COMPARISON OF CYSTATIN-C-BASED FORMULAS FOR EVALUATION OF RESIDUAL RENAL FUNCTION IN PERITONEAL DIALYSIS PATIENTS

Suojian Zhang, Xu Zhang, Haitao Li, Juan Cao*
Department of Nephrology, Taixing People's Hospital, Taizhou 225400 China

ABSTRACT

Introduction*: The present study aims to compare three cystatin-C (cys C)-based formulas which evaluate residual renal function (RRF) in peritoneal dialysis (PD) patients.*

Materials and methods*: 94 patients who were undergoing regular PD treatment were enrolled. The average clearance of 24-h urea and creatinine was taken as the gold standard, which was called measured RRF (mRRF). RRF was also estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Hoek and Yang formulas. We compared the deviation and accuracy of estimated RRF (eRRF) calculated by the three formulas.*

Results*: CysC was not correlated with demographic characteristics, albumin, prealbumin, blood glucose, glycosylated hemoglobin, intact parathyroid hormone or high-sensitivity C-reactive protein, and negatively correlated with mRRF. The mean bias and limit of agreement were -3.9 (-0.7 to -7.1) ml/min/1.73 m2 for the CKD-EPI formula, -0.3 (2.6 to -3.2) ml/min/1.73 m2 for the Hoek formula and 0.9 (3.6 to -1.9)ml/min/1.73 m2 for the Yang formula. The Yang formula showed the smallest relative difference and the CKD-EPI formula showed the largest. Accuracy of the CKD-EPI formula was the worst and there was no difference in accuracy between the Hoek and Yang formulas within 30% and 50%.*

Conclusion*: The CKD-EPI formula showed the largest bias and the lowest accuracy. The Hoek formula showed the smallest mean bias and the Yang formula had the smallest relative differences. There was no difference between the Yang and Hoek formulas for accuracy within 30% and 50%. It may inappropriate to use the CKD-EPI formula to estimate RRF of PD patients.*

Keywords: *peritoneal dialysis, cystatin C, residual renal function, formula.*

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Introduction

Peritoneal dialysis (PD) is an important method of renal replacement therapy for uremic patients. Previous studies have shown that the rate of PD survivors is higher than that of hemodialysis survivors[1-3]. Residual renal function (RRF) has a crucial influence on quality of life and mortality among PD patients[4-6]. RRF is clinically calculated by the mean creatinine and urea clearance over 24-h and is adjusted for body surface area (BSA)[7]. However, patients must collect 24-h urine when they need estimate RRF, which is difficult, especially for older people and juveniles. Therefore, a more feasible way to assess RRF in PD patients is urgently required in routine clinical practice.

Cystatin C(cys C) is a 13-kD cysteine protease inhibitor and it is secreted at a constant level by all nucleated cells in the human body[8]. Cys C is filtered by the glomeruli, absorbed by proximal tubules and then catabolized entirely[9,10]. Serum cys C level is not influenced by diet, muscle mass or activity,

and is an ideal molecular marker reflecting renal function[11,12]. Inker et al.[13], Hoek et al.[14] and Yang et al.[15] have proposed cys C-based formulas to estimate RRF. The degree of accuracy and reliability of the three formulas are not known. This study aimed to validate the three cys C-based formulas for evaluation of RRF in PD patients.

Materials and methods

Patients

We recruited 94 patients (47 male and 47 female) who were undergoing continuous ambulatory PD or daytime ambulatory PD at the PD Center, Department of Nephrology, People's Hospital of Taixing, China between June and December 2018.

The inclusion standard were as follows:

- patients were receiving regular follow-up;
- duration of regular PD >3 months;
- age >18 years;
- 24-h urine volume >100 ml.

The exclusion criteria were as follows:

(1) peritonitis or other serious infection within 1 month of study initiation;

- malignant tumor;
- severe malnutrition;
- thyroid dysfunction;
- consumption of glucocorticoid, cimetidine and contraceptives within 2 weeks of study initiation;
- bleeding or bleeding tendencies within 1 week of study initiation.

Methods

Clinical information. Patient data were collected, including gender, age, height, weight, pre-existing renal diseases, and duration of PD. Urine and PD output fluid over 24-h were collected for analysis of cys C, urea and creatinine. The Jaffe method was applied to determine creatinine levels, the enzymatic method was used to test urea levels, and the latex-enhanced immunoturbidimetric method was applied to determine cys C levels in serum and dialysate. Biochemical data such as albumin, prealbumin, hemoglobin, high-sensitivity C-reactive protein (hsCRP), blood glucose, glycosylated hemoglobin and intact parathyroid hormone (iPTH) were also collected.

Measurement of parameters related to adequacy of PD. All the recruited patients were trained by specialized nurses in our PD center. Patients collected 24-h urine and PD fluid at home or in the hospital. We used PD Adequest 2.0 software to calculate normalized protein catabolic rate (nPCR), weekly creatinine clearance (CCR) and Weekly urea clearance index (Kt/V).

Measurement of RRF

RRF was calculated by averaging creatinine and urea clearance and adjusting for BSA(7). We used the Gehan and George formula in PD Adequest 2.0 software to calculate BSA[16].

$$RRF[7]=\frac{1}{2}\left[\frac{UrineCR(umol/L)}{SerumCR(umol/L)}+\frac{UrineUrea(mmol/L)}{SerumUrea(mmol/L)}\right]\times\frac{UrineVolum(ml)}{1440}$$

$$BSA[16]=0.0235\times height\ (cm)^{0.44246}\times weight\ (kg)^{0.51456}$$

Cys C-based formula for evaluation of RRF. The first formula is Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, the second formula is Hoek formula and the last formula is Yang formula[13]:

$$eRRF=133\times\left(\frac{CysC}{0.8}\right)^{-1.328\times}0.996^{Age}\ [\times 0.932\ \text{if female}]$$

Hoek's formula[14]:

$$eRRF=-0.55+22\left(\frac{1}{Cys\ C}\right)$$

Yang's formula[15]:

$$eRRF=\{\sinh[\ln(6.736-0.566\times Cys\ C)]\}^2$$

Statistical analysis

All data were analyzed by SPSS version 25.0. Normally distributed data were presented as the mean ± standard deviation and non-normally distributed data were presented as medians (1/4, 3/4). The Chi-square test was applied for comparison of rates. The nonparametric rank-sum test was applied to compare the differences among the three groups. Spearman's rank correlation coefficient or Pearson's correlation coefficient was used to describe the correlations. We used the Bland-Altman plot to assess the bias and degree of agreement between eRRF and mRRF graphically[17]. Absolute deviation was defined as the differences between mRRF and eRRF and the relative deviation was calculated by(the following formula:|mRRF-eRRF|)/mRRF. The percentage of eRRF within 30% or 50% of mRRF was used to express the accuracy. We used the receiver operating characteristic (ROC) curve to assess specificity and sensitivity of eRRF calculated by cys C-based formulas[18]. mRRF <2.0 ml/min/1.73 m^2 was taken as a significant RRF loss(19). The area under the curve (AUC) was applied to analyze the diagnostic value of different formulas. The level of significance was $P<0.05$.

Results

Patient characteristics

We enrolled 94 patients (47 male and 47 female). Their mean age was 51.62±9.67 years, height 162.94±9.24 cm and weight 61.33±10.68 kg. The duration of PD was 16.5±5.31 months. The main primary diseases leading to renal failure were chronic glomerulonephritis (38; 40.43%), hypertensive nephropathy (23; 24.47%), diabetic nephropathy (15; 15.96%) and other diseases (18; 38.30%). The serum level of cys C was 7.12±1.45 mg/L, serum level of creatinine was 980.86±303.30 mmol/L and serum level of urea was 21.26±5.58 mmol/L. The level of cys C was 0.71 (0.57-1.03) mg/L, creatinine was 567.5 (443-731) mmol/L and urea was 17.50 (14.40-20.76) mmol/L in 24-h dialysis fluid. The RRF was 2.54±1.79 ml/min/1.73 m^2, Kt/V was 1.88±0.45 and weekly CCR was 58.81±15.99 L/week/1.73 m^2 (Table 1).

Correlation analysis

Table 2 shows that serum cys C was not associated with age, gender, height, weight, BSA, fasting blood glucose or glycosylated hemoglobin. In contrast, serum creatinine showed significant associations with gender, age, height, weight, BSA, fasting blood glucose and glycosylated hemoglobin. Neither serum cys C nor serum creatinine was associated with BMI, diabetes, serum albumin, serum prealbumin, nPCR, hsCRP or iPTH. Both serum cys C and serum creatinine correlated negatively with hemoglobin, 24-h urine volume, mRRF, residual renal Kt/V, total Kt/V, residual renal CCR and total CCR. Conversely, both serum cys C and serum creatinine correlated positively with 24-h infused fluid volume, 24-h output fluid volume, dialysis fluid cys C, dialysis fluid creatinine and dialysis fluid urea. Serum cys C correlated positively with PD Kt/V and PD CCR. Serum creatinine showed no associations with PD Kt/V and PD CCR.

Validation and comparison of formulas

We used a Bland-Altman plot to assess the bias and degree of agreement between eRRF and mRRF (Table 3 and Figure 1). eRRF was 6.41±1.95 ml/min/1.73 m^2 for the CKD-EPI formula, 2.82±0.84 ml/min/1.73 m^2 for the Hoek formula and 1.68±1.11 ml/min/1.73 m^2 for the Yang formula. The mean bias in eRRF was highest for the CKD-EPI formula and lowest for the Hoek formula. The Yang formula underestimated RRF, while the CKD-EPI and Hoek

Characteristics	Results
Male/female	47 (50%) /47(50%)
Age (years)	51.62±9.67
Height (cm)	162.94±9.24
Weight (Kg)	61.33±10.68
BMI (Kg/m^2)	23.02±2.98
BSA (m^2)	1.66±0.18
Time on peritoneal dialysis (month)	16.5 (5,31)
Primary disease	
Chronic glomerulonephritis	38
Hypertensive nephropathy	23
Diabetic nephropathy	15
Other	18
Serum cystatin C (mg/L)	7.12±1.45
Serum creatinine (μmol/L)	980.86±303.30
Serum urea (mmol/L)	21.26±5.58
Serum urea (mmol/L)	21.26±5.58
Serum Albumin (g/L)	40.44±3.57
Serum prealbumin (mg/L)	340.46±76.23
nPCR (g/Kg.d)	0.90±0.19
Hemoglobin (g/L)	109.70±17.59
iPTH (pg/ml)	270.65 (118.90, 416.35)
hsCRP(mg/L)	3.0 (1.41,4.0)
Fasting blood-glucose (mmol/L)	5.42±1.54
Glycosylated hemoglobin (%)	5.7 (5.1,6.2)
24-h urine volume (ml)	800 (400,1200)
24-h infused fluid volume (ml)	6000 (6000, 8000)
24-h output fluid volume (ml)	6732 (6142,8407)
Dialysis fluid cystatin C (mg/L)	0.71 (0.57,1.03)
Dialysis fluid creatinine (μmol/L)	567.5 (443,731)
Dialysis urea (mmol/L)	17.50 (14.40, 20.76)
mRRF [ml/min.1.73m^2]	2.54±1.79
Peritoneal dialysis Kt/V	1.34±0.37
Residual renal Kt/V	0.54±0.37
Total Kt/V	1.88±0.45
Peritoneal dialysis CCR [L/ (week.1.73m^2)]	33.25±9.80
Residual renal CCR [L/ (week.1.73m^2)]	25.56±18.05
Total CCR [L/ (week.1.73m^2)]	58.81±15.99

Table 1: Patient characteristics.
Notes: BMI, body mass index; BSA, body surface area; nPCR, normalized protein catabolic rate; iPTH, intact parathyroid hormone; hsCRP, high-sensitivity C-reactive protein; mRRF, measured renal residual function; Kt/V, urea clearance index; CCR, creatinine clearance.

formulas overestimated RRF. The Yang formula showed the narrowest limit of agreement in the Bland-Altman plots. We used the nonparametric rank-sum Friedman test to compare the relative deviations among the three groups. Relative deviations among the three groups were different (Z=85.04, P<0.001). We used a nonparametric Wilcoxon rank-sum test to compare relative deviations further. The relative deviation of the Yang formula was the smallest and that of the CKD-EPI formula was the largest (CKD-EPI vs Hoek formula, Z= −8.124, P<0.001; CKD-EPI vs Yang formula, Z= −7.725, P<0.001; Hoek vs Yang formula, Z= −2.438, P=0.015).

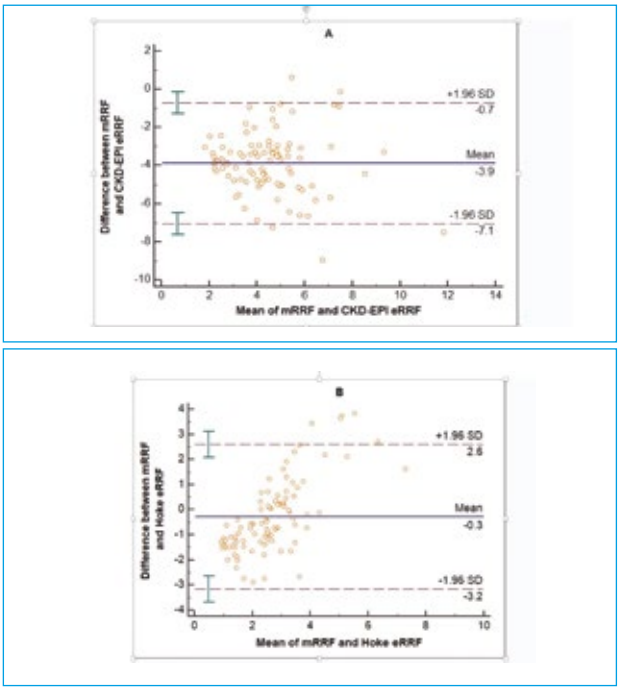
	Serum cystatin C		Serum creatinine	
	r	p	r	p
Gender	-0.142	0.172	-0.321	0.002
Age	-0.153	0.140	-0.452	0.000
Height	0.191	0.066	0.423	0.000
Weight	-0.042	0.686	0.319	0.002
BMI	-0.101	0.334	0.102	0.328
BSA	0.102	0.328	0.383	0.000
Time on peritoneal dialysis	0.133	0.202	-0.065	0.532
Presence of diabetes	-0.093	0.375	-0.059	0.569
Serum albumin	-0.119	0.253	-0.065	0.533
Serum prealbumin	0.168	0.105	0.191	0.063
Hemoglobin	-0.326	0.001	-0.388	0.000
nPCR	0.027	0.799	-0.088	0.401
hsCRP	-0.014	0.892	-0.032	0.762
iPTH	0.082	0.435	-0.095	0.362
Fasting blood-glucose	-0.141	0.176	-0.234	0.023
Glycosylated hemoglobin	-0.198	0.059	-0.298	0.004
24-h urine volume	-0.574	0.000	-0.375	0.000
24-h infused fluid volume	0.480	0.000	0.349	0.001
24-h output fluid volume	0.458	0.000	0.335	0.001
Dialysis fluid cystatin C	0.449	0.000	0.254	0.013
Dialysis fluid creatinine	0.633	0.000	0.811	0.000
Dialysis urea	0.277	0.007	0.456	0.000
mRRF	-0.619	0.000	-0.534	0.000
Peritoneal dialysis Kt/V	0.334	0.001	0.027	0.798
Residual renal Kt/V	-0.616	0.000	-0.522	0.000
Total Kt/V	-0.231	0.025	-0.408	0.000
Peritoneal dialysis CCR	0.364	0.000	0.088	0.402
Residual renal CCR	-0.619	0.000	-0.535	0.000
Total CCR	-0.476	0.000	-0.550	0.000

Table 2: Correlation analysis.
Notes: BMI, body mass index; BSA, body surface area; nPCR, normalized protein catabolic rate; iPTH, intact parathyroid hormone; hsCRP, high-sensitivity C-reactive protein; mRRF, measured renal residual function; Kt/V, urea clearance index; CCR, creatinine clearance.

The accuracy within 30%/50% was 6.38%/10.64% for the CKD-EPI formula, 34.04%/56.38% for the Hoek formula and 35.11%/61.7% for the Yang formula. The accuracy within 30% and 50% for the CKD-EPI formula was worse than that for the Hoek formula (30%: χ^2=22.30, P<0.001; 50%: χ^2=44.14, P<0.001) and Yang formula (30%: χ^2=23.59, P<0.001; 50%: χ^2=53.08, P<0.001). There was no significant difference in accuracy within 30% and 50% between the Hoek and Yang formulas (30%: χ^2=0.024, P=0.878; 50%: χ^2=0.550, P=0.458).The AUC, sensitivity and specificity of the three formulas are presented in Table 4 and Fig. 2. For the CKD-EPI formula, AUC was 0.808 (95% CI 0.719-0.897) (P<0.001), sensitivity was 0.684 and specificity was 0.784. The corresponding values for the Hoek formula were 0.805 (95% CI 0.712-0.897) (P<0.001), 0.807 and 0.703. The corresponding values for the Yang formula were 0.813 (95% CI 0.725-0.902) (P<0.001), 0.737 and 0.811.

Formula	RRF [ml/(min.1.73m^2)]	bias (limit of agreement)	Relative difference (%)	Accuracy within 30%	Accuracy within 50%
CKD-EPI	6.41±1.95	-3.9 (-0.7, -7.1)	198.6 (97.2,388.9)	6.38%	10.64%
Hoek	2.82±0.84	-0.3 (2.6, -3.2)	44.7 (20.1,117.9)	34.04%	56.38%
Yang	1.68±1.11	0.9 (3.6, -1.9)	40.1 (23.41,66.45)	35.11%	61.70%

Table 3: Bias and accuracy of RRF predictive formulas.
Note: RRF, residual renal function, CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.



Discussion

The assessment of RRF is essential for PD patients. Some studies have shown that rapid decline in RRF increases the risk of anuria and mortality[20,21].

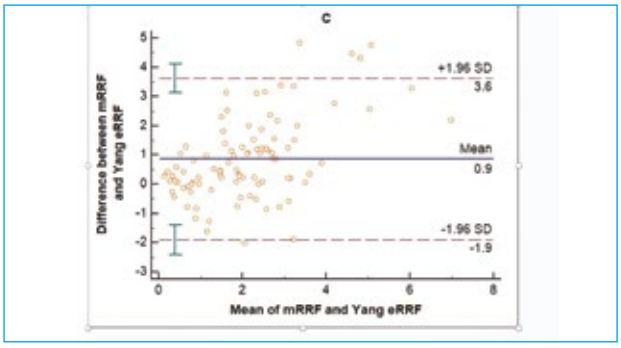


Fig. 1: Bland-Altman plots for differences between eRRF and mRRF in patients on PD. The x axis shows mean mRRF and eRRF and the y axis shows the difference in ml/min/1.73 m2 between mRRF and eRRF derived from the CKD-EPI (**A**), Hoek (**B**) and Yang (**C**) formulas. The mean difference (solid line) and limits of agreement (dotted lines) are also plotted.

RRF cutoff [ml/ (min.1.73m^2)]	eRRF formula	AUC	95% CI	p	Sensitivity	Specificity
6.08	CKD-EPI	0.808	0.719-0.897	<0.001	0.684	0.784
2.52	Hoek	0.805	0.712-0.897	<0.001	0.807	0.703
1.49	Yang	0.813	0.725-0.902	<0.001	0.737	0.811

Table 4: ROC analyses for CKD-EPI, Hoek and Yang formulas in PD patients.+.
Note: RRF, residual renal function; eRRF, estimate RRF; AUC, area under the curve; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

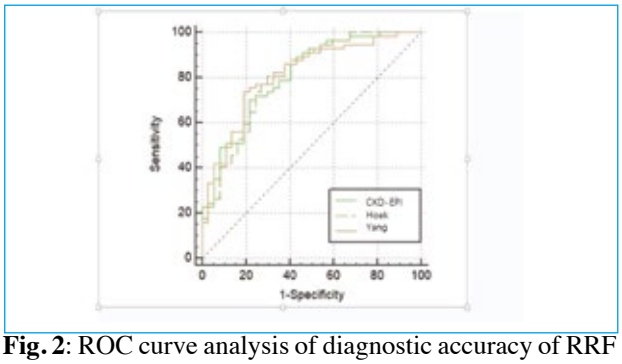


Fig. 2: ROC curve analysis of diagnostic accuracy of RRF estimated from CKD-EPI, Hoek and Yang formulas in PD patients. mRRF <2 ml/min/1.73 m2 was seen as significant renal loss.

Thus, it is necessary to monitor RRF regularly in PD patients so that some possible risk factors damaging RRF can be found and treated. Inulin clearance can accurately reflect RRF[22]. However, it is not used routinely in clinical practice because of its cumbersome operation and expense. Radioisotopic measurement of RRF is another reliable and accurate method to assess renal function[23]. However, Carter[24] found that 51 Cr-EDTA clearance may overestimate RRF in PD patients. Moreover, it is also expensive and rarely used among PD patients. CCR and urea clearance over a 24-h period are often applied to estimate RRF in PD patients. However, this method requires accurate collection of 24-h urine volume, which imposes a substantial burden on patients, especially elderly patients. This suggests that a simple and reliable way to estimate RRF is needed in PD patients. Some researchers have developed cys C-based formulas to evaluate RRF[13-15]. In this study, we compared three cys C-based formulas for evaluation of RRF in PD patients.

In our study serum cys C level in 94 PD patients was 7.12±1.45 mg/L. Serum cys C was not associated with gender, age, height, weight or BSA. In contrast, serum creatinine was negatively related to gender and age and positively related to height, weight and BSA. Serum creatinine is closely related to the total amount of muscle in the body, and female, older and shorter-stature people have less muscle; therefore, serum creatinine is affected by demographic characteristics[25]. In contrast, serum cys C was not influenced by demographic characteristics in our study, which is coincident with the study by Zhong et al.[26]. We also found that serum cys C was not associated with glycosylated hemoglobin or fasting blood glucose but serum creatinine showed a negative correlation with glycosylated hemoglobin and fasting blood glucose.

A recent study found that low creatinine level is related to impaired fasting blood glucose, because serum creatinine increases with additional exercise[27]. This suggests that serum creatinine is affected by blood glucose and serum cys C is not influenced by blood glucose. Yang et al.[15] and Zhong et al.[26] found negative correlation between cys C and prealbumin, but no correlation was found in our study. This may be because the nutritional status of PD patients in our study was better. Both serum cys C and creatinine were negatively associated with hemoglobin in our study, which may be attributed to the high incidence of anemia in patients with lower RRF[28]. Neither serum cys C nor serum creatinine was associated with iPTH or hsCRP. In our study, serum cys C was negatively associated with 24-h urine volume, residual renal Kt/V, total Kt/V, residual renal CCR, total CCR and RRF. Serum cys C was positively associated with the level in PD fluid, 24-h infused fluid volume, 24-h output fluid volume, PD Kt/V and PD CCR. This indicates that serum cys C and the amount of cys C removed by PD fluid increase with RRF loss. Previous researches have shown that serum cys C is mainly excreted by

kidneys and the amount of cys C removed by the PD fluid is limited in PD patients[29,30]. Therefore, even though the amount of cys C removed by PD fluid increases with RRF lost, it cannot offset the decreased amount of cys C removed by the kidneys.

In our study, the bias and relative deviation of the CKD-EPI formula were the largest, with an estimated value that was 2-3-times higher than the measured one. The accuracy within 30% and 50% of the CKD-EPI formula were the lowest among the three formulas. We supposed that the CKD-EPI formula may not be applicable for the PD patients. This may be because the CKD-EPI formula is derived from the non-dialysis population[13], whose renal function is better than in PD patients.

Hoek et al.[14] and Yang et al.[15] discovered that the Modification of Diet in Renal Disease (MDRD) formula overestimates RRF in PD patients, suggesting that the formula for evaluation of RRF in PD patients needs to be derived from a PD cohort. The Hoek[14] and Yang[15] formulas were developed from PD populations, so their bias is smaller and their accuracy is better. We found that the Yang formula underestimated RRF and the Hoek formula overestimated RRF; the Yang formula showed smaller deviation, similar to the results of Yang et al.[15] and Zhong et al.[26]. In our study, the accuracy within 30% and 50% of the Yang formula was higher than that of the Hoek formula, but there was no significant difference between them, which was similar to the results of Zhong et al.[26].

We calculated sensitivity and specificity using a cutoff value for RRF of 2.0 mL/min/1.73 m^2. The AUC of the Yang formula was the largest. However, there was no significant difference among the AUCs of the three formulas (CKD-EPI vs Hoek: Z=0.224, P=0.822; CKD-EPI vs Yang: Z=0.318, P=0.751; Hoek vs Yang: Z=0.441, P=0.659). The specificity and sensitivity of the three formulas were similar.

There were some deficiency to our study. It was a single-center research with few research samples included. Furthermore, the mean clearance rate of urea creatinine over 24- h was used as the gold standard of RRF, which might be not consistent with the real RRF of PD patients. Further researches are needed to explore whether RRF calculated from cys C is associated with patient outcomes.

Conclusions

Cys C was not correlated with gender, height, weight, age, BSA or BMI. It correlated negatively with RRF. Among the three formulas based on cys C, CKD-EPI had the largest deviation and the lowest accuracy. The Hoek formula showed the smallest mean bias and the Yang formula had the smallest relative differences. The accuracy of the Hoek and Yang formulas was similar. The clinical feasibility of the Yang and Hoek formulas should be further studied.

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Corresponding Author:
Juan Cao
Email: 563426261@qq.com
(China)