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Review

Cystatin C: An Improved Estimator of Glomerular Filtration Rate?

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Background: **Glomerular filtration rate (GFR) is routinely assessed by measuring the concentrations of endogenous serum markers such as blood urea nitrogen and serum creatinine (SCr). Although widely used, these endogenous markers are not ideal and do not perform optimally in certain clinical settings. The purpose of this review is to critically review the potential utility of cystatin C (CysC), especially in patient populations in which CysC may have an advantage over routinely used endogenous markers of GFR.**

Approach: **In a narrative approach, we extensively review publications, primarily from the last 5 years, that address the development of methods to measure CysC, reference intervals, and the diagnostic accuracy of CysC to assess GFR. Between June 2000 and September 2001 Medline was searched using "cystatin c" as a textword, and articles that examined >75 individuals (except for renal transplant studies) and/or used accepted "gold standards" for assessing GFR were selected for inclusion. A total of 17 studies are reviewed that provide reference interval data for several populations. A total of 24 studies make conclusions about the utility of CysC vs SCr and/or creatinine clearance, with 20 providing data on the sensitivity and specificity of CysC for detecting impaired GFR. These publications are organized into subgroups that deal with specific patient populations or clinical situations.**

Content: **This review focuses on two areas: (*a*) the evolution of immunoassays used to determine the concentration of CysC in serum, their analytic sensitivity, and reference intervals; and (*b*) the diagnostic performance of CysC against other renal markers in the general population and in specific subpopulations of patients.**

Summary: **Studies of reference intervals for CysC overwhelmingly demonstrated that CysC values in blood are independent of age and sex. Of the 24 studies that examined clinical utility, 15 concluded that CysC is superior to SCr, whereas 9 concluded that CysC is equivalent but provides no advantage. Summary ROC plot analysis of 20 studies that provide sensitivity and specificity data strongly suggests that CysC will be superior to SCr for detecting impaired GFR. Taken together, it is clear that CysC performs at least as well as SCr in the population at large and that it is likely to be superior to SCr in specific patient populations.**

Glomerular filtration rate (GFR)[3] is defined as the volume of plasma that can be completely cleared of a particular substance by the kidneys in a unit of time. The "gold standard" for determining GFR is to measure the clearance of exogenous substances such as inulin, iohexol, ^{51}Cr-EDTA, ^{99m}Tc-labeled diethylenetriamine pentaacetic acid (DTPA), or ^{125}I-labeled iothalamate. These techniques, however, are time-consuming, labor-intensive, expensive, and require administration of substances that make them incompatible with routine monitoring. Thus, the measurement of endogenous blood substances to estimate GFR is a common practice. Properties of an ideal endogenous blood substance to estimate GFR should include release into the blood stream at a constant rate, free filtration by the glomerulus, no reabsorption or secretion by the renal tubules, and exclusive elimination via the kidneys.

Blood urea nitrogen was the first endogenous substance measured in serum or plasma to assess renal

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[3] Nonstandard abbreviations: GFR, glomerular filtration rate; DTPA, diethylenetriamine pentaacetic acid; SCr, serum or plasma creatinine; CrCl, creatinine clearance; CysC, cystatin C; PETIA, particle-enhanced turbidimetric immunoassay; PENIA, particle-enhanced nephelometric immunoassay; and AUC, area under the curve.

function. It is a major by-product of protein metabolism, and >90% of urea is cleared by the kidneys *(1)*. Urea is freely filtered by the glomerulus and not secreted by the tubules. However, a large portion (40–70%) is passively reabsorbed from the renal tubules; thus, its concentration will underestimate GFR in settings of decreased renal perfusion because some of the urea that is filtered will return to the bloodstream. Furthermore, its concentration in the blood can vary with diet, hepatic function, and numerous disease states *(2)*.

In the last 40 years, serum or plasma creatinine (SCr) has become the most commonly used serum marker of renal function. SCr is a metabolic product of creatine and phosphocreatine in muscle tissue *(3)*. Its rate of appearance in the bloodstream is related to muscle mass, so that intraindividual concentrations are relatively constant. However, SCr blood concentrations are affected by age and gender *(4)*. SCr circulates in the blood unbound to any plasma proteins and is freely filtered by the glomerulus. It is not reabsorbed by the proximal tubules, but is secreted in small amounts, which are subject to intra- and interindividual variation *(5)*. As plasma concentrations increase, tubular secretion of SCr increases, leading to an overestimation of GFR in patients with moderate to severe decreases in GFR (<50 mL/min) *(5)*. SCr is also insensitive for detecting small decreases in GFR because of the nonlinear relationship between plasma concentration and GFR *(6)*. Finally, the most common method (picric acid) for analyzing SCr is subject to analytic interferences from substances such as glucose, uric acid, ketones, plasma proteins, and cephalosporins *(7, 8)*. Calculation of creatinine clearance (CrCl) by determining its concentration in timed urine collections and simultaneously in blood correlates with gold standard exogenous methods better than SCr *(6)*. However, collection of timed urine is cumbersome and prone to error in the outpatient setting.

Thus, despite their common use, blood urea nitrogen and SCr have limitations as renal markers, and the search for an ideal endogenous marker of GFR continues *(9)*. Here we review recent studies examining methods, reference intervals, and the diagnostic accuracy of another endogenous substance, cystatin C (CysC), as a marker of GFR.

CysC is a 122-amino acid, 13-kDa protein that is a member of the family of cysteine proteinase inhibitors. It is the product of a "housekeeping" gene expressed in all nucleated cells and is produced at a constant rate *(10)*. Because of its small size and basic pI (~9.0), CysC is freely filtered by the glomerulus. It is not secreted, but is reabsorbed by tubular epithelial cells and subsequently catabolized so that it does not return to the blood flow *(11)*. This latter property negates calculation of a CysC clearance using urine concentrations of CysC. The use of serum CysC to estimate GFR is based on the same logic as the use of blood urea nitrogen and creatinine, but because it does not return to the bloodstream and is not secreted by renal tubules, it has been suggested to be closer to the "ideal" endogenous marker. These properties have recently been reviewed in more detail by Grubb *(12)*.

Methods for Measurement of CysC and Reference Intervals

The first immunoassay to quantify CysC was developed by Lofberg and Grubb in 1979 *(13)*. This was a lengthy competitive RIA that had a detection limit of 30 μg/L, which was more than sufficient to detect CysC in the serum of healthy individuals and allow studies of the value of CysC. Other methods to detect CysC were developed in the following years, based on radio-, fluorescent, and enzymatic immunoassays *(14–17)*. The detection limits of these assays ranged from 0.13 to 1.9 μg/L. With the exception of the values in one study *(14)*, reference intervals were identical for males and females *(15–27)*.

More recently, automated homogeneous immunoassays utilizing latex or polystyrene particles coated with CysC-specific antibodies were developed, and some were approved by the Food and Drug Administration for clinical use *(19–27)*. There are two different versions of the latex immunoassay for CysC, one based on turbidimetry [particle-enhanced turbidimetric immunoassay (PETIA)] *(19–23)* and another based on nephelometry [particle-enhanced nephelometric immunoassay (PENIA)] *(24–27)*. These assays are generally more precise than the earlier methods, and reference intervals seem more consistent than those reported from earlier assays (Table 1). For example, we recently examined 133 adult volunteers with no history of renal disease, diabetes, hypertension, or autoimmune disease and who had not taken any medications that affect renal function. Using a commercial nephelometric assay, we found a reference range that was normally distributed and narrower than most other reports, with a central 95% interval of 0.51–0.92 mg/L (95% confidence interval for the upper reference value, 0.8–1.03 mg/L) *(26)*. This was remarkably similar to the reference interval of 0.51–0.98 mg/L found in a large study (n = 309) with the same analytical method *(27)*. We also found no significant difference in the reference values for men and women or for African-American and Caucasian adults *(26)*.

Some of the earlier differences in reported reference values (Table 1) may have been attributable to differences in values assigned to calibrator materials, selection of participants, and the ages of participants. For example, the PETIA method generally produces reference values that are 20–30% higher than those from PENIA methods (Table 1). Studies with careful selection of participants, including documentation of current health and medication histories, produced remarkably similar reference values within the same methods *(21, 22, 26, 27)*. CysC is higher before the age of 3 months and after the age of 70 *(28, 29)*. Among 401 individuals 65–101 years of age, CysC values increased above the age of 70 in a coincident manner with age-related decreases in GFR, whereas SCr

Table 1. Assay characteristics and reference intervals for CysC.

Method	Detection limit, mg/L	CV, %	Reference interval,[a] mg/L	Population[b]	n	Reference
SRID[c]	0.3	11	0.78–1.52	Adult	46	*(13)*
EIA	0.03	10–12	0.26–1.94	Adult	30	*(13)*
EIA	0.001	3–9	1.26–2.30	Adult (F)	33	*(14)*
			1.52–2.76	Adult (M)	33	
RIA	0.0013	NS	0.56–1.36	Adult	100	*(15)*
EIA	0.002	4–5	0–3.24	Adult	189	*(16)*
EIA	NS	NS	0.47–1.03[d]	Adult	33	*(18)*
PETIA	0.03	3–5	<1.25	NS	206	*(19)*
PETIA	NS	2–7	0.70–1.21[d]	Adult (20–50 years)	242	*(21)*
			0.84–1.55[d]	Adult (>50 years)		
PETIA	0.42	2–8	0.54–1.21[d]	Adult	270	*(22)*
PETIA	NS	NS	0.56–1.22	Adult	249	*(23)*
PENIA	0.17	2–11	0.37–1.22	Adult	52	*(25)*
PENIA	NS	2–4	0.51–0.94[d]	Adult (F)	78	*(26)*
			0.48–0.98[d]	Adult (M)	61	
PENIA	0.17	3–5	0.51–0.98	Adult	309	*(27)*
PENIA	0.17	3–5	0.93–3.35	Adult (>65 years)	401	*(29)*
PENIA	0.25	1–2	0.51–0.95[d]	Ped (1–14 years)	125	*(39)*
PETIA	NS	NS	0.18–1.38[d]	Ped (0.8–18 years)	216	*(40)*
PETIA	NS	1–6	0.70–1.38	Ped (0.2–18 years)	195	*(41)*
PENIA	NS	3	0.63–1.33	Ped (1–16 years)	56	*(42)*

[a] Reference intervals shown are mean ± 2 SD unless indicated.
[b] Ped indicates pediatric population.
[c] SRID, single radial immunodiffusion; EIA, enzyme immunoassay; NS, not stated.
[d] Central 95th percentile.

did not increase *(29)*. Presumably, the failure of SCr to detect age-related decreases in GFR is attributable to a corresponding decrease in muscle mass.

CysC as a Renal Marker

Multiple studies have validated the use of CysC as a renal marker in adult patients *(19, 20, 30–36)*. Grubb et al. *(30)* first reported that both CysC and SCr correlated similarly (r = 0.77 and 0.75, respectively) to GFR determined by ^{51}Cr-EDTA clearance among 135 patients (age range, 7–77 years) with various renal pathologies, including primary and secondary glomerulonephritis, rheumatoid disorders, and diabetic nephropathy. When another group measured CysC and SCr in 76 patients with various kidney diseases and in 61 renal dialysis patients, they also found that the correlations to GFR determined by ^{99m}Tc-DTPA clearance for CysC and SCr were comparable (r = 0.91 and 0.89, respectively) *(31)*. One of the first studies to examine the diagnostic accuracy of CysC found a sensitivity and specificity of 88% and 86% for CysC vs 53% and 100% for SCr for detecting a GFR <82 mL/min determined by ^{99m}Tc-DTPA clearance among 31 adults with renal disease *(14)*. In a study of 27 healthy controls and 24 patients with a reduced GFR (<80 mL · min^{-1} · 1.73 m^{-2}), Kyhse-Andersen et al. *(20)* found a correlation of CysC to GFR determined by clearance of iohexol (r = 0.87) that was significantly greater than that of SCr (r = 0.71). ROC analysis of this study also revealed that the diagnostic accuracy of serum CysC for reduced GFR was superior to that of SCr (P <0.001). For example, if the sensitivity were set at 100% for CysC and SCr, the specificity of these two analytes would be 75% and 0%, respectively. The authors hypothesized that the superiority of CysC was attributable to the unique renal properties and its constant production rate by all tissues.

Newman et al. *(19, 32)* concluded that, in addition to being a better estimator of GFR than SCr, CysC was a more sensitive marker than SCr for small changes in GFR in two studies that examined a total of 469 patients. When the 206 renal disease patients were considered alone, the correlation of CysC to GFR (measured by ^{51}Cr-EDTA clearance) was r = 0.80, significantly better than the correlation for SCr (r = 0.50) *(19)*. Furthermore, the diagnostic sensitivity for clearance <72 mL · min^{-1} · 1.73 m^{-2} was significantly greater for CysC (P <0.05) because 71.4% of the patients with mild renal failure had an abnormally increased CysC (>1.5 mg/L), whereas only 52.4% had increased SCr (>200 μmol/L) *(32)*.

Recent studies further suggest that CysC is an earlier indicator of mild renal failure *(33–36)*. Among 41 normotensive elderly patients with no evidence of renal disease, 11 had GFRs determined by inulin clearance below the 95% reference interval, and all 11 of these patients had increased CysC but normal SCr *(33)*. The increased CysC values were based on reference intervals for adults under 70 years of age, and the normal SCr values likely reflect decreased muscle mass. Among 46 patients with renal disease and 250 blood donors, Randers et al. *(34)* found

that CysC was more sensitive than SCr for mild decreases in GFR by ^{99m}Tc-DTPA clearance as evidenced by ROC analysis [area under the curve (AUC), 0.996 for CysC vs 0.870 for SCr; $P < 0.01$]. However, there was no difference between CysC and CrCl (AUC, 0.95). Interestingly, an earlier study from this same group that examined 76 adults with various renal pathologies found no significant differences between CysC and SCr for detecting a GFR <80 mL · min^{-1} · 1.73 m^{-2} as determined by ^{99m}Tc-DTPA clearance (AUC, 0.97 and 0.95, respectively) *(31)*. A similar study of 75 patients showed greater sensitivity (94%) and specificity (95%) for CysC than for SCr (86% sensitivity and 91% specificity) *(35)*.

A very recent study of 226 adults with various nephropathies found that CysC was more sensitive for detecting a decreased CrCl than SCr (97% vs 83%), and this was confirmed by significant differences in the AUC for ROC analysis *(36)*. In a cross-sectional study, Coll et al. *(37)* concluded that CysC values became increased when GFR was <88 mL · min^{-1} · 1.73 m^{-2} by iothalamate clearance, whereas SCr became abnormal at 75 mL · min^{-1} · 1.73 m^{-2}. ROC analysis, however, showed no significant differences in the diagnostic accuracy of the two tests. Finally, in a study of 138 patients, including 52 renal transplant patients, 45 oncology patients, and 41 patients suspected of renal disease, CysC had a sensitivity of 96% and specificity of 65% for detecting a GFR <70 mL · min^{-1} · 1.73 m^{-2} *(38)*. In contrast, SCr was less sensitive (63%) but more specific (95%) in this heterogeneous population.

Taken together, these studies consistently demonstrate that CysC performs at least as well as SCr as a renal marker in the adult population, with several studies suggesting that CysC is more sensitive to small changes in GFR than SCr (Table 2). It is this latter property that has particularly made it attractive to further examine CysC in certain groups of patients.

Pediatric Populations

CysC has been postulated to have an advantage over SCr in pediatric populations because of the low muscle mass in children, which leads to very low SCr values, where increased assay imprecision is present. Therefore, it can be difficult to accurately detect small changes in GFR with SCr in children <4 years of age in whom normal SCr values are only 2.0–4.0 mg/L. On the other hand, the

Table 2. Summary of studies examining the clinical utility of CysC.

Population[a]	Clearance[b]	Impaired clearance[c]	n	Best estimator(s)[d]	Parameter[e]	Significant[f]	Reference
Adult; renal disease	^{99m}Tc-DTPA	<82	31	CysC	Sensitivity	NS[g]	*(14)*
Adult; healthy and renal disease	Iohexol	<80	51	CysC	Correlation, ROC	Y	*(20)*
Adult; renal disease	^{51}Cr-EDTA	NS	135	SCr = CysC	Correlation	N	*(30)*
Adult; renal disease	^{99m}Tc-DTPA	<80	137	SCr = CysC	Correlation, ROC	N	*(31)*
Adult; renal disease	^{51}Cr-EDTA	<72		CysC	Sensitivity	Y	*(32)*
Adult (>65 years)	Inulin	<96	41	CysC	Correlation	Y	*(33)*
Adult; healthy and renal disease	^{99m}Tc-DTPA	<80	296	CysC & CrCl	ROC	Y	*(34)*
Adult; renal disease	CrCl	<87.5	75	CysC	Sensitivity	Y	*(35)*
Adult; renal disease	CrCl	<83	226	CysC	ROC, sensitivity	Y	*(36)*
Adult; renal disease	[^{125}I]Iothalamate	<88	61	CysC & SCr	ROC	N	*(37)*
Adult; mixed	CrCl	<70	138	CysC = SCr	Sensitivity, PPV	N	*(38)*
Pediatric; renal disease	Inulin	<84	184	CysC	ROC, sensitivity	N	*(41)*
Pediatric; healthy and renal disease	^{51}Cr-EDTA	<75	69	CysC	ROC, correlation	Y	*(42)*
Pediatric; renal disease	Inulin	<90	60	SCr = CysC	Correlation	N	*(46)*
Pediatric; renal disease	^{51}Cr-EDTA	<89	52	CysC	ROC	Y	*(47)*
Adult; chemotherapy	^{51}Cr-EDTA	<78	72	CysC	ROC, correlation	Y	*(49)*
Adult; renal transplant	^{51}Cr-EDTA	<80	25	CysC	Sensitivity	Y	*(54)*
Adult; renal transplant	[^{125}I]Iothalamate	<60	30	CysC & CrCl	ROC, PPV	Y	*(57)*
Adult; renal transplant	CrCl	<80	110	CysC = SCr	ROC, sensitivity	N	*(58)*
Pediatric; renal transplant	CrCl	NS	24	SCr	Sensitivity	N	*(59)*
Adult; renal transplant	CrCl	NS	30	CysC	Graft recovery	Y	*(60)*
Adult; cirrhosis	Inulin	<90	44	CysC	Correlation, sensitivity	Y	*(63)*
Adult; IgA nephropathy	NS	NS	306	CysC	Biopsy	Y	*(64)*
Adult; rheumatoid arthritis	CrCl	<90	56	CysC	Sensitivity	Y	*(65)*

[a] Brief description of population examined. For details see text.
[b] Gold standard method for determining GFR.
[c] Definition of impaired GFR (mL · min^{-1} · 1.73 m^{-2}).
[d] All studies examined at least CysC and SCr. The authors' conclusions of which test performed best as an estimator of clearance are shown.
[e] The parameter examined when comparing CysC vs SCr (and CrCl in some cases). PPV, positive predictive value.
[f] Y(es) indicates $P < 0.05$; N(o) indicates $P \geq 0.05$.
[g] NS, not stated.

plasma concentration of CysC appears to be rather constant in children >1 year of age and similar to that of adults *(39–42)*. For example, in one study, the reference interval for serum CysC was 0.51–0.95 mg/L among 125 healthy children between the ages of 1 and 14 years *(39)*, which is virtually identical to adult reference intervals with this method (Table 1). These authors also showed that immediately after birth, CysC values were approximately twice those of older children and adults, but that they reached a mean value of 0.95 mg/L by 1–2 months of age. In addition to being increased during the first few months of life, CysC was even more increased in the blood of premature infants in at least three studies *(43–45)* (Table 1).

Evidence that CysC concentrations in blood are independent of age after these early months of life was also provided when SCr, CysC, and β_2-microglobulin were measured in 216 pediatric urologic patients 0.8–18 years of age with normal GFR (90–150 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) determined by ^{51}Cr-EDTA clearance *(40)*. Although there was a strong correlation between SCr and age ($r = 0.79$; $P < 0.0001$), both CysC and β_2-microglobulin showed no correlation to age whatsoever ($r = 0.006$ and 0.006, respectively). The reference interval for CysC in these children was 0.18–1.38 mg/L.

Among 184 children with renal disease and a mean age of 11.2 ± 4.5 years (range, 0.24–17.9 years), CysC correlated better ($r = 0.88$) to GFR measured by inulin clearance than did SCr ($r = 0.72$) *(41)*. Furthermore, the area under the ROC curves was larger (0.970 ± 0.135) for CysC than for SCr (0.894 ± 0.131) for detecting an inulin clearance $<84\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$, but this difference was not statistically significant. However, the number of children under 4 years of age, which is the population speculated to benefit most from CysC measurement, was very low. ROC analysis of a smaller population of 69 children 1–16 years of age, including 56 healthy controls and 13 children with reduced GFR, again indicated a superiority ($P < 0.05$) of CysC over SCr as a marker of renal failure determined by ^{51}Cr-EDTA clearance for detecting a GFR $<75\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ in a sex- and age-matched population *(42)*. Furthermore, the correlation of CysC to GFR by ^{51}Cr-EDTA clearance ($r = 0.83$) was significantly greater than that of SCr ($r = 0.67$; $P < 0.05$) *(42)*.

We retrospectively examined the performance of CysC and SCr in 60 pediatric patients (4–19 years of age) with renal disease for whom GFR determined by inulin clearance was available *(46)*. We found that CysC was roughly equivalent to SCr as a single-measure analyte for estimation of GFR in this population even when divided into two age groups: 4–12 years (n = 26) and 12–19 years (n = 34). The correlations of CysC to inulin clearance were $r = 0.765$ and 0.869 for the two age groups, respectively, and those for SCr were $r = 0.841$ and 0.892, respectively. The sensitivity and specificity of CysC and creatinine for impaired GFR (inulin clearance $<90\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) in the two age groups were also not statistically different. However, like the study by Bokenkamp et al. *(41)*, we had few patients under the age of 4 (n = 7). Finally, Ylinen et al. *(47)* examined a population of 52 children (ages 2–16), of whom 19 had a GFR $<90\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ by ^{51}Cr-EDTA clearance. CysC and SCr had similar correlations ($r = 0.89$ and 0.80, respectively) to GFR, but the authors concluded that CysC performed better than SCr to estimate GFR based on the areas under ROC curves (0.9896 vs 0.9171; $P = 0.04$). Using upper reference limits of 1.31 mg/L for CysC and 10.3 mg/L for SCr, they estimated that the sensitivity and specificity were 100% and 97% for CysC and 74% and 97% for SCr for detecting a GFR <90 mL/min.

The available studies in children to date indicate that CysC is at least as useful as useful as SCr to assess GFR, with several indicating that CysC may perform better (Table 2). However, the number of children under 4 years of age, for whom it is hypothesized that CysC may be most effective, has been small. Larger prospective studies still need to be done to validate this hypothesis.

Patients Receiving Chemotherapy

There are two reasons to monitor renal function in cancer patients undergoing chemotherapy: (*a*) direct damage to the renal tubules by the chemotherapeutics and (*b*) increased accumulation of chemotherapeutics and their metabolites in the presence of decreased GFR. For example, the dose of cisplatin must be reduced by one-half when GFR is <60 mL/min *(48)*. Therefore, it should be beneficial to detect changes in renal function as early as possible.

SCr is not a good indicator of early renal insufficiency because its concentration does not change greatly until CrCl drops below $70–80\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ *(6, 33)*. Štabuc et al. *(49)* explored CysC as an early indicator of renal damage in 72 patients receiving cisplatin chemotherapy for malignant melanoma, gastric cancer, or ovarian cancer. All but 12 had a GFR <78 mL/min by ^{51}Cr-EDTA clearance. The correlation to GFR was significantly better for CysC than SCr ($r = 0.84$ vs 0.74; $P = 0.01$), and ROC analysis indicated that CysC was a better indicator than SCr for predicting a GFR <78 mL/min ($P < 0.04$). The sensitivity and specificity were 100% and 87%, respectively, for serum CysC (≥1.33 mg/L) compared with 61% and 98%, respectively, for SCr (>101 μmol/L). They found that these results were independent of the presence of metastases and concluded that CysC may be more useful than SCr for monitoring renal function during cisplatin therapy *(49)*.

The effect of cancer and metastatic disease on CysC values in blood, however, is not yet clear. For example, in previous publications from the same group, it was suggested that serum CysC was significantly higher in patients with metastatic melanoma or colorectal cancer in the absence of any renal disease when compared with patients with primary melanoma *(50)*. This apparent

discrepancy was explained by suggesting, but not confirming, that the alterations in serum CysC concentration were not attributable to malignant progression but rather to early, previously undetectable alterations in renal function because the study *(50)* did not determine actual GFR by CrCl or another approach *(49, 51)*. However, the possibility that dying nucleated cells contributed to this increase was not ruled out. One study of 60 myeloma patients showed no correlation between tumor burden and CysC values, suggesting that in myeloma, at least, the extent of tumor does not affect CysC values *(52)*. Clearly, additional prospective studies will be necessary to assess the utility of CysC for early detection of chemotherapy-induced renal disease and to determine whether increased cell turnover can lead to increased CysC values in blood.

Renal Transplant Patients

After renal transplantation, patients are at risk of acute damage to the transplanted kidney because of rejection or toxicity from immunosuppressant therapy. Earlier detection of renal damage may lead to more effective intervention. In a preliminary study, LeBricon et al. *(53)* first suggested that CysC was more sensitive than SCr for detecting decreases in GFR and delayed graft function in renal transplant patients. As in most studies, plasma CysC measurements correlated well with SCr and CrCl. However, in the three cases of acute renal rejection that were confirmed by biopsy, the increase in plasma CysC values was more pronounced than that observed for SCr. For example, one patient had a 100% increase in CysC vs a 40% increase in SCr 5 days before biopsy-confirmed acute rejection. In this patient, as well as another with confirmed acute rejection and another with FK506 toxicity, CysC increased earlier and more rapidly than did SCr.

More recently, the same group evaluated the renal function of 25 adult renal transplant patients *(54)*. Among these patients, plasma CysC correlated well with plasma creatinine ($r = 0.741$; $P < 0.0001$). Three months after transplantation, the correlations of SCr and CysC to GFR determined by ^{51}Cr-EDTA clearance were 0.784 and 0.879, respectively. The authors concluded that plasma creatinine overestimated GFR by 30%, that CrCl overestimated GFR by 40%, and that CysC underestimated GFR by 14% *(54)*. They also concluded that CysC was more sensitive than SCr and CrCl in post-renal transplant patients ($P < 0.01$) because no false-negative results for detecting impaired renal function (defined as $< 80\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) in these transplant recipients were found, whereas plasma creatinine and CrCl produced ~25% false negatives.

Another study also suggested that CysC might underestimate GFR in transplant patients *(55)*. Forty-four renal transplant patients were compared with 56 nontransplant patients with a GFR $< 84\ mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ by inulin clearance as a result of various renal disorders. This study revealed that, although the GFRs of these two groups were not significantly different, CysC values were significantly higher in the renal transplant group compared with the control group (2.5 ± 0.1 vs 2.1 ± 0.1 mg/L; $P = 0.002$). Linear regression between the reciprocal of CysC and inulin clearance showed a lower slope of the regression line for the transplant group than the nontransplant group (0.0046 vs 0.007; $P = 0.002$). This suggests that CysC may be falsely increased in transplant patients compared with nontransplant patients with a similar GFR. This study confirms the results of previous ones by the same group, in which CysC was found to underestimate GFR by ~25% in transplant patients when GFR was estimated using CysC concentrations and a regression formula. Possible explanations for this observation included interference with the assay by the immunosuppressant drugs, backleak of intact CysC into the circulation attributable to tubulo-interstitial damage, or a reduction in the glomerular filtration of CysC because of increased protein binding. Unfortunately, the performance of SCr was not examined in these studies. Not discussed as a possibility was increased cell turnover/death and its effect on CysC values. Complicating the value of CysC in renal transplant patients is a study in asthmatic patients demonstrating that corticosteroids can increase CysC whereas cyclosporine can decrease CysC values, both of which most transplant patients will receive *(56)*.

Risch et al. *(57)* investigated the role of CysC in 30 renal transplant patients. CysC was superior to SCr and β_2-microglobulin ($P = 0.025$), but it had a positive predictive value for detecting a GFR <60 mL/min determined by [^{125}I]iothalamate clearance similar to that of a 24-h CrCl ($P = 0.76$). With an upper reference value of 1.64 mg/L, the sensitivity and specificity of CysC were 70% and 89%, respectively, producing a positive predictive value of 93%. SCr (upper reference limit, 125 μmol/L) had a positive predictive value of 76%, whereas CrCl had a positive predictive value of 94%. In a prospective study of 110 consecutive adult patients, no statistical differences were found between CysC and SCr for detecting impaired GFR determined by CrCl *(58)*. However, the authors correctly pointed out the flaw of not having any gold standard determinant of GFR. Finally, among 24 pediatric renal transplant patients, CysC did not predict acute rejection any sooner than SCr in the 9 patients who suffered acute rejection *(59)*.

In addition to detecting posttransplant renal damage earlier than SCr, CysC has also been suggested to predict renal function recovery earlier than SCr *(60)*. In a prospective study of 30 renal transplant patients, these authors found that the mean time to spontaneous decrease in CysC occurred at 14.8 days posttransplant vs 18.8 days for the decrease in SCr ($P < 0.002$). They concluded that CysC allowed earlier diagnosis of renal function recovery than SCr, particularly among patients with delayed graft function *(60)*. Nevertheless, because of the mixed conclusions of these studies, it is still unclear whether CysC offers a significant advantage in renal transplant patients (Table 2).

Other Patient Groups

Whereas most studies of CysC have focused on the previously discussed populations, there have been isolated studies examining the utility of CysC in other patient groups. For example, CysC has recently been examined among patients with liver cirrhosis. Patients with advanced cirrhosis who have an abnormal GFR can present with normal SCr values because of their decreased muscle mass and increased tubular secretion of creatinine *(61, 62)*. Woitas et al. *(63)* compared serum concentrations of CysC and SCr to GFR determined by inulin clearance in 44 patients with liver cirrhosis with no evidence of renal disease. The reciprocals of SCr and CysC concentrations correlated reasonably well ($r = 0.662$), but only the reciprocal of CysC significantly correlated with the GFR ($r = 0.661$; $P < 0.0001$ vs $r = 0.279$; $P = 0.066$ for SCr). CysC was increased in 86% of the patients with a GFR <90 mL/min, whereas SCr was increased in only 28% ($P < 0.05$). This observation will likely lead to future studies in cirrhotic patients.

Patients with IgA nephropathy can be divided into four prognostic groups based on renal biopsy findings. A recent study of 306 patients showed that CysC values, but not SCr, were predictive of the biopsy-determined prognostic group ($P < 0.05$) *(64)*. A study of 56 rheumatoid arthritis patients with ≤5-year duration of disease and ≤50 months of nonsteroidal antiinflammatory drug therapy again suggested that CysC is a more sensitive indicator of early renal damage than SCr *(65)*. GFR was decreased (<90 mL · min^{-1} · 1.73 m^{-2}) in 32 of these patients and CysC was increased in 34, but only 3 patients exhibited increased SCr.

ROC Analysis

A problem in trying to reach general conclusions about the utility of CysC is that these studies have large variation in the definition of impaired GFR (Table 2). For example, among the studies reviewed here, the definition ranged from 60 to 90 mL · min^{-1} · 1.73 m^{-2}. Differences in the gold standard methods also complicate making general conclusions about the superiority of CysC. Nevertheless, of the 24 studies reviewed here that make claims about the utility of CysC, 15 conclude that CysC is superior, whereas 9 conclude that it is equivalent to SCr and/or CrCl.

One approach to estimating the diagnostic accuracy of a test where multiple studies have different conclusions is to combine the claimed sensitivities and specificities of all credible studies into a summary ROC plot *(66, 67)*. In this approach to metaanalysis of diagnostic tests, we plotted claimed sensitivities and specificities (or the optimal points from depicted ROC curves) from the 20 studies that examined the diagnostic accuracy of CysC vs SCr (Fig. 1). This approach strongly suggested that CysC is indeed superior to SCr because when all studies were combined, the areas under the summary ROC curves were 0.95 for CysC and 0.91 for SCr ($P = 0.003$). This difference was even greater when the nine studies looking at adult patients were examined (AUC, 0.96 for CysC vs 0.91 for SCr; $P = 0.024$), but less dramatic and not significant for the studies of pediatric (AUC, 0.97 for CysC vs 0.96 for SCr; $P = 0.37$) and renal transplant patients (AUC, 0.91 for CysC vs 0.82 for SCr; $P = 0.23$). The small number of studies in the pediatric and renal transplant groups likely contributes to the lack of significance and indicates the need for further studies in these groups.

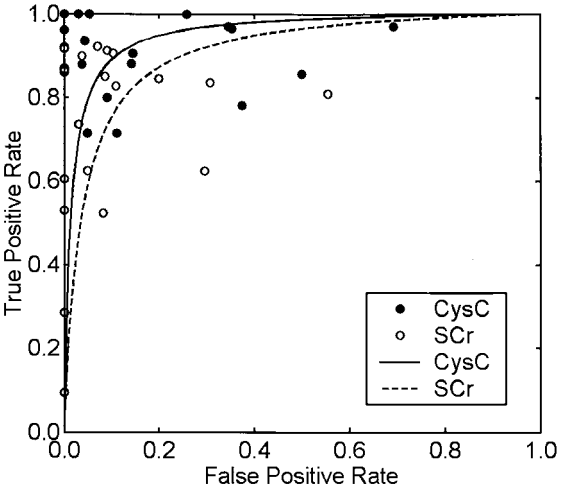

Fig. 1. Summary ROC curve analysis of studies examining the diagnostic accuracy of CysC (●) and SCr (○).

Values shown are the actual, optimal sensitivities and specificities from Refs. *(14, 19, 20, 31, 32, 34–38, 41, 42, 46, 47, 49, 54, 57, 58, 63, 65)*. The curve and calculation of AUC are from the logit transformation of these points as described in Refs. *(66, 67)*, which necessitate the addition of 0.5 to any value of zero.

Conclusions

CysC is clearly an attractive endogenous marker to assess renal function because all studies confirm a strong correlation to SCr and to the clearance of exogenous substances in both healthy volunteers and in patients with impaired renal function. However, it is being proposed to replace a 40-year-old "standard" (SCr) that only "experts" usually challenge based on its limitations. Thus, and correctly so, most studies of CysC have focused on areas where the problems of SCr are most apparent, including pediatric populations and settings where rapid detection of small changes in GFR may be important. The advantage of CysC as an earlier marker of mild renal damage in most of these studies is ascribed to several unique properties of CysC compared with SCr. The most important of these are its constant production, which is independent of muscle mass, age, or sex, and the lack of renal secretion or resorption back into the bloodstream. Studies suggest that CysC may be a more sensitive marker of renal damage in children, although insufficient patients under the age of 4 have been examined to clearly document this. In other settings prone to acute, initially minor, renal damage, such as renal transplant, chemotherapy, cirrhosis, and autoimmune disease, multiple studies now suggest im-

proved utility or at least equivalence to SCr. Indeed, of the 24 studies reviewed here that make claims about the utility of CysC, 15 conclude that CysC is superior whereas 9 conclude that it is equivalent to SCr and/or CrCl; this is supported by ROC plot analysis of the included studies. However, it will ultimately be necessary to document that the demonstrated statistical advantages of CysC in these settings will lead to improved patient outcomes.

The disadvantages of CysC include the higher cost of the immunoassay compared with that for SCr and a suggestion that intraindividual variability might be too high to make it useful for early detection of renal damage *(68, 69)*. This will clearly need to be addressed by future studies. Finally, the observations that CysC may underestimate clearance in transplant patients and that CysC may be increased in cancer patients require additional studies to determine the effect of increased cell turnover/death on values of this protein that is present in every nucleated cell.

Taken together, the recent literature strongly suggests that CysC will have a role in assessing renal function in certain groups of patients for whom the disadvantages of SCr have become apparent. Whether it becomes more commonly used will ultimately depend on the results of outcome-based studies and consideration of some of the possible disadvantages of CysC mentioned above.

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