Estimating Glomerular Filtration Rate in Kidney Transplantation: A Comparison between Serum Creatinine and Cystatin C–Based Methods

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Accurate measurement of GFR is critical for the evaluation of new therapies and the care of renal transplant recipients. Although not accurate in renal transplantation, GFR is often estimated using creatinine-based equations. Cystatin C is a marker of GFR that seems to be more accurate than creatinine. Equations to predict GFR based on the serum cystatin C concentration have been developed, but their accuracy in transplantation is unknown. GFR was estimated using four equations (Filler, Le Bricon, Larsson, and Hoek) that are based on serum cystatin C and seven equations that are based on serum creatinine in 117 adult renal transplant recipients. GFR was measured using radiolabeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA), and the bias, precision, and accuracy of each equation were determined. The mean ^{99m}Tc-DTPA GFR was 58 ± 23 ml/min per 1.73 m^2. The cystatin C–based equations of Filler and Le Bricon had the lowest bias (−1.7 and −3.8 ml/min per 1.73 m^2), greatest precision (11.4 and 11.8 ml/min per 1.73 m^2), and highest accuracy (87 and 89% within 30% of measured GFR, respectively). The cystatin C equations remained accurate even when the measured GFR was >60 ml/min per 1.73 m^2. The creatinine-based equations were not as accurate, with only 53 to 80% of estimates within 30% of measured GFR. Cystatin C–based equations are more accurate at predicting GFR in renal transplant recipients than traditional creatinine-based equations. Further prospective studies with repetitive measurement of cystatin C are needed to determine whether cystatin C–based estimates of GFR will be sufficiently accurate to monitor long-term allograft function.

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Short-term outcomes in kidney transplantation, such as the acute rejection rate and 1-yr renal allograft survival, have improved dramatically over the past decade (1,2). Traditionally, these short-term outcomes served as the end points in trials that have evaluated immunosuppressant therapies. Because so few of these events now occur, markers of renal function, such as the serum creatinine, creatinine clearance, and estimates of GFR derived from creatinine-based equations, are increasingly being used as study end points (1).

The limitations of serum creatinine and urinary creatinine clearance for estimation of estimating GFR are well known (3,4). Serum creatinine concentration is affected by the GFR but is also affected by several factors that are independent of GFR, such as age, race, muscle mass, gender, medication use, and catabolic state (3). Moreover, different laboratories measure serum creatinine using different methods, giving results that are difficult to compare (5). The measurement of urinary creatinine clearance overcomes some of the limitations of serum creatinine but remains inaccurate because of collection errors and changes in creatinine excretion (5). Various creatinine-based equations have been developed in an attempt to improve the estimation of GFR from serum creatinine (5). These equations, however, have not been shown to be accurate in renal transplant recipients, and their suitability in clinical trials has been called into question (6,7).

Serum cystatin C is a low molecular weight protein that functions as a cysteine protease inhibitor and is produced at a constant rate by all nucleated cells (8). In the kidney, it is freely filtered and catabolized in the proximal tubule without being secreted (8). Studies to date suggest that cystatin C is a better marker of GFR than serum creatinine (9). Until recently, however, studies that have evaluated cystatin C have used the serum concentration rather than an estimate of GFR based on the measured concentration. Several prediction equations have been derived from both pediatric and adult patients to estimate GFR from the serum cystatin C concentration (10–13). However, only one (14) has been validated in a separate cohort of adult renal transplant recipients. Accordingly, the objective of this study was to estimate GFR from the serum cystatin C

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concentration using four published equations in an independent sample of adult renal transplant recipients. The bias, precision, and accuracy of the prediction equations were compared with radioisotopic GFR reference measurement. A similar assessment of creatinine-based prediction equations was also performed to determine whether cystatin C had any advantage over serum creatinine at the estimation of GFR.

Materials and Methods

Study Population

Adult renal transplant recipients who were followed at the Ottawa Hospital and were at least 5 mo posttransplantation and had stable renal function were eligible to participate. Patients were excluded for the following reasons: (*1*) Unable or unwilling to provide informed consent, (*2*) pregnant or breastfeeding, (*3*) acute rejection within preceding 3 mo, (*4*) likely to die from another comorbid disease within next 3 mo, or (*5*) likely to require dialysis or repeat transplantation within next 3 mo. Consecutive patients who met these criteria and had all laboratory testing completed by January 31, 2005, were included in this analysis. The study was approved by the Ottawa Hospital Research Ethics Board.

Laboratory Assessment

GFR was measured by the plasma clearance of radiolabeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) (15,16). Ten millicuries (370 Mbq) of ^{99m}Tc-DTPA was given as a single injection with plasma samples drawn at 120, 180, and 240 min after injection (17,18). To ensure reliability of the ^{99m}Tc-DTPA measurements, we performed standard radiochemical and radiopharmaceutical purity tests on each preparation of ^{99m}Tc-DTPA. The product specification was set at 95% purity, but the average purity that was obtained from our radiopharmacy laboratory was approximately 99% pure. In addition, the well counter was verified weekly for count reproducibility. The GFR was corrected for standard body surface area by multiplying the measured value by 1.73 and dividing by the patient's body surface area as estimated by the DuBois formula (19). On the day of the ^{99m}Tc-DTPA GFR measurement, patients were weighed; had their height measured; had a blood sample taken for serum creatinine, urea, cystatin C, and albumin; and provided a 24-h urine collection for the measurement of creatinine. Gender, race, age, medication use, cause of renal failure and number of transplants was recorded.

The serum creatinine was measured using the modified Jaffe reaction on a Beckman Coulter LX20 Pro Clinical System using manufacturer's reagents (Beckman Coulter Inc., Brea, CA). The coefficient of variation for serum creatinine was 4.9% at 0.6 mg/dl (55 μmol/L), 1.7% at 1.7 mg/dl (150 μmol/L), and 1.3% at 6.8 mg/dl (600 μmol/L). Cystatin C was measured using an N Latex cystatin C kit (Dade Behring, Mississauga, Canada) on a Behring BN ProSpec analyzer (Dade Behring, Marburg, Germany). The coefficient of variation of serum cystatin C was 3.1% at 1.06 mg/L, 3.5% at 2.04 mg/L, and 6.7% at 5.26 mg/L.

The use of serum creatinine in the equation derived from the Modification of Diet in Renal Disease (MDRD) study requires that the creatinine be calibrated to the laboratory that developed the equation (5,20). To calibrate the Ottawa Hospital serum creatinine, we sent 50 samples (range 0.6 to 4.0 mg/dl) to the Cleveland Clinic laboratory, which performed the creatinine measurements for the MDRD study (5). Overall, there was excellent agreement between both laboratories (correlation coefficient 0.989). The Ottawa Hospital serum creatinine was calibrated as recommended (5), and the calibrated serum creatinine values were used in the MDRD prediction equations. The calibrated creatinine was calculated as follows:

$$1.076\ (\text{Ottawa Hospital serum creatinine}) - 0.082$$

GFR was estimated with seven equations that used serum creatinine (15,21–26) and four equations that used cystatin C (10–13) (Tables 1 and 2). The prediction equations that were not expressed as ml/min per 1.73 m^2 (13,21,24,25) were adjusted by multiplying the value by 1.73 and dividing by the patient's body surface area as estimated by the DuBois formula (19). The creatinine was measured in the 24-h urine collection, and the creatinine clearance was calculated using the standard formula (27). The creatinine clearance was corrected for body surface area as described above.

Table 1. Equations to predict glomerular filtration rate using serum creatinine[a]

Reference (No. and Type of Subject)	Formula
Original MDRD[b] (22) (n = 1628, CKD)	$(170) \times (\text{Cr})^{-0.999} \times (\text{age})^{-0.176} \times (\text{urea})^{-0.170} \times (\text{albumin})^{0.318} \times (0.762$ if female) $\times$ (1.18 if black)
Abbreviated MDRD (23) (n = 1628, CKD)	$(186) \times (\text{Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742$ if female) $\times$ (1.21 if black)
Cockcroft-Gault (26) (n = 236, 96% male)	$[(140 - \text{age}) \times (\text{weight})]/[\text{Cr} \times 72] \times (0.85$ if female)
Nankivell[c] (15) (n = 146, renal transplant)	$[6700/(\text{Cr} \times 88.4)] + (\text{weight}/4) - (\text{urea}/2) - [100/(\text{height})^2] + 35$ (if male) or 25 (if female)
Walser (25) (n = 85, CKD)	$[7.57/(\text{Cr} \times 0.0884)^{-1}] - (0.103 \times \text{age}) + (0.096 \times \text{weight}) - 6.66$ if male $[6.05/(\text{Cr} \times 0.0884)^{-1}] - (0.08 \times \text{age}) + (0.08 \times \text{weight}) - 4.81$ if female
Jelliffe (21) (not published)	$98 - 16[(\text{Age} - 20)/20]/\text{Cr} \times (0.9$ if female)
Mawer (24) (n = 16, no other details)	$\text{weight} \times [29.3 - (0.203 \times \text{age})] \times [1 - (0.03 \times \text{Cr})]/(14.4 \times \text{Cr}) \times (70/\text{weight})$ if male $\text{weight} \times [25.3 - (0.175 \times \text{age})] \times [1 - (0.03 \times \text{Cr})]/(14.4 \times \text{Cr}) \times (70/\text{weight})$ if female

[a]Cr, serum creatinine in mg/dl; weight in kilograms; MDRD, Modification of Diet in Renal Disease; CKD, chronic kidney disease.
[b]Urea in mg/dl, albumin in g/dl.
[c]Urea in mmol/L, height in meters.

Table 2. Equations to predict GFR using cystatin C[a]

Reference (No. and Type of Subject)	Formula
Filler[b] (12) (n = 536, children with various renal disorders)	Log (GFR) = 1.962 + [1.123 × log (1/cystatin C)]
Le Bricon[b] (10) (n = 25, renal transplant)	GFR = [(78) × (1 / cystatin C)] + 4
Hoek[b] (11) (n = 123, adults with suspected renal disease)	GFR = −4.32 + (80.35 × 1/cystatin C)
Larsson[c] (13) (n = 100, adults and children referred for iohexol clearance study)	GFR = 77.24 × (cystatin $C^{-1.2623}$)

[a]Cystatin C in mg/L.
[b]GFR expressed as ml/min per 1.73 m^2.
[c]GFR expressed as ml/min.

Analysis

The primary aim was to assess the performance of novel prediction equations that used cystatin C to estimate GFR as compared with commonly known equations that use serum creatinine. The evaluation of the prediction equations was performed by calculating the bias, precision, and accuracy as recommended in the National Kidney Foundation guidelines on chronic kidney disease (3). Bias was defined as the mean difference between the measured GFR (using ^{99m}Tc-DTPA) and estimated GFR (3). Precision was defined as the SD of the difference between the measured and estimated GFR (3). Accuracy was defined as the percentage of GFR *estimates* lying within 10 and 30% of the *measured* GFR (using ^{99}Tc-DTPA) (3). The analysis was repeated after stratifying patients by estimated GFR (<60 and ≥60 ml/min per 1.73 m^2) and gender. Calculations were performed using an Excel spreadsheet.

Results

A total of 182 patients were approached for enrollment in this study. Thirty-four declined to participate, 30 withdrew from the study after consent but before any testing was done, and one withdrew because of a severe acute rejection that occurred after consent but before any testing was done. This left 117 patients who met the inclusion criteria and were included in the analysis. The baseline characteristics of the cohort are presented in Table 3. The majority (91%) of patients were white, and only 2.6% were black. The patients had a wide range of renal function that encompassed all five stages of the Kidney Disease Outcomes Quality Initiative chronic kidney disease classification system (3). The median daily dose of prednisone was 7.5 mg. The average measured GFR using ^{99}Tc-DTPA was 58 ± 23 ml/min per 1.73 m^2 with a range of 11 to 121 ml/min per 1.73 m^2 (Table 4). The mean, median, and range of estimated GFR with the different prediction equations are shown in Table 4.

Table 3. Patient characteristics[a]

Characteristic	n = 117
Age (yr)	52 ± 11
Male (n [%])	79 (68)
Race (n [%])	
white	106 (90.6)
black	3 (2.6)
Asian	4 (3.4)
other	4 (3.4)
Smoker (n [%])	14 (12)
Weight (kg)	81.2 ± 18.7
Height (cm)	168 ± 92
Body surface area (m^2)	1.90 ± 0.33
Living donor (n [%])	42 (36)
Time posttransplantation (yr)	7.5 ± 10.8
Primary transplant (n [%])	111 (95)
Causes of renal disease (n [%])	
diabetes	15 (13)
polycystic kidney disease	20 (17)
glomerulonephritis	42 (36)
hypertension	6 (5)
other	34 (29)
Medication (n [%])	
prednisone	116 (99)
cyclosporine	55 (47)
tacrolimus	45 (38)
sirolimus	3 (3)
mycophenolate mofetil	82 (70)
azathioprine	16 (14)
trimethoprim-sulfamethoxazole	21 (18)
CKD stage (n [%])	
1: GFR ≥90	11 (9)
2: GFR 60 to 89	47 (40)
3: GFR 30 to 59	46 (39)
4: GFR 15 to 29	10 (9)
5: GFR <15	3 (3)

[a]GFR expressed as ml/min per 1.73 m^2.

Bias, Precision, and Accuracy of Estimated GFR

The performance of the various estimates of GFR is shown in Table 5 and Figure 1. The cystatin C–based equations of Filler and Le Bricon were the most accurate at estimating GFR. The Filler and Le Bricon equations had the least bias (−1.7 and −3.8 ml/min per 1.73 m^2, respectively), the best precision (11.4 and 11.8 ml/min per 1.73 m^2), and the highest percentage of values that fell within 30% of the true GFR (87 and 89%, respectively). In addition, 42% of GFR estimates for both equations fell within 10% of the measured GFR. The Nankivell equation was the most accurate of the creatinine-based estimates with a bias of −1.4 ml/min per 1.73 m^2 and 36% of GFR estimates were within 10% of the measured GFR. The original and abbreviated MDRD equations did not perform well in this population with a bias of −11.5 and −10.0 ml/min per 1.73 m^2, respectively

Table 4. Measured and estimated GFR[a]

	Mean	Median	Range
Measured values			
^{99}Tc-DTPA GFR	58 ± 23	58	11 to 121
creatinine clearance	61 ± 27	59	10 to 176
Estimates using serum creatinine			
Cockcroft-Gault	55 ± 20	55	9 to 113
abbreviated MDRD	48 ± 20	46	9 to 117
original MDRD	46 ± 20	44	8 to 118
Walser	46 ± 18	49	10 to 111
Jelliffe	43 ± 18	42	14 to 118
Mawer	68 ± 31	63	5 to 180
Nankivell	56 ± 20	56	−8.5 to 128
Estimates using cystatin C			
Filler	56 ± 22	56	18 to 130
Le Bricon	54 ± 17	55	22 to 111
Larsson	42 ± 20	41	10 to 122
Hoek	47 ± 18	48	14 to 106

[a]All values expressed as ml/min per 1.73 m^2; DTPA, diethylenetriaminepentaacetic acid.

Table 5. Bias, precision, and accuracy of creatinine and cystatin C estimates[a]

	Bias	Precision	Accuracy % Within	
			10%	30%
Measured values				
creatinine clearance	3.8	16.8	32	74
Estimates using creatinine				
Cockcroft-Gault	−3.1	13.6	28	80
abbreviated MDRD	−10.0	13.1	24	74
original MDRD	−11.5	12.2	18	69
Walser	−12.2	14.2	20	62
Jelliffe	−14.6	15.8	19	53
Mawer	10.3	24.2	19	58
Nankivell	−1.4	13.3	36	79
Estimates using cystatin C				
Filler	−1.7	11.4	42	87
Le Bricon	−3.8	11.8	42	89
Larsson	−16.1	14.2	9	53
Hoek	−10.6	11.7	24	79

[a]Bias was defined as the mean difference between measured (^{99}Tc-DTPA) and estimated GFR; precision was defined as the SD of the difference between measured (^{99}Tc-DTPA) and estimated GFR. Both precision and bias were expressed as ml/min per 1.73 m^2; accuracy was defined as the proportion of values that were within 10 or 30% of the measured (^{99}Tc-DTPA) GFR.

(Table 5). Neither MDRD equation was accurate, with both having <25% of GFR estimates within 10% of measured ^{99}Tc-DTPA GFR.

Table 6 shows the performance of the GFR equations when the estimated GFR was < or ≥60 ml/min per 1.73 m^2. The Filler and Le Bricon equations remained accurate when the estimated GFR was either above or below 60 ml/min per 1.73 m^2. The Filler equation was the most accurate formula when the estimated GFR was ≥60 ml/min per 1.73 m^2, with 56% of estimates within 10% of the measured GFR (Table 6). The Le Bricon equation was the most accurate formula when the estimated GFR was <60 ml/min per 1.73 m^2, with 36% of estimates within 10% of the measured GFR (Table 6). Tables 7 and 8 show the performance of the GFR estimates stratified by gender. In general, the bias was lower and the accuracy was higher in women compared with men. However, the Filler and Le Bricon equations had nearly identical measures of accuracy in both male and female patients (Tables 7 and 8).

Discussion

This study demonstrates that the cystatin C–based prediction equations of Le Bricon and Filler are more accurate at estimating GFR than the conventional creatinine-based equations. Importantly, the Filler equation and, to a lesser degree, the Le Bricon equation performed well at GFR values both above and below 60 ml/min per 1.73 m^2. This is a significant advantage over the creatinine-based equations in which the accuracy varies considerably with the degree of renal impairment.

The findings of this study are clinically relevant given the previous research that evaluated renal function in kidney transplant recipients. Mariat *et al.* (7), Gaspari *et al.* (6), and Poge *et al.* (28) evaluated the performance of creatinine-based equations in renal transplant recipients. The accuracy of the creatinine-based equations was variable among the three studies. However, it should be noted that the methods used to measure serum creatinine differed in the studies (6,7,28). In addition, evaluation of the MDRD equation requires calibration of the serum creatinine to the laboratory used in the MDRD study (20), which was not done in these studies (6,7,28). In a recent study that evaluated markers of renal function in 29 kidney transplant recipients, Risch and Huber (14) used a calibrated serum creatinine to estimate GFR using the MDRD equation. Using the calibrated serum creatinine, they found that 66% of estimates were within 30% of the measured GFR (14). In our study, we showed similar accuracy of the MDRD equation using a calibrated serum creatinine.

Cystatin C has been studied to a limited extent in renal transplantation. Risch *et al.* (29) compared cystatin C with measured GFR in 30 renal transplant recipients. Using receiver operating characteristic curves, they showed that cystatin C had greater diagnostic accuracy than creatinine at detecting GFR <60 ml/min. Christensson *et al.* (30) measured cystatin C and iohexol clearance in 125 renal transplant patients. They found that cystatin C was significantly more sensitive than the serum creatinine in the ability to detect a fall in the GFR <60 ml/min. However, they found no difference in the area under the receiver operating characteristic curves for cystatin C (0.94) and serum creatinine (0.90), suggesting that there was no real difference in diagnostic accuracy (30). These studies were limited by the use of the serum cystatin C concentration rather than an estimate of GFR based on the measured concentration.

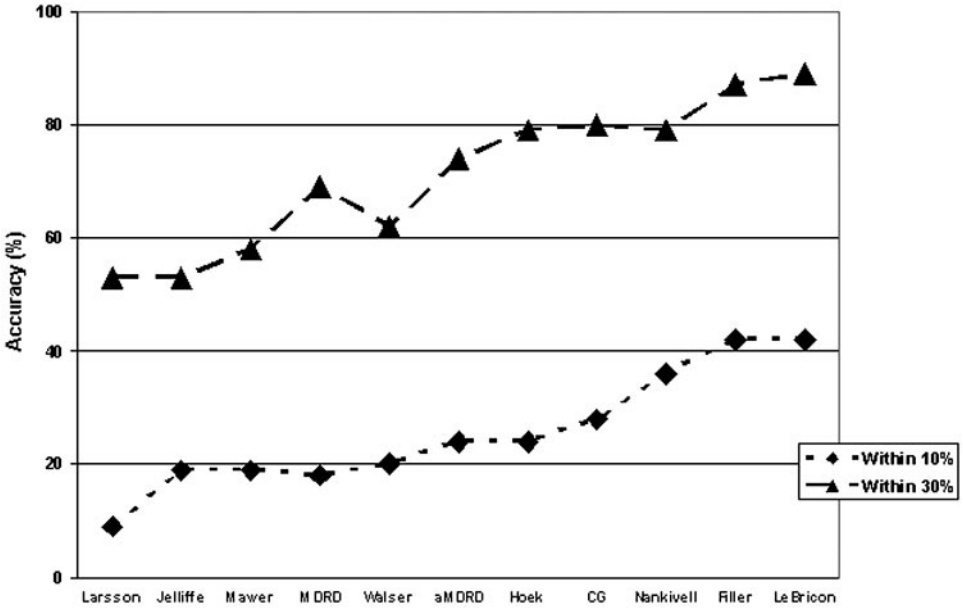

Figure 1. Accuracy of GFR prediction equations. Accuracy was defined as the proportion of values that were within 10 or 30% of the measured (radiolabeled diethylenetriaminepentaacetic acid) GFR. MDRD, original Modification of Diet in Renal Disease equation; aMDRD, abbreviated MDRD equation; CG, Cockcroft-Gault equation.

In the previously mentioned study by Risch and Huber (14), GFR was estimated using one cystatin C–based equation. They found that the estimated GFR from the cystatin C–based Larsson equation had a bias of −4.7 ml/min per 1.73 m^2 and that 69% of estimates were within 30% of the measured GFR (14). These results were substantially better than the performance of the Larsson equation in our study, which actually had the highest bias and lowest accuracy of all of the equations evaluated. These discrepant results are likely due to the different methods used to measure cystatin C and estimate GFR. Larsson *et al.* (13) published two separate equations to estimate GFR depending on which cystatin C assay was used. In the paper by Risch and Huber (14), cystatin C was measured using the Dako turbidimetric immunoassay, whereas we used the N Latex cystatin C kit by Dade Behring. Although Risch and Huber found the Dako-based Larsson equation to be more accurate than the Larsson equation that we used, it was far less accurate at estimating GFR than either the Filler or the Le Bricon equation.

The four cystatin C–based prediction equations that we evaluated were derived in a variety of populations, including both adult and pediatric age groups as well as transplant and nontransplant patients (10–13). The Le Bricon equation was derived from 25 adult renal transplant recipients (10), and the Filler equation was derived from 536 pediatric patients (12). These two equations, which were the most accurate in our study, were derived from populations thought to have lower muscle mass. It is possible that accuracy of the Filler and Le Bricon equations was due in part to the similarity between the populations from which the equations were derived and our study population. Although it has been reported that cystatin C is independent of factors such as age and weight, others have shown contradictory findings (31). In a study involving 8058 patients from the Netherlands, Knight *et al.* (31) showed that increasing age, male gender, increasing weight, current smoking, and higher C-reactive protein level were independently associated with a higher cystatin C concentration. These associations were independent of renal function as measured using urinary creatinine clearance (31). These findings suggest that cystatin C concentration may be influenced by factors other than renal function. This fact should be taken into consideration when interpreting our results.

Strengths of this study included the measurement of cystatin C, serum creatinine, and ^{99}Tc-DTPA GFR on the same day to ensure that a similar degree of renal function was present when each measurement was made. The serum creatinine values all were measured at the same laboratory using the same method to avoid differences in calibration (5). In addition, our serum creatinine was calibrated to the Cleveland Clinic laboratory, which performed the creatinine measurements for the MDRD study. This allowed us to use a calibrated serum creatinine to estimate GFR with the MDRD equations as recommended (5,20).

Limitations to this study should be noted. First, the study population was predominantly made up of white patients and only 2.6% of the patients were black. Although cystatin C concentrations have been shown to be independent of race (32,33), firm conclusions about the accuracy of the cystatin C equations in black, Asian, and other populations cannot be made with our data. Second, all of our patients were on low-dose steroids as they were clinically stable. Cystatin C is influenced by high-dose steroids (34); as such, our data cannot be used to support the use of cystatin C to monitor renal function in the setting of high-dose steroid use (*e.g.*, allograft rejection).

Table 6. Bias, precision, and accuracy of creatinine and cystatin C estimates for patients with estimated GFR <60 and ≥60 ml/min per 1.73 m^2 [a]

GFR	*N*	Bias	Precision	Accuracy % Within	
				10%	30%
Estimates using creatinine					
Cockcroft-Gault					
<60	72	−4.0	12.9	19	76
≥60	45	−1.6	14.6	42	87
abbreviated MDRD					
<60	90	−10.5	12.6	20	68
≥60	27	−8.3	14.5	37	93
original MDRD					
<60	92	−11.7	11.6	15	64
≥60	25	−10.8	14.2	28	88
Walser					
<60	97	−12.5	14.1	15	57
≥60	20	−11.1	15.2	40	85
Jelliffe					
<60	103	−15.1	15.8	15	48
≥60	14	−11.0	16.0	50	93
Mawer					
<60	51	−4.0	14.5	24	69
≥60	66	21.3	24.5	15	50
Nankivell					
<60	68	0.0	12.0	32	73
≥60	49	−3.4	14.7	41	88
Estimates using cystatin C					
Filler					
<60	65	−0.9	9.6	31	85
≥60	52	−2.6	13.4	56	90
Le Bricon					
<60	70	−0.3	9.7	36	87
≥60	47	−8.8	13.0	51	91
Larsson					
<60	100	−16.9	13.1	8	49
≥60	17	−11.5	19.8	12	76
Hoek					
<60	88	−8.6	9.6	26	80
≥60	29	−16.4	15.2	17	79

[a]Bias was defined as the mean difference between measured (^{99}Tc-DTPA) and estimated GFR; precision was defined as the SD of the difference between measured (^{99}Tc-DTPA) and estimated GFR. Both precision and bias were expressed as ml/min per 1.73 m^2; accuracy was defined as the proportion of values that were within 10 or 30% of the measured (^{99}Tc-DTPA) GFR.

Table 7. Bias, precision, and accuracy of creatinine and cystatin C estimates in male patients (n = 79)[a]

	Bias	Precision	Accuracy % Within	
			10%	30%
Measured values creatinine clearance	3.7	14.4	34	73
Estimates using creatinine				
Cockcroft-Gault	−3.4	14.9	29	77
abbreviated MDRD	−9.6	13.5	25	76
original MDRD	−11.3	12.5	19	71
Walser	−14.1	14.4	19	54
Jelliffe	−18.0	15.5	15	43
Mawer	11.6	24.5	20	56
Nankivell	−1.4	13.8	27	76
Estimates using cystatin C				
Filler	−3.8	10.9	39	87
Le Bricon	−5.3	11.8	42	89
Larsson	−19.5	13.1	8	41
Hoek	−12.2	11.6	23	75

[a]Bias was defined as the mean difference between measured (^{99}Tc-DTPA) and estimated GFR; precision was defined as the SD of the difference between measured (^{99}Tc-DTPA) and estimated GFR. Both precision and bias were expressed as ml/min per 1.73 m^2; accuracy was defined as the proportion of values that were within 10 or 30% of the measured (^{99}Tc-DTPA) GFR.

Whether low-dose steroids increase cystatin C levels remains unclear. Risch *et al.* (35) showed that renal transplant recipients on low-dose prednisone (5 to 10 mg/d) had a higher cystatin C concentration compared with those on steroid-free immunosuppression. In contrast, Bökenkamp *et al.* (36) found that pediatric renal transplant recipients had higher cystatin C concentrations compared with other children with nontransplant renal disease, but there was no correlation between cystatin C and steroid dose. Third, we did not simultaneously measure thyroid function to rule out hypothyroidism or hyperthyroidism, which both are known to influence cystatin C concentration (37). However, in this stable population of renal transplant recipients with close medical follow-up, it would be unlikely that a significant number would have unrecognized thyroid dysfunction. Fourth, we measured cystatin C only once in each study participant. There is some controversy about the intrapatient variability of cystatin C with a study in healthy volunteers showing a higher coefficient of variation for cystatin C compared with creatinine (38), whereas a recent study in pediatric renal transplant patients did not confirm this (39). The intrapatient variability of cystatin C in adult renal transplant patients has not been assessed. It is plausible that a high coefficient of variation could be seen in the adult transplant population, making cystatin C an impractical marker for long-term follow-up. This issue will require further study in renal transplant recipients. Fifth, only three patients had stage 5 chronic kidney disease; thus, no conclusions about the accuracy of the prediction equations at this level of function can be made from our data. Finally, although we used a calibrated serum creatinine for the MDRD equation, calibration for the other creatinine-

Table 8. Bias, precision, and accuracy of creatinine and cystatin C estimates in female patients ($n = 38$)[a]

	Bias	Precision	Accuracy % Within	
			10%	30%
Measured values				
creatinine clearance	4.0	20.8	29	76
Estimates using creatinine				
Cockcroft-Gault	−2.4	12.5	26	87
abbreviated MDRD	−11.0	12.1	21	69
original MDRD	−11.9	11.4	16	66
Walser	−8.4	13.0	21	76
Jelliffe	−7.7	13.9	26	74
Mawer	7.6	23.2	16	63
Nankivell	−1.4	12.1	55	87
Estimates using cystatin C				
Filler	2.9	11.1	47	87
Le Bricon	0.5	11.3	42	89
Larsson	−9.0	13.9	11	79
Hoek	−7.2	11.2	26	90

[a]Bias was defined as the mean difference between measured (^{99}Tc-DTPA) and estimated GFR; precision was defined as the SD of the difference between measured (^{99}Tc-DTPA) and estimated GFR. Both precision and bias were expressed as ml/min per 1.73 m^2; accuracy was defined as the proportion of values that were within 10 or 30% of the measured (^{99}Tc-DTPA) GFR.

based equations (Cockcroft-Gault, Nankivell, Walser, Jelliffe, and Mawer) and cystatin C was not done. This may account for some of the bias that we found in these other equations. In addition, it is not known whether calibration is an important issue with cystatin C, but it may become relevant with future use of these prediction equations.

In conclusion, this analysis has shown that GFR can be estimated accurately in renal transplant recipients using the cystatin C–based prediction equations of Filler and Le Bricon. We have also confirmed that cystatin C–based estimates of GFR are more accurate than traditional creatinine-based equations. Further prospective studies with repetitive measurement of cystatin C are needed to determine whether cystatin C–based estimates of GFR will be sufficiently accurate to monitor long-term allograft function.

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