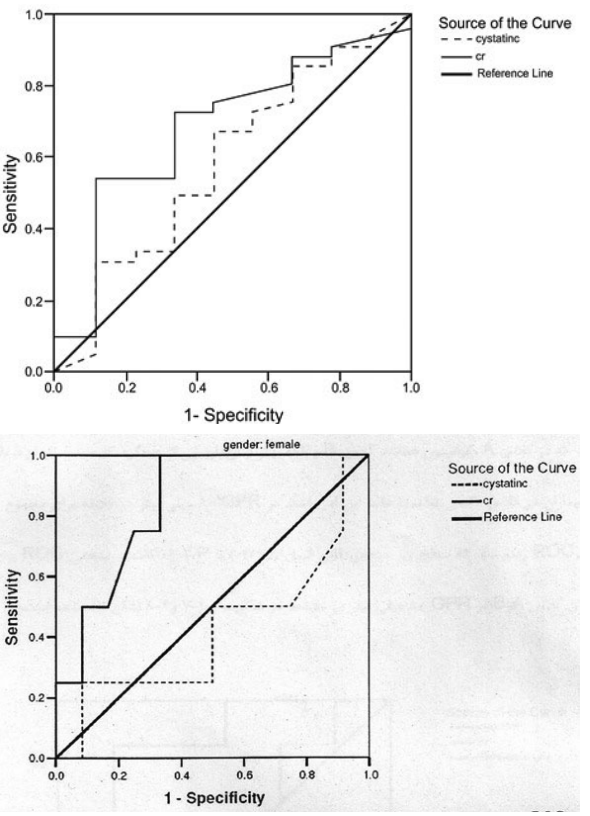

Fig. 2: ROC curves for SCr and CysC for males(a) and females(b)

significantly more sensitive for detecting reduced GFR (90 mL/min) than serum creatinine level (85.7% vs. 28.5%; *p*=0.045). In this study mean of GFR Child-A cirrhotics was 64 ml/min and for Child B and C patients was 32 ml/min. In a second study of 26 patients with cirrhosis, serum Cys-C concentrations correlated with GFR measured by 99mTc-DTPA (*p*=0.006); however, neither serum creatinine level nor measured creatinine clearance correlated (*p*=0.06 and *p*=0.775, respectively).[37] A third study assessing performance of CyS-C for prediction of of renal dysfunction (GFR<72ml/min) in 36 cirrhotic patients, the reciprocal of Cys-C correlated with GFR measured by inulin clearance and was shown to be more sensitive than either serum creatinine level or calculated creatinine clearance (sensitivities of 88%, 23%, and 53%, respectively).[38] However, this study also found that the sensitivity of measured 12-hour creatinine clearance (81%) was similar to that of Cys-C at GFRs more than 72 ml/min (i.e. normal GFR). The

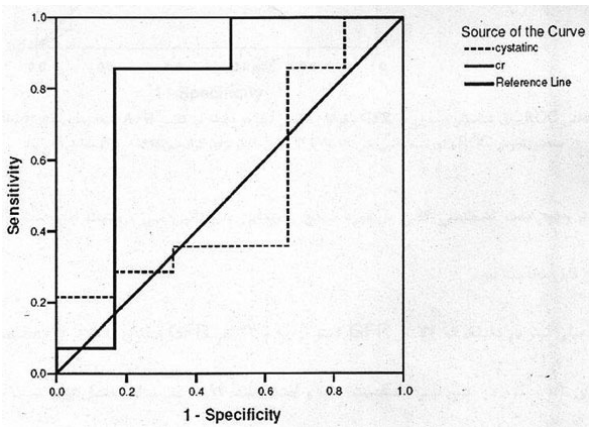

Fig. 3: ROC curves for Serum cystatin cwas0.48,*p*=0.87 and for serum creatinine was 0.8,p=0.03at cutoff level 80ml/min GFR in class B

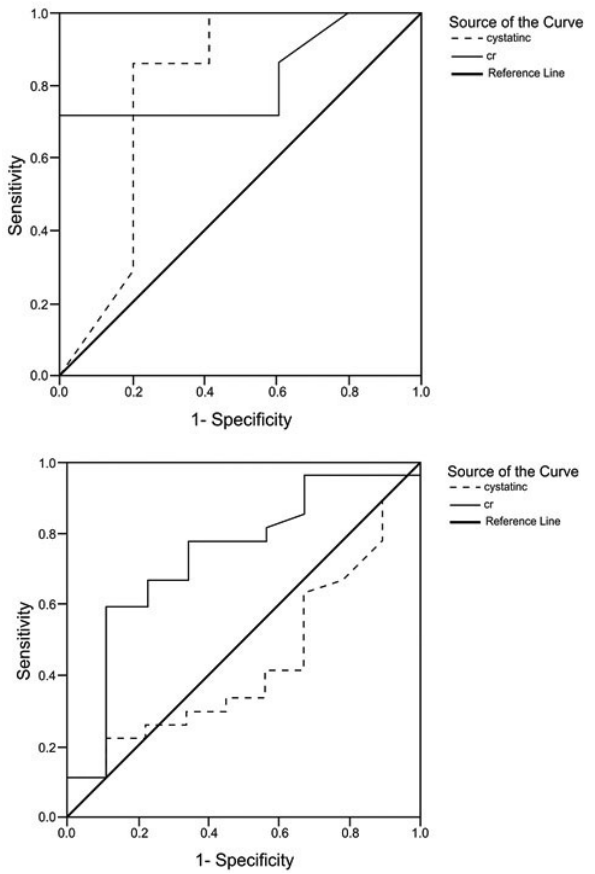

Fig. 4: ROC curves for S cystatin c and for serum creatinine at cutoff level 80ml/min GFR in patients with BMI<20(up-a) and BMI>20(down-b)

4th study,[2] compared performance of serum Cys-C and creatinine against inulin clearance in 44 cirrhotic patients. The investigators showed that both tests correlated well with inulin clearance and with each other ($p<0.01$). However, the correlation coefficients were low and found to be 0.51 for Cockroft-Gault and 0.52 for "Modification of Diet in Renal Disease, MDRD formula", and 0.61 for the Larsson and Hoek formula. All calculated GFRs overestimated inulin clearance ($p<0.0001$).[2] It is important to note that although Cys-C level generally correlated well with GFR in these studies, there was substantial variability among individual patients. In other studies, like that of Oustundog et al Cys-C performed well at GFRs<70ml/min but not at GFRs > 80ml/min.[36] We assessed serum Cys-C and serum creatinine performance at different levels of measured GFR for predicting renal impairment. Cys-A did not perform well, while serum creatinine had an acceptable AUC of 0.764 ($p=0.004$) for GFRs<80 ml/min. Serum creatinine at a cutoff of 1.4mg/dl had a sensitivity of 20% and a specifity of 92% for predicting renal function impairment an da and at a cutoff of 0.89 mg/dl 77% sensitive and 72% specific. We also assessed Cys-C performance at various GFR levels, with different Child-Pugh classes, males and females, and those with BMIs less than and more than 20 kg/m^2. Serum Cys-C performance was far from acceptable in all these subgroups. Serum creatinine could predict GFR of less than 65 ml/min in cirrhotic females (AUC: 0.844, $p=0.045$). It performed also well in patients with a BMI>20kg/m^2 with GFRs<80 ml/min (AUC: 0.739, $p=0.034$). Overall the serum creatinine performed better than Cys-C in Child A and B cirrhotic patients with GFR<80 ml/min (AUC=0.795, $p=0.01$). It did not perform adequately in patients with Child-C cirrhosis who were probably in greatest need for a test to accurately assess their renal function. Muscle wasting, being maintained on a low protein diet, and lower creatine synthesis in decompensated cirrhostics, may partially explain for the poor performance in decompensated cirrhosis patients.We do not know exactly why Cys-C could not predict impaired renal function in our cirrhotic patients, but using multiple drugs among these patients, multiple organ dysfunction, impaired immune function, and active inflammation could contribute to this poor

Table 5: Studies Comparing Methods of Clearance Determinations for Assessment of Renal Function in cirrhotic patients& their results

Refrence	Clearance	Number	Impaired clearance	Best stimation	Parameter	REF. no.
W oitas RP	inulin	44	<90	Cysc	Correlation, sensityvity	12
Demirtas	99mTc-DTPA	26	<64	Cysc	Correlation	40
Orlando R	inulin	36	<72	Cl Cr.= Cysc	Sensitivity, ROC analysis	41
Po¨ ge	inulin	44		Cysc	Correlation	25
Ustundag	99mTc-DTPA	25	<70	Cysc	Correlation	36

performance.[39] Another contributing factor may be that serum Cys-C levels are subject to variations when measured by different methods (i.e. Gentian method DAKO method).[40] Additionally, there is an ongoing controversy regarding the biological variation of Cys–C levels. It has been suggested that Cys-C serum concentrations may exhibit a high within-subject variation.[25,41] The other source of inaccuracy may be the relatively small number of subjects studied. Overall, according to our data, neither serum creatinine levels, nor serum Cys-C levels can accurately predict GFR in cirrhostic patients, although serum creatinine may be better for Child A and B cirrhostics with GFRs < 80 ml/min. Further studies are needed to better address the issue.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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