Is cystatin C a better marker than creatinine for evaluating residual renal function in patients on continuous ambulatory peritoneal dialysis?

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Abstract

Background. Current clinical assessments of residual renal function (RRF) for continuous ambulatory peritoneal dialysis (CAPD) patients usually require 24 h of urine collection, which is sometimes difficult for patients and contributes to random errors.

Objective. Our study aims to investigate whether serum cystatin C (CysC) can serve as a better marker of RRF than serum creatinine (Cr) in CAPD and to develop a formula to estimate RRF with CysC levels.

Methods. One hundred and sixty CAPD patients from a single dialysis unit were randomly divided into modeling (n1 = 120) and validation (n2 = 40) groups. RRF was assessed as the average of the renal clearances of urea and creatinine. We then derived RRF formulas based on the CysC and Cr levels from the modeling group and validated them by comparison with a published CysC-based equation and Modification of Diet in Renal Disease formula.

Results. CysC levels were inversely related to RRF, Kt/Vare and total weekly Ccr but were unrelated to age, gender, body mass index, diabetes or peritoneal clearance. The RRF formulas derived from CysC and Cr were (sinh(ln(6.736–0.566 CysC)))^2 and (sinh(ln(6.097–0.265 Cr)))^2, respectively. When applied to the validation group, the estimated RRF based on CysC (2.8 ± 1.2 mL/min/1.73 m^2) was similar to that of on Cr (2.8 ± 1.3 mL/min/1.73 m^2) and the measured RRF (2.9 ± 1.7 mL/min/1.73 m^2). The CysC formula showed a small bias, with the best 30 and 50% accuracy and had a larger area under the curve and higher sensitivity and specificity when compared to the Cr formula and other formulas.

Conclusion. Serum CysC may be a good marker for the estimation of RRF in CAPD patients. The derived CysC formula may be used to reliably estimate RRF in CAPD patients without the need for collection of 24 h urine.

Keywords: cystatin C; peritoneal dialysis; residual renal function

Introduction

Peritoneal dialysis (PD) is a safe, effective and convenient modality of renal replacement therapy. Residual renal function (RRF) has been recognized as a significant factor influencing morbidity, mortality and quality of life in chronic dialysis patients. RRF also plays an important role in the maintenance of fluid equilibrium in dialysis patients [1, 2]. Clinically, RRF is assessed by evaluating 24-h urine clearances and determining the arithmetic average of creatinine clearance (Clc) and urea clearance (Clu) [3]. However, the measurement of RRF can be problematic, especially in children and elderly patients, because it requires accurate urine collection and measurement for 24 h. Thus, it is imperative to establish a simple and precise indicator or equation that can be used to estimate the RRF of patients undergoing continuous ambulatory peritoneal dialysis (CAPD).

Cystatin C (CysC) is a 13.3-kDa nonglycosylated low-molecular weight protein that is one of the cystatins superfamily (cysteine proteinase inhibitors) and is constantly produced by most nucleated cells and completely filtrated by the glomerulus [4]. It is then fully reabsorbed, rapidly metabolized and decomposed by proximal tubular epithelial cells, so that it will not be reabsorbed by the blood. Serum CysC levels are not affected by age, gender, weight, muscle mass or inflammation [4]. Numerous studies have suggested that the CysC is a more sensitive marker for the prediction of early changes in the glomerular filtration rate (GFR) of patients with acute renal injury or chronic renal disease [4–6]. Thus far, few studies have examined the potential use of CysC for assessment of the RRF of patients undergoing dialysis and have produced conflicting results [7–11]. For example, Hoek et al. [7] first reported that the CysC equation was more accurate than the Modification of Diet in Renal Disease (MDRD) equation in estimating the RRF of dialysis patients, and Delaney et al. [8] found that CysC level may be a simple and practical alternative to the measurement of the RRF. Ros et al. [9] found that CysC produced the same results as plasma creatinine in the prediction of the RRF in
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PD patients, while Mulay et al. [10] reported that CysC exhibited no advantage over serum creatinine (Cr).

By using the clinical data in a large cohort of 160 patients undergoing CAPD in our Peritoneal Dialysis Center, the present study attempted to evaluate whether CysC can act as a good marker of RRF and develop CysC equation and Cr equations that can be used reliably to assess the RRF of CAPD patients. Additionally, we sought to determine whether the CysC equation provides a better estimation of RRF when compared with the Cr equation and the published formulas (Hoek’s CysC formula and the simplified MDRD formula [12]).

Patients and methods

Patients

All the patients were from the Peritoneal Dialysis Center of the Department of Nephrology of The First Affiliated Hospital, Sun Yat-sen University (Guangzhou, China). The inclusion criteria were as follows: (1) patients undergoing the CAPD treatment for >1 month; (2) age >18 years; (3) a residual urine volume >100 mL and (4) voluntary signing of an Informed Consent Form. Patients with the following were excluded: (1) major surgery, bleeding or bleeding tendencies within the previous 3 days; (2) advanced cancer, thyroid dysfunction, severe malnutrition, high catabolism or critical illness; (3) mental disorder or uncooperativeness; (4) the consumption of contraceptives within the past 6 months or the consumption of drugs that could potentially affect Cr, including cimetidine and trimethoprim in the preceding 2 weeks.

A total of 160 patients (85 men and 75 women) were enrolled from March to June 2008. The mean age was 49.1 ± 14.8 years. Seventy-five percent of these patients were randomly assigned to the modeling group (n = 120) to derive the equations and the others were assigned to the validation group for validation of these equations (n = 40). Additionally, 38 of these patients (22 men and 16 women; mean age 50.9 ± 16.6 years) were randomly selected for analysis of the CysC concentration in their PD fluid over a 24-h period.

Methods

Clinical information. Age, gender, body weight, height, duration of PD, preexisting renal diseases, mean arterial pressure and 24-h urine volume were recorded. The 24-h urine specimen and PD fluid were collected for the detection of creatinine and urea. Fasting venous serum was isolated and stored at −80°C prior to the determination of CysC levels and the levels of other serum biochemical parameters [lipids, calcium, phosphorus, intact parathyroid hormone (iPTH) and high-sensitivity C-reactive protein (hs-CRP)]. Moreover, 38 patients were randomly selected for measurement of CysC in their mixed PD effluent over a 24-h period.

Estimation of RRF.

The RRF, in mL/min/1.73 m², was estimated from the mean values of Cr, and Crₜ and adjusted for body surface area (BSA) [3]. BSA was calculated by the Gehan and George equation [13]. All data were analyzed using PD Adequest 2.0 (Baxter Healthcare Ltd, Newbury, UK).

\[
\text{RRF} = \frac{1}{2} \left( \frac{\text{UrineCr} \times \text{UrineUrea}}{\text{SerumCr} \times \text{SerumUrea}} \right) \left( \frac{\text{UrineVolume}}{\text{BSA}} \right)
\]

BSA (m²) = 0.0235 × height (cm)^{0.4424} × weight (kg)^{0.51456}.

Measurement of CysC and Cr concentration. The Dade Behring BN II special protein analyzer (N Latex Cystatin C Kit; Dade Behring Marburg GmbH, Marburg, Germany) was used for the measurement of CysC with a particle-enhanced nephelometric immunoassay. Cr was measured using a kinetic colourimetric assay (Jaffé method) in a Roche Cobas Integra 400 automatic biochemical analyzer (Creatinine Determination Kit, Roche Diagnostics and GmbH).

Measurement of parameters related to the adequacy of PD. Kt/Vₚₑₚₑ₉ normalized protein catabolic rate (nPCR) and total weekly creatinine clearance (total weekly Ccr) were determined using PD Adequest 2.0.

Establishment and validation of equations for the estimation of RRF.

The RRF in the modeling group (n₁ = 120) was regarded as the dependent variable, and the concentrations of CysC and Cr were regarded as the independent variables. Equations based on CysC and Cr were developed to calculate the RRF. Then the values of CysC and Cr were substituted into the developed CysC and Cr equations or substituted into previously described equations (Hoek’s CysC equation and the simplified MDRD equation) for comparison to estimated and measured values of RRF. Hoek’s CysC equation [7] is RRF (mL/min/1.73 m²) for PD = −0.55 + 22.1/CysC and the simplified MDRD equation [12] is estimated glomerular filtration rate (eGFR) = 186 × Cr (mg/dL)^{-1.143} × (age)^{-0.203} × 0.742 (if female).

Statistical analysis

Normally distributed data were presented as the mean ± SD, and non-normally distributed data were presented as medians with quartile intervals. The Student’s t-test was used to assess the significance of differences between groups for normally distributed data and the Wilcoxon rank-sum test was used for the nonnormal distributions. For categorical data, the Pearson’s chi-square test was used to assess the significance of differences between groups. The Pearson’s correlation coefficient (data with a normal distribution or that could be transformed to a normal distribution) and the Spearman’s rank correlation coefficient (data with a nonnormal distribution) were applied to assess correlations. Regression analysis was used to derive equations and a multiple regression analysis was used to analyze the influence of various factors on CysC. The best model (equation) was selected with the Akaike’s Information Criterion (AIC), which is a criterion of model selection that describes the tradeoff between model accuracy and complexity. A Bland–Altman plot was adopted to evaluate the bias and degree of agreement between the estimated RRF and the measured RRF [14]. The difference between the estimated RRF and the measured RRF was defined as bias: relative difference (%) = bias/ measured RRF × 100%. The probability of the estimated RRF falling within 30 or 50% of the measured RRF was defined as the 30 or 50% coincidence rate of the derived equation. The Receiver Operating Characteristic (ROC) curve was used to assess the specificity and sensitivity of the derived equation [15].

Results

Patient characteristics

There was no significant difference between the modeling group and the validation group in gender, age, height, weight, duration of CAPD, 24-h urine volume, pre-existing renal diseases and thyroid-stimulating hormone levels (Table 1). Thyroid functions were normal and the patients did not possess any symptoms of hyper- or hypothyroidism. In the modeling group, RRF was 3.0 ± 2.8 mL/min/1.73 m², Cr was 9.0 ± 3.0 mg/dL and CysC was 5.5 ± 1.7 mg/L. In the validation group, RRF was 2.9 ± 1.7 mL/min/1.73 m², Cr was 9.6 ± 2.9 mg/dL and CysC was 5.6 ± 1.1 mg/L. There were no significant differences in RRF CysC, Kt/Vₚₑ₉ total weekly Ccr, nPCR or serum albumin between the two groups.

Factors influencing Cr and CysC

Table 2 shows that the Cr levels in the modeling group were influenced by gender, age, height, weight, body mass index (BMI) and the presence of diabetes and were positively correlated with the duration of PD, the level of pre-albumin, the concentration of iPTH and the concentration
of phosphorus ($r_s = 0.644, P < 0.001$). In addition, serum Cr was negatively correlated with the 24-h urine volume and RRF ($r_s = -0.595, P < 0.001$, Figure 1, left panel) and inversely related to total $Kt/V$ and total weekly Ccr.

There were no significant associations between CysC and the presence of diabetes, gender, age, height, weight, haemoglobin, albumin, calcium, IPTh, hs-CRP and nPCR (Table 2). However, CysC was related inversely to the 24-h urine volume and RRF ($r_s = -0.593, P < 0.001$, Figure 1, right panel) and was also inversely related to total $Kt/V$ and total weekly Ccr. There were positive relationships between the CysC levels, the duration of PD and the serum levels of prealbumin or phosphorus.

As shown in Table 2, further analysis of the correlations between CysC, Cr and the parameters of dialysis adequacy showed that the Cr level was inversely related with both peritoneal and renal $Kt/V$ and Ccr, whereas the CysC level was only inversely correlated with renal $Kt/V$ and Ccr.

In the modeling group, the CysC concentration of 24-h dialysate in randomly selected patients ($n = 38$) was $0.5 \pm 0.3$ mg/L, and the serum CysC concentration was $5.0 \pm 1.3$ mg/L. The level of dialysate CysC did not correlate with serum levels of CysC, Cr, RRF, $Kt/V$ or total weekly Ccr.

**Development of equations for estimation of RRF**

We considered the RRF of the modeling group as the dependent variable and the CysC concentration as the independent variable and analyzed these variables in a simple regression model to develop an equation to estimate RRF. As the variable failed to meet the prerequisites of normality and homogeneity of linear regression analysis, we transformed the dependent variable as follows: transformative residual renal function (TRRF) = $\sqrt{RRF} + \sqrt{RRF} + 1$.

If we let sinh(x) be the hyperbolic sine function, the derived CysC equation was derived as:

$$CysC \text{ RRF} = (6.736 - 0.566 \text{ CysC})^2 \times 1/4$$

$$+ (6.736 - 0.566 \text{ CysC})^{-2} \times 1/4 - 1/2$$

$$= (\sinh(\ln(6.736 - 0.566 \text{ CysC}))^2)$$

$$\text{ (Adjusted } R^2 = 0.333, P < 0.001)$$

(1)

Similarly, with the RRF of the modeling group regarded as a dependent variable and Cr concentration as an independent variable, the derived Cr equation was:

$$Cr \text{ RRF} = (6.0 - 970.265 \text{ Cr(mg/dL)})^2 \times 1/4$$

$$+ (6.097 - 0.265 \text{ Cr(mg/dL)})^{-2}$$

$$\times 1/4 - 1/2 = (\sinh(\ln(6.097 - 0.265 \text{ Cr}))^2)$$

$$\text{ (Adjusted } R^2 = 0.356, P < 0.001)$$

(2)

In the modeling group, TRRF was used as the dependent variable and serum and urine creatinine and urea nitrogen (used to calculate RRF) were excluded. In the multiple regression models, we accounted for mean arterial pressure, duration of PD, CysC, phosphorus and prealbumin, which were significantly correlated with RRF when adjusted by age and gender. We performed a stepwise regression, and the CysC level, mean arterial pressure, serum phosphorus and duration of PD were incorporated into a model (adjusted $R^2 = 0.430, P < 0.001$) in which CysC conferred the greatest effect on the TRRF. However, the value of the adjusted $R^2$ from the stepwise regression was greater than that from the simple regression model, and this model was significantly more complex and unwieldy. To select the best model, we used the AIC, which balances the model accuracy and complexity. Using this criterion, the favored model will be the one with the lowest AIC value. Simple calculations yielded AIC values for simple regression (CysC equation) and stepwise regression of $-0.153$ and $0.004$, respectively. Thus, we chose the simple regression model for subsequent analyses.

**Validation and comparisons between equations**

Next, CysC and Cr from the validation group were substituted into the CysC and the Cr equations to get the estimated RRF. In the CysC equation, the estimated RRF was $2.8 \pm 1.2$ mL/min/1.73 m², which was very close to the measured RRF of $2.9 \pm 1.7$ mL/min/1.73 m² ($P = 0.795$). In the Cr equation, the estimated RRF was $2.8 \pm 1.3$ mL/min/1.73 m², which was also very close to the measured RRF ($P = 0.812$).

We then used a Bland–Altman plot to evaluate the bias and degree of agreement between the estimated RRF from our CysC and Cr equations, Hoek’s CysC and the simplified MDRD equations compared with the measured RRF (Table 3 and Figure 2). The CysC and Cr equations derived from the present study seemed to provide the least variability in bias and the narrowest limit of agreement in the Bland–Altman plots. However, the simplified MDRD equation appeared to have the largest variability in bias (bias = $-3.24, P < 0.001$), with an estimated RRF 2- to 3-fold greater than the measured RRF. The accuracy within 30 and 50% of the measured RRF in the CysC equation were 57.5 and 77.5%, respectively. These values demonstrated the greatest accuracy and the smallest relative differences (%). Paired $t$-test analysis showed a significant difference between the estimated and measured RRF for the simplified MDRD and Hoek’s CysC equations, indicating that these two equations may not be suitable for the patients enrolled in this study.

The ROC curves used for determining the diagnostic accuracy of the detection of RRFs from different equations were shown in Figure 3 and the ROC analysis was summarized in Table 4. The cutoff value of RRF set at 2.0 mL/min/1.73 m² was chosen to define the sensitivity and specificity of the estimates of RRF in identifying significant RRF ($>2.0$ mL/min/1.73 m²). The AUC [95% confidence interval (CI)] of the simplified MDRD equation was 0.78 (0.64, 0.92) ($P = 0.004$), and the sensitivity and specificity were 0.72 and 0.73, respectively. Within the prescribed cutoff values, the AUC (95% CI), sensitivity and specificity of Hoek’s CysC equation and our CysC equation were
Table 1. Patient characteristics in the modeling group and validation group^a

<table>
<thead>
<tr>
<th></th>
<th>Modeling group</th>
<th>Validation group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>120</td>
<td>40</td>
<td>0.085</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.0 ± 23.5</td>
<td>45.5 ± 14.5</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>63/57</td>
<td>22/18</td>
<td>0.785</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>59.4 ± 10.9</td>
<td>58.4 ± 8.6</td>
<td>0.570</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.0 ± 11.8</td>
<td>164.1 ± 8.1</td>
<td>0.312</td>
</tr>
<tr>
<td>BMI</td>
<td>22.3 ± 3.2</td>
<td>21.7 ± 2.6</td>
<td>0.246</td>
</tr>
<tr>
<td>Time on PD (month)</td>
<td>7.5 (13.0)</td>
<td>5.5 (13.0)</td>
<td>0.528</td>
</tr>
<tr>
<td>Primary diseases (chronic glomerulonephritis/diabetic nephropathy/hypertensive nephropathy/others^b)</td>
<td>69/27/12/12</td>
<td>28/5/2/5</td>
<td>0.347</td>
</tr>
</tbody>
</table>

^aData are given as mean ± SD when it is normal distribution and given as median (interquartile range) when it is nonnormal distribution; MAP, mean arterial pressure; FT3, free triiodothyronine; FT4, free tetraiodothyronine; TSH, thyroid-stimulating hormone; Cr, serum creatinine; BUN, blood urea nitrogen; CysC, serum cystatin C; nPCR, normalized protein catabolic rate.

^bIncluding polycystic kidney disease, gouty nephropathy, etc.

Discussion

The present study, performed using a large cohort of 160 CAPD patients, suggested that the CysC level in CAPD patients was not associated with the presence of diabetes, gender, age, height, body mass index (BMI) or iPTH and was not predominantly influenced by the peritoneal clearances. Moreover, CysC had a correlation with RRF that was similar to that of Cr (r_s = -0.593, P < 0.001 for CysC, r_s = -0.595, P < 0.001 for Cr). The CysC and Cr equations (see the Results section) were derived and included the square of the composition of the hyperbolic sine function (sinh(x)) and the natural logarithm (ln(x)). The estimated RRFs based on CysC (2.8 ± 1.2 mL/min/1.73 m²) were similar to those of Cr (2.8 ± 1.3 mL/min/1.73 m²) and the measured RRFs (2.9 ± 1.7 mL/min/1.73 m²). The Bland–Altman plots indicated a small variability in bias, a narrow limit of agreement, a small relative difference (%) and a high accuracy within 30 and 50% of the CysC equation when compared with the Cr equation, one published CysC-based (Hoek) formula and the MDRD formula. Moreover, the ROC curves revealed that our derived CysC equation was more sensitive and specific than our derived Cr equation.

CysC and Cr have been used as endogenous markers for the estimation of GFR. CysC has been proposed as a more reliable marker of GFR than Cr [4–6]. However, the superiority of CysC in the estimation of RRF and the PD clearance of CysC has not heretofore been established. Delaney et al. [8] evaluated 109 patients undergoing PD and found that CysC (r_s = -0.65, P < 0.001) was superior to Cr (r_s = -0.36, P < 0.001) in the estimation of RRF. Conversely, a study of 68 PD patients by Mulay et al. [10] showed that CysC was inferior to Cr (CysC: r_s = -0.28, P = 0.02; Cr: r_s = -0.66, P < 0.001). Our results from a study of 120 CAPD patients suggested that CysC was similar to Cr for the estimation of RRF, which was in agreement with the results of a study by Hoek et al. [7] that used 95 PD patients (CysC: r_s = -0.55, P < 0.001, Cr: r_s = -0.56, P < 0.001) and a study reported by Ros et al. [9] that included 80 patients undergoing automated PD or CAPD (CysC: r_s = -0.60, P < 0.001, Cr: r_s = -0.61, P < 0.001). For the peritoneal clearance of CysC, our study showed that the 24-h peritoneal dialysate CysC concentration was relatively...
low (0.5 ± 0.3 mg/L) and was not associated with CysC, Cr, RRF, Kt/Vurea and total weekly Ccr. In agreement with the results of Delaney et al. [8], there were no correlations between peritoneal Kt/Vurea and peritoneal Ccr and CysC. This indicated that CysC clearance occurs predominantly through renal elimination and that PD clearance would be rather minimal. In contrast, Cr was significantly influenced by peritoneal clearance. We also found that, in contrast to Cr, CysC was not associated with the presence of diabetes, gender, age, height, BMI and or iPTH. Together, these results indicate that CysC may be superior to Cr for the estimation of RRF in patients undergoing CAPD with fewer influencing factors.

CysC has been reported to be generated at a relatively constant rate that is irrespective of muscle mass; however, it may be susceptible to a variety of nonrenal influences, including thyroid function. Thyroid hormones may influence CysC levels by altering the production rate of CysC in the context of a changed cell turnover and/or metabolic rate in thyroid dysfunction. Therefore, thyroid function has to be considered when CysC is used as a marker of kidney function [16]. To exclude the possible effect of thyroid function, we only recruited the patients who were without thyroid dysfunction. Recent studies have also shown that CysC is influenced by factors such as age, BMI, sex and high concentrations of C-reactive protein (CRP) [17, 18] and that patients with higher CysC levels appear to have increased cardiovascular risk profiles [19]. However, our results showed that CysC was not associated with sex (r < 0.001, P = 0.587), age (r = 0.002, P = 0.986), BMI (r = 0.008, P = 0.935), nPCR (r = 0.069, P = 0.456) or hs-CRP (r = 0.032, P = 0.726). In regard to nutritional indicators, there was only a weak association between CysC and serum prealbumin (r = 0.200, P = 0.031). In contrast, the correlation between serum Cr and prealbumin was closer (r = 0.361, P < 0.001). These results imply that Cr might be more susceptible to the influence of nutritional status than CysC. Macdonald et al. [20] noted that total lean (LM) was an important factor affecting CysC levels (accounting for 6% of the observed variance of CysC) and suggested that CysC-based GFR estimation improves when accounting for body composition. Delaney et al. [8] found an influence of nPCR on CysC for the CAPD patients. Therefore, future studies are needed to perform a subjective global assessment of nutritional status as well as assess the influence of additional indicators of nutritional status, including LM, skinfold thickness, mid-arm muscle circumference, mid-arm muscle diameter and area and bioelectrical impedance. A plausible link among increased CysC, inflammation and impaired cardiovascular outcome, as reported in most of the studies so far, is renal dysfunction [19]. It was believed that increased CysC with decreased RRF might be correlated with increased hs-CRP. However, none of these relationships have been addressed in our

### Table 2. Relationships between serum CysC, serum creatinine and clinical variables using The Pearson's correlation or Spearman rank correlation analysis

<table>
<thead>
<tr>
<th></th>
<th>Serum CysC</th>
<th>Serum creatinine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>0.002</td>
<td>0.986</td>
</tr>
<tr>
<td>Weight</td>
<td>0.059</td>
<td>0.524</td>
</tr>
<tr>
<td>Height</td>
<td>0.089</td>
<td>0.336</td>
</tr>
<tr>
<td>BMI</td>
<td>0.008</td>
<td>0.935</td>
</tr>
<tr>
<td>Gender</td>
<td>0.069</td>
<td>0.456</td>
</tr>
<tr>
<td>Time on PD</td>
<td>0.225</td>
<td>0.013</td>
</tr>
<tr>
<td>MAP</td>
<td>0.063</td>
<td>0.858</td>
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<tr>
<td>Serum albumin</td>
<td>0.028</td>
<td>0.760</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>-0.145</td>
<td>0.115</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>0.200</td>
<td>0.031</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.170</td>
<td>0.064</td>
</tr>
<tr>
<td>iPTH</td>
<td>0.059</td>
<td>0.520</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.117</td>
<td>0.204</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.334</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>0.032</td>
<td>0.726</td>
</tr>
<tr>
<td>Urine volume</td>
<td>-0.445</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RRF</td>
<td>-0.593</td>
<td>&lt;0.001</td>
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<tr>
<td>nPCR</td>
<td>-0.069</td>
<td>0.456</td>
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<tr>
<td>Kt/Vurea</td>
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<td>&lt;0.001</td>
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<td>Residual renal Kt/Vurea</td>
<td>-0.575</td>
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<td>Total weekly creatinine</td>
<td>-0.469</td>
<td>&lt;0.001</td>
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<tr>
<td>clearance (Ccr)</td>
<td>-0.545</td>
<td>&lt;0.001</td>
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*P-values of <0.05 were considered significant.

![Fig. 1. Relationship (scatter plots) between serum CysC or serum creatinine (Cr) and RRF in the patients receiving CAPD.](https://academic.oup.com/ndt/article/26/10/3358/1902954)
study. Further well-designed trials involving other proinflammatory cytokines such as Interleukin 6 are required to be done in patients with PD to explain their predictive values for future cardiovascular risk.

Many studies have attempted to identify simple and effective indicators or equations to estimate RRF. The RRF and CysC levels may be affected by ethnicity, environmental factors, preexisting renal diseases and dialysis modality [11]. Thus, for the monitoring of Asian dialysis patients in clinical practice, it is imperative to develop an RRF equation based on the data collected from Asian patients. Hoek et al. [7] calculated RRF from CysC and, using 1/CysC as the dependent variable, obtained the following equation: \[ y = a + b \left( \frac{1}{x} \right) \] for the estimation of the RRF of patients undergoing hemodialysis and PD. They concluded that their equation was superior to the MDRD equation. In the present study, we used RRF data from 120 Asian patients in combination with CysC data to derive a simple

<table>
<thead>
<tr>
<th>Formula</th>
<th>Mean (SD) mL/min/1.73 m²</th>
<th>P</th>
<th>Bias (limit of agreement)</th>
<th>Relative difference%*</th>
<th>Accuracy (%) within 30%</th>
<th>Accuracy (%) within 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplified MDRD</td>
<td>6.1 ± 1.9</td>
<td>&lt;0.001</td>
<td>-3.2 (-6.2, -0.3)</td>
<td>137.4 (68.7, 207.4)</td>
<td>5.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Hoek’s PD CysC</td>
<td>3.6 ± 1.1</td>
<td>0.011</td>
<td>-0.7 (-4.0, 2.6)</td>
<td>44.8 (13.9, 87.8)</td>
<td>40.0</td>
<td>55.0</td>
</tr>
<tr>
<td>CysC formula</td>
<td>2.8 ± 1.2</td>
<td>0.795</td>
<td>0.1 (-3.2, 3.3)</td>
<td>27.7 (12.9, 48.1)</td>
<td>57.5</td>
<td>77.5</td>
</tr>
<tr>
<td>Cr formula</td>
<td>2.8 ± 1.3</td>
<td>0.812</td>
<td>0.1 (-3.0, 3.1)</td>
<td>38.3 (23.8, 67.9)</td>
<td>55.0</td>
<td>65.0</td>
</tr>
</tbody>
</table>

*Relative difference (%) is given as median. Differences between estimated RRF and measured RRF were evaluated by paired t-test. P-values of <0.05 were considered significant.

Fig. 2. Bland–Altman plots for differences between estimated RRF and measured RRF in patients on CAPD. On the x-axis, the mean of the measured and estimated RRF is given and on the y-axis the difference in mL/min/1.73 m² between the measured RRF and estimated RRF derived from the simply MDRD formula (A, MDRD RRF), the Hoek’s CysC formula (B, Hoek’s CysC RRF), CysC formula (C, CysC RRF) or the Cr formula (D, Cr RRF) is given. The mean difference (solid lines) and the limit of agreement (dotted lines) are also plotted.
regression equation. If RRF is used as a dependent variable, the residuals did not meet the assumptions of normal distribution and uniform variance. When regression of the complex square root transformation of RRF (called $T_{RRF}$) was used as the independent variables, this transformed regression was determined to meet the assumptions quite well. Additionally, the adjusted $R^2$ value of the transformed linear regression was better than that of the linear regression that used RRF as a dependent variable. Thus, our results indicated that the converted data were suitable for regression analysis and that the value of the adjusted $R^2$ was greater than that of other nonlinear models including the curve and reciprocal models. Inverse transformation of the transformed equation led to the final derived CysC equation and Cr equations of the form $y = (\sinh(ln(a + bx)))^{2}$ which happens to be the hyperbolic sine function. $\sinh()$ is the hyperbolic sine function, $\ln()$ is the natural logarithm function and $a$ and $b$ are constants.

In our study, the RRF values estimated by serum CysC or Cr levels were close to the measured values. We also analyzed the bias, degree of agreement and accuracy for our CysC and Cr equations compared with the simplified MDRD equation [12] and the Hoek CysC equation [7], and we found that the biases of our derived CysC and Cr equations were less than those of the simplified MDRD equation and the Hoek CysC equation. It is to be noted that the bias of the MDRD equation was the largest, with an estimated value that was 2- to 3-fold higher than the measured one; Hoek et al. [7] achieved similar results. To reduce the bias associated with creatinine, we used the Jaffe method to measure Cr because the NECOSAD study showed that results from compensated Jaffe and enzymatic creatinine methods can be used in the MDRD formula without restandardization [21]. In addition, the effect of creatinine calibration bias and imprecision on the eGFR decreases as the Cr increases [22]. Therefore, creatinine calibration may have less effect on the bias of the MDRD formula. The MDRD formula can be expected to give an overestimation of the RRF at low ranges. This implies that the MDRD may be inapplicable for the assessment of RRF in our CAPD patients, as supported by the results of Hoek et al. [7].

Because Caravaca et al. [23] reported a decrease in GFR to $<2.0 \text{ mL/min/1.73 m}^2$ as a loss of significant RRF, we set the cutoff value of RRF at $2.0 \text{ mL/min/1.73 m}^2$. The AUC of ROC curves was used to detect how sensitive and specific the estimates of RRF were for the identification of significant RRF ($>2.0 \text{ mL/min/1.73 m}^2$). Our results showed that the AUC of the MDRD equation was the highest of all the equations but the differences in AUC between the simplified MDRD and CysC formulas were not statistically significant. As for the sensitivity and specificity, the CysC equations may have improved diagnostic accuracy for identifying significant RRF ($>2.0 \text{ mL/min/1.73 m}^2$). Although the sensitivity and specificity of the Hoek’s CysC equation were similar to ours, a paired $t$-test showed significant differences between the estimated versus measured value in the Hoek’s CysC equation, suggesting that the Hoek’s CysC equation may not be suitable for our patients.

A limitation of the present study lies in the absence of a gold standard GFR measurement (e.g. inulin or iothalamate clearance), which may have enabled us to better describe the relationship between CysC concentration and RRF. Although the use of a gold standard would be preferable, it is difficult to apply this method to a large study population due to the complexities of measurements and also the high cost. In addition, it was suggested that renal clearance estimations for the patients undergoing PD should be based on the collection of blood samples 24 h after injection of the exogenous substance and may be confoundingly affected by the significant peritoneal clearance of an exogenous tracer. These factors are rarely considered in clinical practice, making the assessment of RRF more difficult. Van Olden et al. [3] compared RRF values that were calculated as the mean values of $Cl_c$ and $Cl_u$ (3.0 mL/min), with median inulin clearance (3.2 mL/min), and found no significant differences. They concluded that the mean of $Cl_c$.

Fig. 3. ROC curve analysis of diagnostic accuracy of RRF estimated from CysC, Cr, Hoek’s CysC and MDRD formulas in patients with CAPD. The discrimination point was set at RRF = 2.0 mL/min/1.73 m^2.

Table 4. ROC analyses for CysC, Cr, Hoek’s CysC and MDRD formulas in patients with CAPD

<table>
<thead>
<tr>
<th>RRF cutoff</th>
<th>RRF estimate</th>
<th>AUC</th>
<th>95% CI</th>
<th>P</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 mL/min/1.73 m^2</td>
<td>CysC formula</td>
<td>0.74</td>
<td>0.56–0.91</td>
<td>0.013</td>
<td>0.76</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Cr formula</td>
<td>0.61</td>
<td>0.43–0.78</td>
<td>0.270</td>
<td>0.52</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>Hoek’s CysC</td>
<td>0.74</td>
<td>0.56–0.91</td>
<td>0.013</td>
<td>0.76</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Simplified MDRD</td>
<td>0.78</td>
<td>0.64–0.92</td>
<td>0.004</td>
<td>0.72</td>
<td>0.73</td>
</tr>
</tbody>
</table>
and Cl_{cr} can be used to estimate RRF, especially for large study populations. The guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) also recommend the use of the mean of Cl_{cr} and Cl_{cre} to estimate RRF, and this method has been increasingly adopted in recent studies. However, we should realize that proper urine collection is very important for this method. The CysC-based equation formulated in the present study is based on this method. Further studies are still required to explore the advantages of a CysC-based equation over a Cr-based equation in terms of sensitivity and specificity.

Conclusions

CysC is unaffected by gender, age, body weight or peritoneal clearance. The derived CysC formula uses the square of the composition of the hyperbolic sine function (sinh(x)) and the natural logarithm (ln(x)), offers comparable estimation of the RRF and exhibits superiority in accuracy, sensitivity and specificity when compared with the Cr equation, a published CysC-based (Hoek) formula and the MDRD formula. These results suggest that CysC may serve as a good indicator for RRF in patients undergoing CAPD and that the derived CysC formula may be used to reliably estimate RRF in CAPD patients without collection of 24-h urine specimens.

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Conflict of interest statement. None declared.

References


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