Development and Validation of Residual Kidney Function Estimating Equations in Dialysis Patients

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Rationale & Objective: Measurement of residual kidney function is recommended for the adjustment of the dialysis prescription, but timed urine collections are difficult and prone to errors. Equations to calculate residual kidney function from serum concentrations of endogenous filtration markers and demographic parameters would simplify monitoring of residual kidney function. However, few equations to estimate residual kidney function using serum concentrations of small solutes and low-molecular-weight proteins have been developed and externally validated.

Study Design: Study of diagnostic test accuracy.

Setting & Participants: 823 Chinese peritoneal dialysis (PD) patients (development cohort) and 826 PD and hemodialysis patients from the Netherlands NECOSAD study (validation cohort).

Tests Compared: Equations to estimate residual kidney function (estimated clearance [eCl]) using serum creatinine, urea nitrogen, cystatin C, β_2-microglobulin (B2M), β-trace protein (BTP), and combinations, as well as demographic variables (age, sex, height, and weight). Equations were developed using multivariable linear regression analysis in the development cohort and then tested in the validation cohort. Equations were compared with published validated equations.

Outcomes: Residual kidney function measured as urinary clearance (mCl) of urea nitrogen (mCl_{UN}) and average of creatinine and urea nitrogen clearance (mCl_{UN-cr}).

Results: In external validation, bias (difference between mCl and eCl) was within ± 1.0 unit for all equations. Accuracy (percent of differences within ± 2.0 units) was significantly better for eCl_{BTP}, eCl_{B2M}, and $eCl_{BTP-B2M}$ than eCl_{UN-cr} for both mCl_{UN} (78%, 80%, and 81% vs 72%; $P < 0.05$ for all) and mCl_{UN-cr} (72%, 78%, and 79% vs 68%; $P < 0.05$ for all). The area under the curve for predicting $mCl_{UN} > 2.0$ mL/min was highest for eCl_{B2M} (0.853) and $eCl_{BTP-B2M}$ (0.848). Results were similar for other validated equations.

Limitations: Development cohort only consisted of PD patients, no gold-standard method for residual kidney function measurement.

Conclusions: These results confirm the validity and extend the generalizability of residual kidney function estimating equations from serum concentrations of low-molecular-weight proteins without urine collection.

Residual kidney function is associated with morbidity and mortality in patients with chronic kidney failure treated by peritoneal dialysis (PD).[1-5] Guidelines recommend regular assessment of residual kidney function in PD patients to adjust the dialysis prescription.[6] Residual kidney function is generally quantified as measured clearance (mCl) using timed urine collections of small solutes, such as mCl of urea nitrogen (mCl_{UN}) or mCl of the average of urea nitrogen and creatinine (mCl_{UN-cr}).[6-8] However, timed urine collections are difficult and prone to errors. Therefore, estimated clearance (eCl) from serum concentrations of endogenous filtration markers without urine collection, as routinely performed in earlier stages of chronic kidney disease,[9] could simplify clinical practice.

In principle, eCl from serum concentrations of small solutes would not be expected to perform well in dialysis patients, due in part to extrarenal elimination of the solutes during dialysis.[10] Serum concentrations of low-molecular-weight proteins (LMWPs), such as β-trace protein (BTP [molecular weight, 23-29 kDa], β_2-microglobulin (B2M [molecular weight, 11.6 kDa]), and cystatin C (molecular weight, 13.3 kDa), could be useful for eCl because LMWPs are eliminated by glomerular filtration as efficiently as small solutes, but less efficiently by dialysis.[7,11-19]

Prior studies have developed estimating equations for residual kidney function using serum concentrations of small solutes or LMWPs,[10,20-23] but only the study by Shafi et al[10] included an external validation cohort. In that study, estimating equations were developed in a small cohort of dialysis patients in the United States (Residual Kidney Function [RKF] Study) and validated in hemodialysis (HD) and PD patients in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD).[10] Equations using BTP, B2M, and cystatin C levels were more accurate than equations using small solute levels, but to our knowledge, they have not been evaluated in other populations.

Residual kidney function estimating equations could be of particular interest in countries with a high prevalence of PD patients and limited resources, such as China, to simplify medical treatment and reduce costs.[24] The aim of our study was to assess the validity and generalizability of residual kidney function estimating equations using

LMWPs without urine collections. We developed equations using serum concentrations of small solutes and LMWPs in a large Chinese cohort of prevalent PD patients (Guangzhou PD Study), validated the equations in NECOSAD, and compared them with the residual kidney function estimating equations previously developed by Shafi et al.[10]

METHODS

Study Design

This is a cross-sectional study for the development and internal validation of residual kidney function estimation equations in a Chinese PD cohort and external validation in a European HD and PD cohort. The study was approved by the Institutional Review Board (IRB) of the First Affiliated Hospital of Sun Yat-sen University (IRB approval no. [2013] 051), the Tufts Medical Center IRB (no. 10890), and medical ethics boards involved in NECOSAD. The study adheres to the ethical principles of the Declaration of Helsinki. All patients who took part in these studies gave their written informed consent.

Participants

The Guangzhou PD Study was used for equation development and internal validation. It consists of prevalent patients treated by continuous ambulatory PD (CAPD) from the First Affiliated Hospital at Sun Yat-Sen University in Guangzhou and affiliated outpatient dialysis units between January 2013 and December 2015. Inclusion criteria were 18 years or older and treatment with CAPD for 3 or more months. Exclusion criteria were critical illness or major surgery at the time of study enrollment, active bleeding within the previous 3 days before enrollment, advanced stage of malignancy, peritonitis within 4 weeks before enrollment, untreated clinical disorders of the thyroid gland, and medications that significantly affect tubular secretion of creatinine. We further excluded patients with missing demographic data, missing samples on 24-hour urine and dialysate collections, and anuric patients (ie, urine output of 0 mL/d).

After completion of data collection, we randomly divided the study population into a development data set (two-thirds of patients) and an internal validation data set (one-third of patients). NECOSAD was used for external validation of the equations. It is a large multicenter cohort of incident HD and PD patients older than 18 years recruited from 38 dialysis units in the Netherlands between January 1997 and January 2005.[2,25,26] The present analysis includes 826 patients at 3 or 12 months after dialysis initiation with stored specimens and available data for residual kidney function.

Test Methods

The reference test is mCl of small solutes (urea nitrogen and creatinine) and the index tests are equations for eCl based on serum concentrations of small solutes, LMWPs

(BTP, B2M, and cystatin C), demographic variables (age and sex), and body size (height and weight). Because clinical laboratories might not be able to assay all 3 LMWPs, we developed single-marker and multiple-marker LMWP equations.

Clearance Measurements

In both study populations, mCl of small solutes was ascertained as UV/P, where UV is urine solute excretion rate (urine solute concentration × urine volume) and P is plasma (serum) solute concentration. mCl_{UN} was expressed as mL/min and mCl_{UN-cr} was expressed as mL/min/1.73 m² body surface area. In Guangzhou PD Study patients and NECOSAD PD patients, samples from 24-hour collections of dialysate and urine and a serum sample were obtained before a routine visit to the PD clinic. In NECOSAD HD patients, all urine during the interdialytic interval was collected, and blood samples were drawn at the end of the preceding HD session and directly before the next session, with the mean of these 2 values used for clearance calculations.[27] Aliquots of all specimens were stored at −80°C until analyses were performed.

Filtration Marker Assessment
Small Solutes

For the Guangzhou PD study, urea nitrogen and creatinine measurements were performed at the University of Minnesota Advanced Research and Diagnostic Laboratory, Minneapolis, MN (Table S1). Serum and urinary urea nitrogen were measured on the Roche Cobas 6000 using a standardized enzymatic method. Serum and urinary creatinine were measured using an isotope-dilution mass spectrometry–traceable enzymatic method on the Roche Cobas 6000. In NECOSAD, urea nitrogen and creatinine (mainly using the alkaline picrate method) had previously been measured at the local laboratories.[10] Earlier analyses in NECOSAD had shown that the method of creatinine measurement had a negligible effect on creatinine concentrations and that the interlaboratory variation at low ranges of creatinine measurements is low.

Low-Molecular-Weight Proteins

For both studies, LMWP measurements were performed at the University of Minnesota Advanced Research and Diagnostic Laboratory, Minneapolis, MN (Table S1). In the Guangzhou PD Study, BTP was measured using an immunonephelometric assay. B2M and cystatin C were measured using an immunoturbidimetric method. In the NECOSAD cohort, all measurements were performed using an immunonephelometric assay.[10]

Analyses in the Guangzhou PD Study
Development Data Set

For both mCl_{UN} and mCl_{UN-cr}, our goal was to develop an equation containing only small solutes (eCl_{UN-cr}) that could readily be used in clinical practice without

measurement of additional filtration markers, 3 single-marker LMWP equations (eCl_{BTP}, eCl_{B2M}, or eCl of cystatin C [eCl_{cys}]), and 1 multiple-marker LMWP equation. Small solutes were considered for inclusion in equations containing LMWPs, and demographic characteristics and body size were considered for inclusion in all equations.

We prespecified a process for equation development similar to methods published previously.[9,10,28] We transformed serum concentrations of filtration markers and mCls to natural logarithmic scale to stabilize variance. We used least squares linear regression and analysis of variance to assess linearity between the filtration markers and clearances. In case nonlinearity was detected, we determined the optimal number and location of breakpoints for spline functions for each filtration marker. For the small-solute equation, we forced urea nitrogen level, creatinine level, age, and sex into the equation. For the single-marker LMWP equations, we forced urea nitrogen level, creatinine level, age, and sex into the equation. For the multiple-marker LMWP equation, we evaluated all three 2-marker combinations and one 3-marker combination. At each step we retained a variable if it was significant in the model and improved (reduced) the root-mean-square error (RMSE; standard deviation of the mean difference between mCl and eCl) of the model by ≥2% compared to the model without the variable (a lower RMSE implies better model fit).

Internal Validation Data Set

All equations selected in the development data set were evaluated in the internal validation data set. Equations were excluded from further analysis if 1 of the filtration markers had a nonsignificant coefficient ($P > 0.05$) or the polynomial form of the filtration marker did not improve the RMSE of the model by ≥1% compared to the model with the linear form of the marker. In this case, the linear form was retained.

Combined Data Set

The remaining equations were refitted in the combined data set to determine coefficients for the final equations. The final multiple-marker LMWP equation was selected as the model with the lowest RMSE.

Analyses in the NECOSAD (external validation) Data Set

We compared mCl versus eCl graphically by plotting the residuals of the regression model (difference between mCl and eCl) against eCl. We defined bias as the median of the residuals and precision as the interquartile range of the residuals.[9,10,29] As in the study by Shafi et al,[10] we defined accuracy as the percentage of eCls within ± 2.0 mL/min of mCl_{UN} and 2.0 mL/min/1.73 m² of mCl_{UN-cr}, respectively. We acknowledge that the range of ± 2.0 units for accuracy is wide but considered that a

narrower range was not practical given the uncertainty in the reference test. We also considered a definition of accuracy based on a relative scale, as is generally used at higher glomerular filtration rates (GFRs), but concluded that it was not necessary because the GFR range is narrow. We calculated 95% confidence intervals for bias, precision, and accuracy by bootstrapping with 2,000 replicates.[30] We compared accuracy between equations using the McNemar test for paired data. We compared the accuracy of each equation between HD versus PD patients using χ^2 test for independent data. We assessed the area under the receiver operating characteristic curve (AUC) for estimating $mCl_{UN} < 2.0$ mL/min and $mCl_{UN-cr} < 2.5$ mL/min/1.73 m². $mCl_{UN} > 2$ mL/min has been proposed by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines as a residual kidney function threshold, below which the treating physician should perform a thrice-weekly HD regimen.[31] The threshold for mCl_{UN-cr} was chosen based on published literature to compare results.[10] The optimal cutoff was defined as the value with the highest combined sensitivity and specificity (Youden index[32]). Finally, we compared the accuracy of the equations developed in the Guangzhou PD Study with equations previously published by Shafi et al[10] using χ^2 test. Analyses were performed using R, version 3.4.1 (R Development Core Team). $P < 0.05$ was considered to be significant. Results have not been adjusted for multiple testing.

RESULTS

Participants

A total of 1,241 participants were included in the Guangzhou PD Study. After excluding participants with missing demographic data (n = 13), missing filtration marker measurements (n = 248), and anuria (n = 157; Table S2), 823 participants were selected (Fig S1). Mean age was 50 years and 63% were men (Table 1). Mean urinary output was 710 mL/d, mCl_{UN} was 2.0 mL/min, and mCl_{UN-cr} was 3.1 mL/min/1.73 m². All patients were on CAPD treatment with 4 exchanges per day; total dwell volume used was 7.7 ± 1.2 L/d. Mean ultrafiltration was 505 ± 595 mL/d. NECOSAD included 826 participants (587 HD and 239 PD; Table 1). Mean age was 60 years and 60% were men. Mean urinary output was 897 mL/d, mCl_{UN} was 2.9 mL/min, and mCl_{UN-cr} was 3.8 mL/min/ 1.73 m².

Test Results: Correlations Among Clearances and Serum Concentrations of Filtration Markers

In both studies, B2M level showed the strongest correlation with mCl_{UN} (r = −0.56 and −0.69 in the Guangzhou PD Study combined data set and NECOSAD, respectively) and mCl_{UN-cr} (r = −0.58 and r = −0.75), whereas urea nitrogen level had the weakest correlation with mCl_{UN} (r = −0.19 and r = −0.24) and mCl_{UN-cr} (r = −0.23 and

Table 1. Participants' Baseline Characteristics in the Guangzhou PD Study and NECOSAD Study

	Guangzhou PD Study (n = 823)	NECOSAD		
		Total (n = 826)	HD (n = 587)	PD (n = 239)
Demographics				
Characteristics				
Age, y	49.9 ± 14.5	60.2 ± 14.4	63.4 ± 13.3	52.2 ± 14.0
Men	62.8%	60.0%	59.1%	67.8%
White	0%	87.7%	91.8%	77.4%
Body mass index, kg/m²	22.2 ± 3.2	25.1 ± 4.1	24.9 ± 4.2	25.5 ± 4.1
Height, cm	162.9 ± 7.4	171.3 ± 9.9	170.4 ± 9.8	173.6 ± 9.8
Weight. kg	59.1 ± 10.3	73.8 ± 14.2	72.5 ± 14.0	77.0 ± 14.2
Body surface area, m²	1.6 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2
Total-body water, L	32.9 ± 05.5	38.0 ± 6.7	37.1 ± 6.4	40.1 ± 7.0
Diabetes mellitus	16.7%	21.3%	23.7%	15.5%
Residual kidney function				
Urinary output, mL/d	710 ± 538	897 ± 675	826 ± 623	1,069 ± 762
Measured clearances				
Urea nitrogen, mL/min	2.0 ± 1.9	2.9 ± 2.1	2.8 ± 2.1	3.1 ± 2.2
Urea nitrogen, mL/min/1.73 m²	2.1 ± 2.1	2.7 ± 1.9	2.6 ± 1.9	2.8 ± 1.9
Cr, mL/min	3.7 ± 3.9	4.6 ± 3.5	4.6 ± 3.7	4.6 ± 3.2
Cr, mL/min/1.73 m²	4.0 ± 4.2	4.9 ± 3.7	4.8 ± 3.7	5.0 ± 3.5
Mean of urea nitrogen and Cr, mL/min	2.9 ± 2.9	3.6 ± 2.6	3.6 ± 2.7	3.6 ± 2.4
Mean of urea nitrogen and Cr, mL/min/1.73 m²	3.1 ± 3.1	3.8 ± 2.7	3.7 ± 2.7	3.9 ± 2.6
Weekly kidney Kt/V	0.6 ± 0.6	0.7 ± 0.5	0.7 ± 0.5	0.7 ± 0.5
Filtration marker serum concentrations				
SUN, mg/dL	49.3 ± 15.5	64.9 ± 17.1	66.9 ± 16.7	60.1 ± 17.2
Cr, mg/dL	9.9 ± 3.4	8.7 ± 2.8	8.5 ± 2.7	9.2 ± 3.0
β_2-microglobulin, mg/L	29.9 ± 10.5	25.5 ± 9.5	25.6 ± 9.6	25.2 ± 9.3
β-Trace protein, mg/L	8.6 ± 2.9	6.9 ± 2.6	6.8 ± 2.4	7.3 ± 2.9
Cystatin C, mg/L	6.6 ± 1.4	5.1 ± 1.1	5.0 ± 1.1	5.2 ± 1.2

Note: Values expressed as mean ± standard deviation or percent. Conversion factors for units: SUN in mg/dL to mmol/L, ×357; Cr in mg/dL to μmol/L, ×88.4.
Abbreviations: Cr, creatinine; HD, hemodialysis; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; PD, peritoneal dialysis; SUN, serum urea nitrogen.

r = −0.26; Tables S3 and S4). Correlation among filtration markers was strongest between B2M and cystatin C levels (r = 0.85 and r = 0.75) and weakest for BTP and urea nitrogen levels (r = 0.27 and r = 0.20). Adjusting for clearances moderately attenuated the correlations among filtration markers (Table S4).

Equation Development in the Guangzhou PD Study
Development Data Set, Internal Validation, and Combined Data Set
Equation development in the development data set and internal validation are described in Tables S5 and S6. Table 2 shows the final equations developed in the combined data set. Performance of the final equations in the combined data set is shown in Table S7.

Comparison to Published Equations
Coefficients of equations containing similar LMWP markers in the equations that we developed differ from equations published by Shafi et al,[10] in part due to the use of spline B2M and the absence of a coefficient for sex in equations for both mCl$_{UN}$ and mCl$_{UN-cr}$ and the

presence of a coefficient for creatinine in the single-marker LMWP equations for mCl$_{UN-cr}$ (Table S8). The performance of equations published by Shafi et al[10] in the Guangzhou PD Study combined data set is shown in Table S9.

Equation Validation in NECOSAD
Estimating mCl$_{UN}$ and mCl$_{UN-cr}$
Bias was within ± 1.0 mL/min and within ± 1.0 mL/min/1.73 m², respectively, for all equations (Table 3). eCl$_{B2M}$ and eCl$_{BTP-B2M}$ were unbiased across the range of eCl; other equations overestimated mCl at higher levels of eCl (Fig 1). Precision was between 1.5 and 2.1 mL/min for mCl$_{UN}$ and 1.8 and 2.3 mL/min/1.73 m² for mCl$_{UN-cr}$. Accuracy was nominally highest for eCl$_{B2M}$ and eCl$_{BTP-B2M}$ for mCl$_{UN}$ (80% and 81%, respectively) and mCl$_{UN-cr}$ (78% and 79%, respectively) and significantly higher than eCl$_{UN-cr}$ for mCl$_{UN}$ (72%) and mCl$_{UN-cr}$ (68%; Table 3). Accuracy was similar for HD and PD patients, except for eCl$_{B2M}$ and eCl$_{BTP-B2M}$, which were more accurate in HD patients estimating mCl$_{UN}$ (Table 4).

Table 2. Guangzhou PD Study Equations for Estimation of Residual Kidney Function in Dialysis Patients

Markers	Covariables	Equation
Equations to estimate mCl$_{UN}$, mL/min		
UN-creatinine	Age, sex	$60 \times cr^{-2.271} \times UN^{0.369} \times 0.989^{Age}$ (× 1.536 if male)
BTP		$98 \times BTP^{-2.128}$
B2M		For B2M ≤ 24 mg/L: $2 \times (B2M/24)^{-0.678}$ For B2M > 24 mg/L: $2 \times (B2M/24)^{-2.880}$
Cystatin C		$571 \times cys^{-3.349}$
BTP-B2M		For B2M ≤ 24 mg/L: $16 \times BTP^{-1.02} \times (B2M/24)^{0.159}$ For B2M > 24 mg/L: $16 \times BTP^{-1.02} \times (B2M/24)^{-2.187}$
Equations to estimate mCl$_{UN\text{-}cr}$, mL/min/1.73m^2)		
UN-creatinine	Age, sex	$207 \times cr^{-2.539} \times UN^{0.334} \times 0.988^{Age}$ (× 1.427 if male)
BTP	Creatinine	$445 \times BTP^{-1.301} \times cr^{-1.274}$
B2M	Creatinine	For B2M ≤ 23 mg/L: $39 \times (B2M/23)^{0.144} \times cr^{-1.152}$ For B2M > 23 mg/L: $39 \times (B2M/23)^{-2.129} \times cr^{-1.152}$
Cystatin C	Creatinine	$1,53 \times cys^{-2.082} \times cr^{-1.228}$
BTP-B2M		For B2M ≤ 23 mg/L: $32 \times BTP^{-1.126} \times (B2M/23)^{0.271}$ For B2M > 23 mg/L: $32 \times BTP^{-1.126} \times (B2M/23)^{-2.133}$

Note: Coefficients for creatinine are in mg/dL; for BTP, B2M, and cystatin C, in mg/L.
Abbreviations and definitions: B2M, β$_2$-microglobulin; BTP, β-trace protein; cr, creatinine; cys, cystatin C; mCl$_{UN}$, measured clearance of urea nitrogen in mL/min; mCl$_{UN\text{-}cr}$, average measured clearance of urea nitrogen and creatinine in mL/min/1.73 m^2; UN, urea nitrogen.

The AUC to detect mCl$_{UN}$ > 2.0 mL/min and mCl$_{UN\text{-}cr}$ > 2.5 mL/min/1.73 m^2 was highest for eCl$_{B2M}$ (0.85 and 0.88, respectively) and eCl$_{BTP\text{-}B2M}$ (0.84 and 0.89, respectively (Fig 2; Table S10). Findings were similar in HD and PD patients (Table S10).

Among LMWP equations, eCl$_{B2M}$ and eCl$_{BTP\text{-}B2M}$ were more accurate than eCl$_{cys}$ to detect mCL$_{UN}$ > 2.0 mL/min (P = 0.02 and P < 0.01, respectively) and mCl$_{UN\text{-}cr}$ > 2.5 mL/min/1.73 m^2 (P < 0.01 and P = 0.04, respectively).

Table 3. Performance of Estimating Equations in the NECOSAD Cohort

Variables	Guangzhou PD Study Equations				Shafi et al[10] Equations
	RMSE[a]	Bias[b]	Precision[c]	Accuracy (95% CI)[d]	Accuracy (95% CI)[d]
Equations to estimate mCl$_{UN}$ (mL/min)					
		mL/min (95% CI)	mL/min (95% CI)		
UN-creatinine	0.694 (0.656 to 0.730)	0.8 (0.7 to 0.9)	2.1 (1.9 to 2.3)	72% (69% to 75%)	75% (72% to 78%)[e]
BTP	0.630 (0.594 to 0.665)	0.4 (0.3 to 0.5)	1.8 (1.6 to 1.9)	78% (75% to 80%)[f]	81% (78% to 83%)[e,g]
B2M	0.588 (0.549 to 0.622)	0.7 (0.6 to 0.8)	1.7 (1.5 to 1.8)	80% (77% to 83%)[f]	79% (76% to 81%)[g]
Cystatin C	0.667 (0.626 to 0.702)	−0.3 (−0.4 to −0.2)	2.0 (1.8 to 2.2)	75% (72% to 78%)	79% (76% to 82%)[e,g]
BTP-B2M	0.514 (0.483 to 0.545)	0.5 (0.4 to 0.6)	1.5 (1.4 to 1.8)	81% (78% to 84%)[f]	81% (78% to 84%)[g]
Equations to estimate mCl$_{UN\text{-}cr}$ (mL/min/1.73 m^2)					
		mL/min/1.73 m^2 (95% CI)	mL/min/1.73 m^2 (95% CI)		
UN-creatinine	0.606 (0.569 to 0.642)	0.7 (0.6 to 0.9)	2.2 (2.0 to 2.4)	68% (65% to 71%)	68% (65% to 72%)
BTP	0.550 (0.519 to 0.582)	0.2 (0.1 to 0.4)	2.1 (1.9 to 2.3)	72% (69% to 75%)[h]	71% (68% to 74%)
B2M	0.513 (0.482 to 0.546)	0.5 (0.4 to 0.6)	1.8 (1.7 to 2.0)	78% (75% to 80%)[f]	69% (66% to 72%)[i]
Cystatin C	0.572 (0.536 to 0.607)	−0.2 (−0.4 to −0.1)	2.3 (2.1 to 2.5)	71% (68% to 74%)	72% (69% to 75%)[g]
BTP-B2M	0.511 (0.478 to 0.543)	0.2 (0.1 to 0.4)	1.8 (1.6 to 2.0)	79% (77% to 82%)[f]	75% (72% to 78%)[e,g]

Note: n = 826. All associations between filtration marker and outcome are linear except for B2M (2-slope polynomial model, breakpoint for B2M at 24 [mCl$_{UN}$] and 23 [mCl$_{UN\text{-}cr}$] mg/L). UN-creatinine equations also contain age and sex as covariables. Of note, equations developed by Shafi et al[10] contained in part different covariables.
Abbreviations: B2M, β$_2$-microglobulin; BTP, β-trace-protein; CI, confidence interval; RMSE, root-mean-square error; mCl$_{UN}$, measured clearance of urea nitrogen in mL/min; mCl$_{UN\text{-}cr}$, average measured clearance of urea nitrogen and creatinine in mL/min/1.73 m^2; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; PD, peritoneal dialysis; UN, urea nitrogen.
[a]RMSE defined as the standard deviation of mean difference between (ln) measured and (ln) estimated clearance.
[b]Bias defined as the median difference between measured and estimated clearance.
[c]Precision defined as interquartile range of the differences between measured and estimated total clearance.
[d]Accuracy defined as the percentage of estimates within ± 2 units of measured clearance.
[e]Significance level of P < 0.05.
[f]Significance level of P < 0.001 for the difference between the accuracy of the corresponding equation and the UN-creatinine equation.
[g]Significance level of P < 0.05 for difference between the corresponding equation and the UN-creatinine equation published by Shafi et al.[10]
[h]Significance level of P < 0.05.
[i]Significance level of 0.01 for the difference between the accuracy of the corresponding equation and the similar Guangzhou PD Study equation (ie, same row).
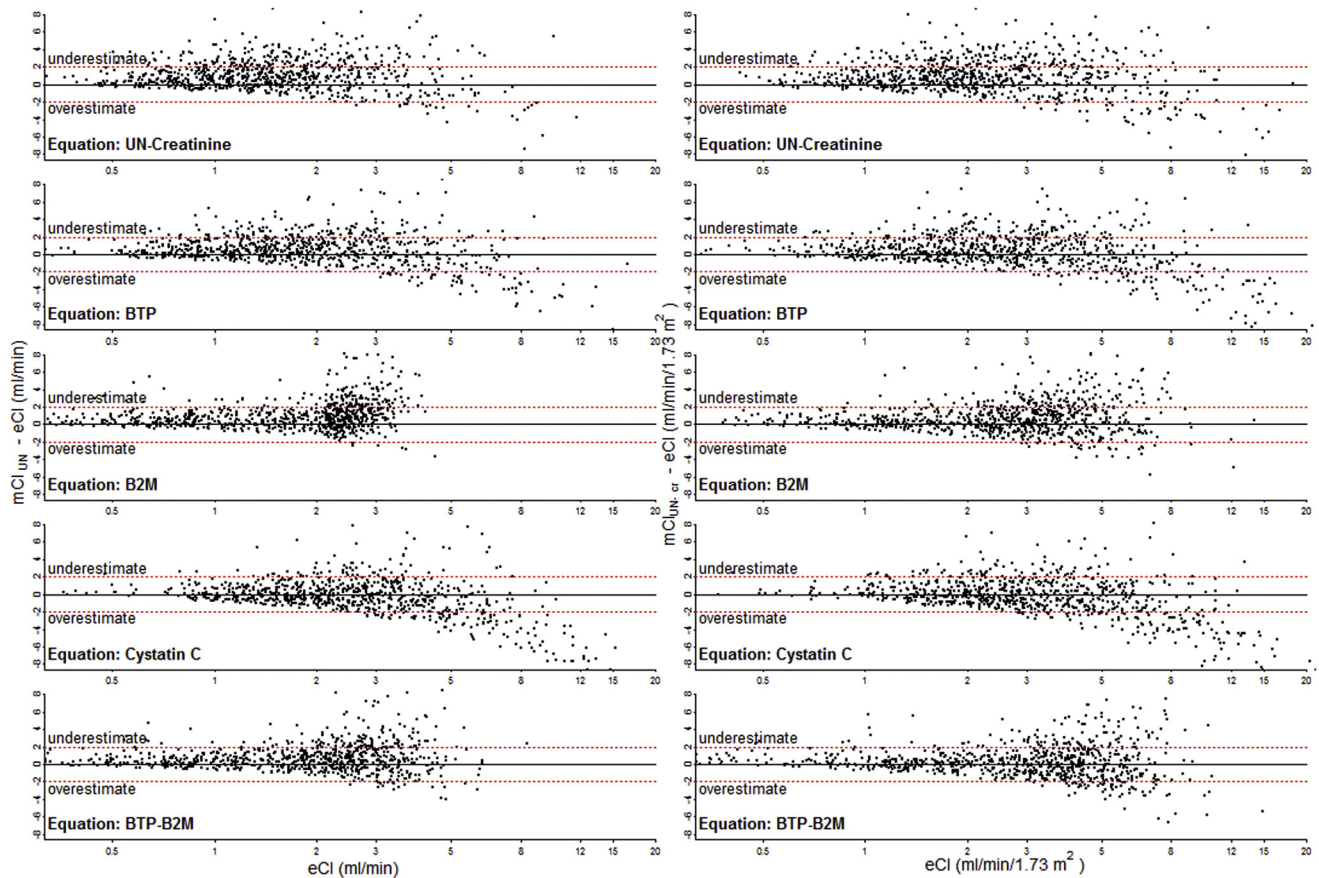
Figure 1. Associations between estimated clearances (eCls) and difference between measured (mCl) and eCl in the total Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) cohort (n = 826). Differences between mCls and eCls are presented on the y-axis; eCl, on the x-axis. The specific markers used in the eCl equations are indicated within the graphs. Positive differences indicate underestimation of mCl by the eCl; negative differences, overestimation. All associations between filtration marker and outcome are linear except for β_2-microglobulin (B2M; 2-slope polynomial model, breakpoint at 24 [mCl of urea nitrogen; mCl_{UN}] and 23 [mCl or urea nitrogen-creatinine; mCl_{UN-cr}] mg/L). Abbreviations: BTP, β-trace-protein; eCl (mL/min), estimated clearance of urea nitrogen in mL/min; eCl (mL/min/1.73 m²), estimated average clearance of urea nitrogen and creatinine in mL/min/1.73 m²; UN, urea nitrogen.

Comparison to Published Equations

In general, the LMWP equations of Shafi et al[10] were more accurate than the small-solute equations of Shafi et al[10] for both mCl_{UN} and mCl_{UN-cr} (Table 3). Our eCl_{B2M} and $eCl_{BTP-B2M}$ equations had similar accuracy to the equations of Shafi et al[10] for mCl_{UN}, but were significantly more accurate for mCl_{UN-cr}. Our eCl_{BTP} and eCl_{cys} equations were significantly less accurate than the equations of Shafi et al[10] for mCl_{UN}, but had similar accuracy for mCl_{UN-cr}.

DISCUSSION

We developed equations containing small solutes (urea nitrogen and creatinine) and LMWPs (BTP, B2M, and cystatin C) for the estimation of residual kidney function, assessed as mCl_{UN} and mCl_{UN-cr}, in a large cohort of prevalent Chinese CAPD patients and externally validated these equations in a large European cohort of incident HD and PD patients. All LMWP equations performed

moderately well in terms of bias, precision, and accuracy and outperformed the small-solute equation for the detection of clinically relevant residual kidney function thresholds. Equation performance was generally similar to results of Shafi et al,[10] except in our data, equations with B2M appeared to be consistently more accurate than equations with other LMWP markers. Results were generally consistent between PD and HD patients. These results add substantially to the evidence of validity and generalizability of estimation of residual kidney function from serum levels of endogenous LMWP filtration markers without urine collection.

Both small solutes and LMWPs are eliminated by glomerular filtration, and creatinine and cystatin C are recommended for use in GFR estimating equations in patients not treated by dialysis.[33] We hypothesized that LMWPs would be more useful than small solutes to estimate residual kidney function because there is less extrarenal elimination of LMWPs by dialysis than small solutes.

Table 4. Performance of mCl$_{UN}$ and mCl$_{UN-cr}$ Estimating Equations Developed in the Guangzhou PD Study Data Set and in NECOSAD, Comparing HD Versus PD Patients

Markers	Modality	Bias[a]	Precision[b]	Accuracy (95% CI)[c]	
Equations to estimate mCl$_{UN}$ (mL/min)					
		mL/min (95% CI)	mL/min (95% CI)		P
UN-creatinine	HD	0.8 (0.6 to 0.8)	2.1 (1.8 to 2.2)	73% (69% to 76%)	0.4
	PD	1.2 (0.8 to 1.3)	2.1 (1.8 to 2.5)	69% (63% to 75%)	
BTP	HD	0.2 (0.1 to 0.3)	1.7 (1.5 to 1.9)	79% (76% to 82%)	0.2
	PD	0.8 (0.6 to 1.0)	1.8 (1.6 to 2.2)	74% (69% to 80%)	
B2M	HD	0.6 (0.6 to 0.7)	1.5 (1.4 to 1.7)	82% (79% to 85%)	0.02
	PD	0.9 (0.6 to 1.1)	1.9 (1.6 to 2.3)	75% (69% to 80%)	
Cystatin C	HD	−0.5 (−0.6 to −0.3)	1.9 (1.8 to 2.3)	75% (71% to 78%)	0.6
	PD	0.1 (−0.2 to 0.3)	1.8 (1.6 to 2.2)	77% (71% to 82%)	
BTP-B2M	HD	0.4 (0.3 to 0.5)	1.5 (1.3 to 1.6)	84% (81% to 87%)	0.001
	PD	0.8 (0.6 to 1.0)	1.9 (1.6 to 2.2)	74% (69% to 80%)	
Equations to estimate mCL$_{UN-cr}$ (mL/min/1.73 m^2)					
		mL/min/1.73 m^2 (95% CI)	mL/min/1.73 m^2 (95% CI)		
UN-creatinine	HD	0.7 (0.5 to 0.8)	2.0 (2.0 to 2.5)	67% (63% to 71%)	0.4
	PD	0.9 (0.7 to 1.2)	2.0 (1.7 to 2.4)	71% (65% to 77%)	
BTP	HD	0.1 (−0.1 to 0.2)	2.0 (1.8 to 2.3)	73% (69% to 76%)	0.9
	PD	0.7 (0.5 to 1.0)	2.0 (1.7 to 2.2)	72% (66% to 77%)	
B2M	HD	0.4 (0.4 to 0.5)	1.8 (1.6 to 2.0)	79% (76% to 82%)	0.2
	PD	0.8 (0.6 to 1.0)	2.0 (1.7 to 2.3)	74% (69% to 79%)	
Cystatin C	HD	−0.4 (−0.6 to −0.3)	2.2 (2.0 to 2.5)	71% (68% to 75%)	0.99
	PD	0.1 (−0.1 to 0.4)	2.1 (1.8 to 2.5)	72% (66% to 78%)	
BTP-B2M	HD	0.1 (0.0 to 0.3)	1.8 (1.6 to 2.0)	79% (76% to 82%)	1.00
	PD	0.5 (0.3 to 0.7)	1.8 (1.4 to 2.1)	79% (74% to 84%)	

Note: Total N = 826; HD, n = 587; PD, n = 239. UN-creatinine equations also contain age and sex as covariables. All associations between filtration marker and mCl are linear except for B2M (2-slope polynomial model, breakpoint for B2M at 24 [mCl$_{UN}$] and 23 [mCl$_{UN-cr}$] mg/L). P value for the difference of accuracy of the corresponding equation in HD versus PD subcohort.

Abbreviations: B2M, β$_2$-microglobulin; BTP, β-trace-protein; CI, confidence interval; mCl$_{UN}$, measured clearance of urea nitrogen in mL/min; mCl$_{UN-cr}$, average measured clearance of urea nitrogen and creatinine clearance in mL/min/1.73 m^2; HD, hemodialysis; NECOSAD, Netherlands Cooperative Study on the Adequacy of Dialysis; PD, peritoneal dialysis. UN, urea nitrogen.

[a]Bias defined as the median difference between measured and estimated clearance.
[b]Precision defined as interquartile range of the differences between measured and estimated clearance.
[c]Accuracy defined as the percentage of estimates within ± 2 units of measured clearance.

BTP is produced primarily in the central nervous system.[34,35] Moderate removal by HD has only been reported for high-flux HD.[12,36] Clearance through PD is unknown. B2M and cystatin C are produced by nucleated cells.[37,38] Compared to BTP, B2M and cystatin C have lower molecular weight; low-flux HD eliminates neither marker but both can be removed by high-flux HD and PD.[16,36,39-41]

Prior studies have shown better performance of LMWPs than small solutes in estimating residual kidney function,[10,20,21,23] including one study of 160 CAPD patients in China using cystatin C.[22] Comparison of our results with these studies is limited due to differences in assays for the filtration markers and absence of external validation, except in the study by Shafi et al.[10] The generally similar performance of equations previously developed by Shafi et al[10] in a US population of predominantly HD patients and our study in a Chinese population of CAPD patients is strong evidence for the validity and generalizability of these equations. Of note, in contrast to our study, Shafi et al[10] did not detect substantial differences among LMWP equations. The equations that we developed differ slightly from the equations of Shafi et al,[10] which likely reflects

differences in study populations and dialysis modality in the cohorts used for equation development and equation development methods.

It is noteworthy that the BTP-B2M equations that we developed did not perform substantially better than the B2M equations without BTP. In principle, a multiple-marker LMWP equation would perform better than a single-marker equation due to a smaller contribution to error from variation in the non-GFR determinants of each marker.[42] Prior studies in people not treated by dialysis have shown better performance of a GFR estimating equation including both BTP and B2M compared to B2M alone.[28,43,44] Possibly the inability to detect improvement with a multiple-marker equation reflects measurement error in the reference test (nonsupervised timed urine collections). Similar findings in the study by Shafi et al[10] with more accurate measurements (supervised timed urine collections) may reflect the limited number of participants in the development database in that study.

We anticipate 2 clinical settings in which residual kidney function estimating equations might be useful. First, they could be used to reduce the frequency of urine
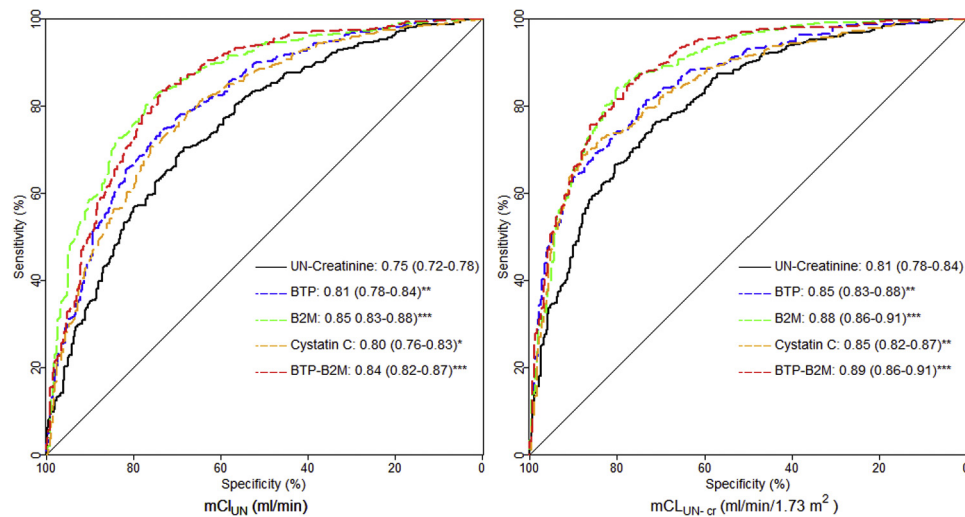
Figure 2. Receiver operating characteristic curves for the diagnostic accuracy of estimating equations to detect urea clearance in mL/min (Cl_{UN}) < 2 mL/min and average clearance of urea and creatinine in mL/min/1.73 m² (Cl_{UN-cr}) < 2.5 mL/min/1.73 m² in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) data set (n = 826), respectively. Sensitivity is presented on the y-axis; specificity, on the x-axis. Equations can be identified by the markers that were used. The area under the curve result for every equation is presented with confidence intervals in brackets. All associations between filtration marker and outcome are linear except for β₂-microglobulin (B2M; 2-slope polynomial model, breakpoint at 24 measured Cl_{UN} [mCl_{UN}] and 23 [mCl_{UN-cr}] mg/L). *P < 0.05; **P < 0.01; ***P < 0.001 of the difference between area under the curve of corresponding equation and UN-creatinine equation. Abbreviations: BTP, β-trace protein; UN, urea nitrogen.

collections for adjustment of the dialysis prescription, thereby reducing patient burden and potentially reducing costs. These considerations may be more relevant for countries with a high prevalence of PD patients, such as China. However, the accuracy of equations is not sufficient to make fine adjustments in PD prescription recommended by guidelines (eg, a 15% reduction in weekly effluent volume for each 1–mL/min/1.73 m² higher mCl_{UN}[45]). This suggests that residual kidney function estimating equations may be most useful as a screening test to determine whether urine collection for clearance measurement is necessary. Clinical trials will be necessary to evaluate these strategies.

Second, residual kidney function estimating equations could be used in settings when urine collection is not practical, such as in patients with voiding difficulties, but ascertainment of residual kidney function is important for medical decision making, such as whether iodinated contrast media can be administered. Our results suggest that a single-marker LMWP may be as accurate as a multiple-marker equation. The differences in accuracy among LMWPs appears small, so the decision as to which LMWP to measure would be influenced by the availability of laboratory methods and costs. Of note, the assays for BTP and B2M are not standardized, so it will be important to harmonize laboratory measurement procedures for application of the equations. Our study has several strengths. We developed equations in a large data set, which enabled us to assess the form of variables for the filtration markers and the need for covariables. We included patients with minimal urine output, providing a

wide range for serum concentrations of endogenous filtration markers and allowing application of the equations to patients with even a low level of residual kidney function. We assessed 2 small solutes and 3 different LMWPs, enabling us to test a wide spectrum of currently available filtration markers. All patients in the development data set were treated with CAPD; in contrast to HD, stable serum concentrations of endogenous filtration markers can be assumed. Because the external validation cohort included both HD and PD patients, we were able to address the question of applicability of our equations to both treatment modalities. The cohorts differed substantially in terms of age, body size, race, and level of residual kidney function, which enhances the generalizability of results. We used the same laboratory as Shafi et al[10] for measurement of serum LMWP concentrations, thus eliminating an important source of bias in comparing estimating equations from different studies.

Our study also has limitations. The reference tests, mCl_{UN} and mCl_{UN-cr}, reflect only small-solute clearances and may differ from measured GFR. However, standardized methods for assessing other measures of residual kidney function have not been defined, and few studies of residual kidney function have included measurement of exogenous filtration markers for assessment of GFR. As mentioned, urine collection was not supervised in both cohorts; therefore, errors in urine collection cannot be excluded. Modalities other than CAPD and low-flux HD were not frequently used in NECOSAD, so our results apply primarily to these modalities. We did not adjust for clinical conditions that could affect non-GFR determinants

such as inflammation. This could have had an impact on equation performance. Finally, we did not have longitudinal data to evaluate the performance of the equations in detecting change in mCl.

In conclusion, we present equations developed in a Chinese PD cohort to estimate residual kidney function from serum concentrations of LMWPs without urine collection in both European HD and PD patients. These findings confirm the findings of Shafi et al[10] and may have clinical implications for routine care for dialysis patients. Studies in other cohorts are necessary to compare the accuracy and clinical utility of these equations. In addition, future research should evaluate these equations to assess other measures of residual kidney function.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Analytical measurements characteristics in the Guangzhou PD Study.

Table S2: Baseline demographics of excluded patients.

Table S3: Correlations between clearances and filtration markers in the combined, development, and internal validation cohort of the Guangzhou PD Study.

Table S4: Correlations between clearances and filtration markers and partial correlations between filtration markers adjusted for clearances in the Guangzhou PD Study and NECOSAD.

Table S5: Comparison of root-mean-square error (RMSE) of equations in the Guangzhou PD Study development data set during equation development (n = 552).

Table S6: Comparison of root-mean-square error (RMSE) of equations in the Guangzhou PD Study internal validation data set during equation validation (n = 271).

Table S7: Performance of equations in the Guangzhou PD Study combined data set (n = 823).

Table S8: Intercept and coefficients for the estimating equations developed in the Guangzhou PD Study combined data set compared to similar equations from Shafi et al.[10]

Table S9: Performance of estimating equations published by Shafi et al[10] in the Guangzhou PD Study combined data set.

Table S10: Diagnostic accuracy of estimating equations to identify $mCl_{UN} < 2$ mL/min and $mCl_{Un-cr} < 2.5$ mL/min/1.73 m^2 BSA in total NECOSAD, hemodialysis, and peritoneal dialysis subcohort.

Figure S1: Flow chart for patient inclusion in the Guangzhou PD Study.

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