Not Residual Kidney Removal but Peritoneal Clearance Dominates in Uric Acid Control in Peritoneal Dialysis

Xi Xiao
Sun Yat-sen University First Affiliated Hospital
Hongjian Ye
Sun Yat-sen University First Affiliated Hospital
Chunyan Yi
Sun Yat-sen University First Affiliated Hospital
Jianxiong Lin
Sun Yat-sen University First Affiliated Hospital
Yuan Peng
Sun Yat-sen University First Affiliated Hospital
Xuan Huang
Sun Yat-sen University First Affiliated Hospital
Meiju Wu
Sun Yat-sen University First Affiliated Hospital
Haishan Wu
Sun Yat-sen University First Affiliated Hospital
Haiping Mao
Sun Yat-sen University First Affiliated Hospital
Xueqing Yu
Sun Yat-sen University First Affiliated Hospital
Xiao Yang (yangxsysu@126.com)
The First Affiliated Hospital, Sun Yat-sen University https://orcid.org/0000-0003-0437-2015

Research article

Keywords: Peritoneal dialysis, Uric acid, Clearance

Posted Date: December 7th, 2019

DOI: https://doi.org/10.21203/rs.2.18171/v1

Version of Record: A version of this preprint was published at BMC Nephrology on April 25th, 2020. See the published version at https://doi.org/10.1186/s12882-020-01800-1.

Abstract

Background: There's a paucity of systematic study focusing on clearance of uric acid (UA) in peritoneal dialysis (PD). The aim of this study was to investigate peritoneal UA removal and its influencing factors in PD patients.

Methods: This was a cross-sectional study. Patients who performed peritoneal equilibration test (PET) and Kt/V from April 1, 2018 to August 31, 2019 were enrolled. The demographic data, clinical and laboratory parameters including the UA levels in the dialysate, blood and urine samples were collected.

Results: Finally, there were 180 prevalent PD patients (52.8% male). Compared with normal serum UA (SUA) group, the hyperuricemia group showed significantly lower peritoneal UA clearance (39.1±6.2 vs. 42.0±8.0 L/week/1.73m2, P=0.008). Peritoneal UA clearance but not residual kidney removal was revealed to be independently associated with continuous [standardized coefficients (β) -0.21, 95% confidence interval (CI) -0.07, -0.006] and categorical SUA level [odds ratio (OR) 0.91, 95% CI 0.84,0.98]. Furthermore, the higher (high or high-average) transporters showed greater peritoneal UA clearance than the lower (low or low-average) transporters (42.0±7.0 vs. 36.4±5.6 L/week/1.73 m2, P<0.001). Among the widely used solute removal indicators, peritoneal creatinine clearance (CCL) performed best to predict higher peritoneal UA clearance in ROC analysis [area under curve (AUC) 0.96, 95% CI 0.93-0.99]. In multiple linear regression, lower albumin level (β -0.06, 95%CI -2.09, -0.19), higher transporters (β 0.06, 95%CI 0.05, 1.69) and greater peritoneal CCL (β 0.95, 95%CI 0.81, 0.93) were independently associated with higher peritoneal UA clearance.

Conclusions: It was peritoneal removal but not residual kidney function that dominated in SUA balance of PD patients. Albumin level, peritoneal transport type and peritoneal CCL were identified as independent determinants of peritoneal UA clearance.

Background

Uric acid (UA, 2,6,8-trihydroxypurine; C5H4N4O3), as the end-products of endogenous and dietary purine metabolism for the lack of uricase, is a weak diprotic acid of two dissociable protons with a pKa1 of 5.4 and pKa2 of 10.3, respectively [1]. At a physiology PH of 7.4, 98% of the UA was demonstrated to exist as monosodium urate in the extracellular milieu [2]. Since UA is poorly soluble in aqueous media and can't freely move through the cytomembrane, it is excreted mainly by means of the UA transporters substantially consisting in the kidney and intestines. It's reported that about 70% of UA is excreted by kidney and 30% by gastrointestinal tract [3, 4]. Owing to the leading role of kidney in excreting UA and maintaining the balance of UA in internal environment, almost 90% hyperuricemia is caused by the impairment of renal UA excretion [5]. In the same way, the hyperuricemia was common in patients of chronic kidney disease (CKD) which showed a five-fold increase of prevalence of hyperuricemia than the patients with normal renal function [6].

Peritoneal dialysis (PD), a widespread used dialysis modality, is becoming increasingly important in renal replacement therapy of patients with end-stage renal disease for its distinct strength in economic cost and improvements in techniques and patient survival [7]. The prevalence of hyperuricemia was increased as renal function declined, which ranging from 40–70% in CKD stages 1–5 and was similar in hemodialysis (HD) and PD patients [8–10]. The SUA level in PD population was reported at a range of 6.7–8.6 mg/dL (mean 7.6 mg/dL) and increased over the lengthening of dialysis vintage [9, 11]. As for the role of SUA in PD patients, our previous study demonstrated that the higher SUA level was independently associated with mortality in PD patients [12, 13]. In fact, apart from using UA lowering agents or optimizing the dietary and lifestyle factors [14], the dialysis therapy itself can play a role in SUA control in PD populations [15]. However, whether the peritoneal UA clearance or residual renal function plays a dominant role in SUA control in PD patients is still indeterminate. Since there are little studies referring to UA clearance on PD modality especially excluding the effects of medical history of using UA lowering agents, we aimed to conduct a systematic study to investigate the role of peritoneal UA clearance in SUA control and its relative influencing factors in PD patients.

Methods

Study population

This was a single center cross-sectional study. Patients who performed peritoneal equilibration test (PET) and Kt/V test in our PD center from April 1, 2018 to August 31, 2019 were enrolled. The inclusion criteria included prevalent patients older than 18 years old and have initiated PD therapy at least 1 month at the time of performing PET and Kt/V tests. The patients who had taken UA lowering agents within 1 month before the PET and Kt/V tests, transferred from the long-term HD (more than 3 month), failed renal transplant, or with malignant tumors were excluded. All patients enrolled used the standard lactate-glucose peritoneal dialysate (1.5%, 2.5%, or 4.25% dextrose, from Baxter, Guangzhou, China). The relevant clinical parameters were tested in the clinical lab of our hospital by standard methods. All patients had signed informed consent. And the study has conformed to the ethical principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee.

Data collection

The demographic data collected included age, gender, body mass index (BMI), diabetes, cardiovascular disease (CVD), primary kidney disease and so on. Data of the first PET and Kt/V tests during the study period were collected. The PD related information included the dialysis vintage, dialysis dose, average glucose concentration of dialysate, measured glomerular filtration rate (mGFR), Kt/V, weekly total creatinine clearance (CCL), 24h residual urine volume, normalized protein catabolic rate (nPCR) and standard PET data covering the urea, creatinine and UA level in dialysate, blood and urine samples with 2L of 2.5% dextrose dialysate dwelling for 0, 2 or 4 h (0 h was the time point in PET test when all of the 2L

dialysate flow into abdominal cavity, and the duration of this process was recorded). The PD patients was classified into high (H), high average (HA), low average (LA) or low (L) transporters according to the classical Twardowski's criterion [16]. And the clinical parameters included the blood pressure, hemoglobin, neutrophil/lymphocyte, high sensitivity C-reactive protein, alkaline phosphatase, serum albumin, prealbumin, corrected calcium, phosphorus, total cholesterol, triglyceride, serum urea nitrogen, creatinine, SUA and intact parathyroid hormone. The medication history was also collected according to the follow-up records of patients who would regularly revisit our PD center for condition assessing and therapeutic regimen adjustment about once 1-3 months. CVD was defined as angina, myocardial infarction, congestive heart failure, cerebrovascular events or peripheral vascular disease [17]. The charlson comorbidity score was used to evaluate the comorbidity condition of patients enrolled [18]. Male with SUA over 420 μmol/L or female over 360 μmol/L was identified as hyperuricemia status. The data of mGFR, Kt/V, CCL and nPCR were obtained using the PD Adequest software 2.0 (Baxter, Deerfield, IL). The body surface area (BSA) was calculated on the basis of the widely used DuBois & DuBois formula [19], and the UA clearance was calculated according to the formulate as follows:

$$\text{Renal UA clearance (L/week/1.73m}^2\text{)} = \frac{\text{UA}_{\text{urine}}\ (\mu\text{mol/L}) \times 24\text{h urine output (L)} \times 7 \times 1.73\ (m^2)}{\text{SUA}\ (\mu\text{mol/L}) \times \text{BSA}(m^2)}$$

$$\text{Peritoneal UA clearance (L/week/1.73m}^2\text{)} = \frac{\text{UA}_{\text{dialysate}}\ (\mu\text{mol/L}) \times 24\text{h dialysate output (L)} \times 7 \times 1.73\ (m^2)}{\text{SUA}\ (\mu\text{mol/L}) \times \text{BSA}(m^2)}$$

$$\text{Total UA clearance} = \text{Renal UA clearance} + \text{Peritoneal UA clearance}$$

Statistical analysis

Patients enrolled were divided into 2 groups according to the peritoneal UA clearance. Data were presented as mean standard deviation for normally distributed continuous variables, median (interquartile range) for quantitative variables of skewed distribution and frequencies and percentages for categorical variables. Difference between the lower and higher peritoneal UA clearance group was analyzed by independent sample T-test for normally distributed continuous variables, Mann-Whitney U test for quantitative variables of skewed distribution and Chi-squared test for categorical variables. Pearson correlation or Spearman rank correlation test were used to evaluate the correlation between variables of normal or skewed distribution, respectively. Multiple linear regression and binary logistic regression were performed to explore the independent influencing factors of continuous and categorical SUA and peritoneal UA clearance, respectively. After excluding the potential effects of multicollinearity, the variables significant in the univariate analysis ($P < 0.05$) or possessed clinical correlation were selected into the final model. The performance of different small solute removal indicators for predicting higher peritoneal UA clearance were tested in the area under the ROC curve (AUC) analysis. A two-sided P value < 0.05 was regarded as statistically significant. All of the statistical analyses were conducted in the SPSS software (version 20.0).

Results

Patients’ characteristics

As shown in Fig. 1, there were 180 patients (52.8% of male) participating in the study in total. Baseline characteristics of patients enrolled was detailedly presented in Table 1. The patients had a mean age of 45.0 ± 13.4 years old and a median dialysis vintage of 1.6(1.4–19.8) month. The leading primary kidney disease was chronic glomerulonephritis (67.2%), followed by diabetic nephropathy (8.9%), hypertensive lesions (7.8%) and others (16.1%). Mean SUA and peritoneal UA clearance was 6.9 ± 1.2 mg/dL and 40.2 ± 7.1 L/week/1.73 m^2, respectively. At enrollment, there were 15.0% patients using diuretic during one month before the PET and Kt/V tests. The patients of higher peritoneal UA clearance were older, had a greater proportion of female and H transporters, smaller proportion of LA transporters, and had longer PD vintage, higher level of average glucose concentration of dialysate, peritoneal Kt/V, peritoneal CCL, corrected calcium and lower level of BMI, residual renal Kt/V, renal CCL, residual urine volume, serum albumin, and SUA.

Table 1

The characteristics of patients enrolled in the study.

Variables	Total (n = 180)	Lower peritoneal UA clearance (n = 90)	Higher peritoneal UA clearance (n = 90)	P value
Peritoneal UA clearance(L/week/1.73 m^2)	40.2 ± 7.1	34.6 ± 3.5	45.8 ± 5.0	–
Age (y)	45.0 ± 13.4	42.9 ± 13.2	47.1 ± 13.3	0.04
Male (n, %)	95(52.8)	55(61.1)	40(44.4)	0.04
Diabetes (n, %)	24(13.3)	13(14.4)	11(12.2)	0.83
CVD (n, %)	25(13.9)	10(11.1)	15(16.7)	0.39
Charlson comorbidity score	3(2–4)	2(2–4)	3(2–4)	0.09
Chronic glomerulonephritis (n, %)	121(67.2)	63(70.0)	58(64.4)	0.53
Diabetic nephropathy (n, %)	16(8.9)	8(8.9)	8(8.9)	1.00
Hypertensive kidney lesion (n, %)	14(7.8)	5(5.6)	9(10.0)	0.41
PD vintage (m)	1.6(1.4–19.8)	1.5(1.3–8.4)	2.3(1.4–49.9)	0.01
Average dialysate glucose concentration (%)	1.5(1.5–1.7)	1.5(1.5–1.5)	1.5(1.5–1.8)	< 0.001
DAPD (n, %)	12(6.7)	4(3.2)	8(4.8)	0.37
Total Kt/V	2.3 ± 0.5	2.2 ± 0.4	2.4 ± 0.6	0.03
Residual renal Kt/V	0.7 ± 0.5	0.8 ± 0.4	0.6 ± 0.5	0.02
Peritoneal Kt/V	1.7 ± 0.3	1.5 ± 0.3	1.8 ± 0.3	< 0.001
CCL (L/week/1.73 m^2)	76.1(60.4–93.1)	76.8(63.2–94.7)	74.7(59.0-91.5)	0.36
Residual renal CCL (L/week/1.73 m^2)	30.4(10.4–49.8)	38.3(20.4–56.1)	22.5(1.5–44.0)	< 0.001

Note: Values are presented as means ± standard deviation or median (interquartile range) for continuous variables and count (percentage) for categorical variables.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; CCL, weekly total creatinine clearance; CVD, cardiovascular disease; DAPD, Day Ambulatory Peritoneal Dialysis; HsCRP, high sensitivity C-reactive protein; iPTH, intact parathyroid hormone; mGFR, measured glomerular filtration rate; N/L, neutrophil to lymphocyte ratio; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; PET, peritoneal equilibration test; UA, uric acid;.

Variables	Total (n = 180)	Lower peritoneal UA clearance (n = 90)	Higher peritoneal UA clearance (n = 90)	P value
Peritoneal CCL (L/week/1.73 m^2)	46.1(41.0-51.3)	41.3(38.7–43.2)	50.9(48.0-56.6)	< 0.001
mGFR (mL/min/1.73 m^2)	3.1 ± 2.4	3.8 ± 2.4	2.3 ± 2.3	< 0.001
Residual urine volume (L)	0.700(0.300–1.200)	0.850(0.550–1.225)	0.555(0.050–1.100)	0.003
nPCR (g/kg/d)	0.889(0.769–1.076)	0.856(0.765–1.028)	0.934(0.785–1.126)	0.05
PET category (%)				
High	15(8.3)	1(1.1)	14(15.6)	0.001
High average	107(59.4)	47(52.2)	60(66.7)	0.07
Low average	54(30.0)	38(42.2)	16(17.8)	0.001
Low	4(2.2)	4(4.4)	0(0.0)	0.13
Systolic pressure (mmHg)	135.0 ± 18.0	134.6 ± 17.4	135.5 ± 18.7	0.73
Diastolic pressure (mmHg)	85.5 ± 14.2	87.5 ± 12.7	83.5 ± 15.4	0.06
Hemoglobin (g/dL)	11.2 ± 1.7	11.4 ± 1.6	11.0 ± 1.7	0.11
N/L	3.5(2.7–4.5)	3.2(2.6–4.2)	3.7(2.9–4.8)	0.11
HsCRP (mg/L)	1.4(0.5–4.7)	1.5(0.6–4.9)	1.3(0.5–4.8)	0.79
ALP (U/L)	82.0(69.0-104.8)	80.5(69.8-104.3)	85.5(68.0-110.3)	0.45
Serum albumin (g/dL)	3.7 ± 0.4	3.8 ± 0.3	3.5 ± 0.4	< 0.001
Serum prealbumin (mg/L)	351(320–402)	354(319–406)	347(319–387)	0.26
Corrected calcium (mg/dL)	9.2 ± 1.0	9.1 ± 0.6	9.3 ± 1.2	0.22

Note: Values are presented as means ± standard deviation or median (interquartile range) for continuous variables and count (percentage) for categorical variables.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; CCL, weekly total creatinine clearance; CVD, cardiovascular disease; DAPD, Day Ambulatory Peritoneal Dialysis; HsCRP, high sensitivity C-reactive protein; iPTH, intact parathyroid hormone; mGFR, measured glomerular filtration rate; N/L, neutrophil to lymphocyte ratio; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; PET, peritoneal equilibration test; UA, uric acid;.

Variables	Total (n = 180)	Lower peritoneal UA clearance (n = 90)	Higher peritoneal UA clearance (n = 90)	P value
Serum phosphorus (mg/dL)	4.5 ± 1.3	4.5 ± 1.1	4.5 ± 1.5	0.93
Total cholesterol (mg/dL)	193.4(162.4-228.2)	193.4(158.5-230.1)	193.4(166.3-228.2)	0.62
Triglyceride (mg/dL)	136.4(97.8-190.8)	142.1(102.7-196.8)	131.9(94.7-185.1)	0.27
Serum urea nitrogen (mg/dL)	45.5(37.5–55.7)	45.4 (37.7–55.8)	45.9(36.6–55.9)	0.91
Serum creatinine (mg/dL)	8.6(7.3–10.8)	8.4(7.1–10.8)	8.9(7.3–10.9)	0.75
Serum UA (mg/dL)	6.9 ± 1.2	7.2 ± 1.2	6.6 ± 1.2	< 0.001
iPTH (pg/mL)	256.2(149.4-401.4)	256.2(164.0-391.1)	258.0(139.6-454.3)	0.82
BMI (kg/m^2)	21.8 ± 3.2	22.6 ± 3.2	21.0 ± 3.0	0.001
Diuretic use (n, %)	27(15.0)	11(12.2)	16(17.8)	0.40

Note: Values are presented as means ± standard deviation or median (interquartile range) for continuous variables and count (percentage) for categorical variables.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; CCL, weekly total creatinine clearance; CVD, cardiovascular disease; DAPD, Day Ambulatory Peritoneal Dialysis; HsCRP, high sensitivity C-reactive protein; iPTH, intact parathyroid hormone; mGFR, measured glomerular filtration rate; N/L, neutrophil to lymphocyte ratio; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; PET, peritoneal equilibration test; UA, uric acid;.

Peritoneal UA removal and its relationship with SUA in PD patients

The distribution of SUA in PD patients was shown in Fig. 2a. The average mass transfer of urea, creatinine or UA with 2L of 2.5% dextrose dialysate for a dwell time of 0 or 4 hours of all PD patients were described in detail in Fig. 2b. Similar to the small molecular of urea and creatinine, the peritoneal mass transfer of UA was remarkably declined with the lengthening of dwell time. Different from the positive correlation between average UA mass transfer for 4 hours' dwell and SUA ($r = 0.55$, $P < 0.001$), the peritoneal UA clearance was found to be inversely correlated to the SUA ($r=-0.25$, $P = 0.001$) level (Fig. 2c and 2d). In comparison to normal SUA group, the hyperuricemia group showed significantly lower peritoneal UA clearance (39.1 ± 6.2 vs. 42.0 ± 8.0 L/week/1.73 m^2, $P = 0.008$). The further analysis of multiple linear regression (β -0.21, 95%CI -0.07, -0.006, $P = 0.02$) and binary logistic regression (OR 0.91,

95%CI 0.84, 0.98, P = 0.02) shown in Table 2 and Table 3 both revealed that it was not the residual kidney function of mGFR but the peritoneal UA clearance that was independently associated with SUA in PD patients.

Table 2
Associated factors of SUA in multiple linear regression.

Variables	**β (95%CI)**	**P value**
Age (y)	-0.17 (-0.03, -0.001)	0.04
Sex (M/F)	0.08 (-0.15, 0.54)	0.27
Diabetes	-0.05 (-0.70,0.33)	0.48
CVD	-0.08 (-0.81,0.25)	0.30
Using diuretics	-0.12 (-0.54, 0.40)	0.78
PD vintage (m)	-0.08 (-0.01, 0.004)	0.39
Mean arterial pressure (mmHg)	-0.02 (-0.01,0.01)	0.80
BMI (kg/m^2)	0.28 (0.05, 0.17)	< 0.001
Albumin (g/dL)	-0.05 (-0.62, 0.31)	0.51
nPCR (g/kg/d)	0.38 (1.11, 2.79)	< 0.001
mGFR ($mL/min/1.73\ m^2$)	-0.09 (-0.13, 0.04)	0.32
Peritoneal UA clearance ($L/week/1.73\ m^2$)	-0.21 (-0.07, -0.006)	0.02
Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; mGFR, measured glomerular filtration rate; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; SUA, serum uric acid; UA, uric acid.		

Table 3
Independent determinants of higher SUA in binary logistic regression.

Variables	Adjusted OR (95%CI)	P value
Age (y)	0.95 (0.92, 0.99)	0.005
Sex (M/F)	0.12 (-0.15, 0.54)	< 0.001
Diabetes	0.90 (0.29,2.74)	0.85
CVD	1.30 (0.38,4.44)	0.68
Using diuretics	0.94 (0.34, 2.60)	0.90
PD vintage (m)	1.00 (0.99, 1.02)	1.00
Mean arterial pressure (mmHg)	1.01 (0.98,1.04)	0.39
BMI (kg/m^2)	1.09 (0.95, 1.25)	0.21
Albumin (g/dL)	0.91 (0.32, 2.64)	0.86
nPCR (every 0.1 g/kg/d)	1.39 (1.12, 1.73)	0.003
mGFR ($mL/min/1.73\ m^2$)	0.99 (0.82,1.19)	0.88
Peritoneal UA clearance ($L/week/1.73\ m^2$)	0.91 (0.84, 0.98)	0.02

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; mGFR, measured glomerular filtration rate; nPCR, normalized protein catabolic rate; OR, odds ratio; PD, peritoneal dialysis; SUA, serum uric acid; UA, uric acid.

The relationship between peritoneal UA clearance and peritoneal transport characteristics

The distribution of the peritoneal UA clearance in different peritoneal transport characteristics was shown in Fig. 3a, which indicated a progressively increase of peritoneal UA clearance with the elevating of the peritoneal transport rate. It was revealed that the higher (H or HA) transporters possessed significantly higher peritoneal UA clearance than the lower (LA or L) transporters (42.0 ± 7.0 vs. 36.4 ± 5.6 $L/week/1.73\ m^2$, $P < 0.001$). Besides, as shown in Fig. 3b, the 4 h dialysate to plasm (D/P) UA was highly correlated with the 4 h D/P creatinine ($r = 0.97$, $P < 0.001$). And the correlation between the 4 h D/P UA and peritoneal UA clearance ($r = 0.47$, $P < 0.001$) and between the 4 h D/P creatinine and peritoneal UA clearance ($r = 0.46$, $P < 0.001$) were similar (Fig. 3c and Fig. 3d).

Independent influencing factors of peritoneal UA clearance

As shown in Table 4, after adjusting the common variables such as age, sex, dialysis vintage, mGFR, BMI and the history of using diuretics in multiple linear regression model, the serum albumin level was found to be negatively associated with peritoneal UA clearance (β -0.06, 95%CI -2.09, -0.19, P = 0.02), while the higher transporters (β 0.06, 95%CI 0.05, 1.69, P = 0.04) and peritoneal CCL (β 0.95, 95%CI 0.81, 0.93, P < 0.001) were positively associated with peritoneal UA clearance. Similarly, the further binary logistic regression analysis (shown in Table 5) revealed that every 1L/week/1.73 m^2 increase of the peritoneal CCL (OR 1.95, 95%CI 1.53,2.50, P < 0.001) or every 1 g/dL decrease of albumin level (OR 0.15, 95%CI 0.05,0.47, P = 0.001) were independently associated with greater peritoneal UA clearance (> 39.8 L/week/1.73 m^2). Furthermore, the peritoneal CCL was found to perform best in ROC analysis (AUC = 0.96, 95%CI 0.93–0.99, P < 0.001) to predict higher peritoneal UA clearance among the widely used small solute removal indicators (shown in Fig. 4).

Table 4
Associated factors of peritoneal UA clearance in multiple linear regression.

Variables	β (95%CI)	P value
Age (y)	0.02 (-0.02, 0.04)	0.49
Sex (M/F)	0.02 (-0.48, 0.92)	0.53
Using diuretics	0.003 (-0.90, 1.03)	0.90
Albumin (g/dL)	-0.06 (-2.09, -0.19)	0.02
PD vintage (month)	-0.05 (-0.02, 0.004)	0.16
Average glucose concentration of dialysate (0.1%)	0.01 (-0.14, 0.22)	0.64
BMI (kg/m^2)	-0.002 (-0.12, 0.11)	0.95
nPCR (g/kg/d)	0.007 (-1.46, 1.79)	0.80
mGFR (mL/min/1.73 m^2)	0.06 (-0.02, 0.34)	0.07
Higher peritoneal transport status [a]	0.06 (0.05, 1.69)	0.04
Peritoneal CCL (L/week/1.73 m^2)	0.95 (0.81, 0.93)	< 0.001
[a] The reference group was the lower (low average or low) peritoneal transporters.		
Abbreviations: BMI, body mass index; CCL, weekly total creatinine clearance; CI, confidence interval; mGFR, measured glomerular filtration rate; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; UA, uric acid.		

Table 5

Independent determinants of higher peritoneal UA clearance in binary logistic regression.

Variables	Adjusted OR (95%CI)	P value
Age (y)	1.01 (0.96, 1.06)	0.61
Sex (M/F)	0.46 (0.13, 1.60)	0.22
Using diuretics	0.68 (0.13, 3.48)	0.64
Albumin (g/dL)	0.15 (0.05, 0.47)	0.001
PD vintage (month)	0.98 (0.95, 1.02)	0.35
Average glucose concentration of dialysate (0.1%)	1.27 (0.85, 1.90)	0.24
BMI (kg/m^2)	1.02 (0.82, 1.27)	0.85
nPCR (g/kg/d)	0.52 (0.04, 6.54)	0.61
mGFR (mL/min/1.73 m^2)	1.31 (0.92, 1.87)	0.32
Higher peritoneal transport status [a]	1.61 (0.40, 6.44)	0.50
Peritoneal CCL (L/week/1.73 m^2)	1.95 (1.53, 2.50)	< 0.001

[a] The reference group was the lower (low average or low) peritoneal transporters.

Abbreviations: BMI, body mass index; CCL, weekly total creatinine clearance; CI, confidence interval; mGFR, measured glomerular filtration rate; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; UA, uric acid.

Discussion

In this study, we found the inverse association between peritoneal UA clearance and SUA level and further revealed that it was the peritoneal UA removal which significantly played a role in SUA control but not the residual kidney function. Moreover, we demonstrated that lower albumin level, higher peritoneal transporters and higher peritoneal CCL were independently associated with greater peritoneal UA clearance.

To our knowledge, this is the first systematic study specifically focusing on the UA clearance and its independent influencing factors in PD regimen. As a small molecular solute, the vast majority of UA is in the ionized form and no more than 5% of the circulating UA is albumin bound [4]. Since UA presents as high hydrophilic and has a sieving coefficient of 1.01 which allows it to easily diffuse through the dialysis membrane, it is speculated to be sufficiently cleared by PD therapy to some extent [2, 9]. The previous study found that UA clearance was inversely proportional to the dwell time on PD, in which the average UA mass transfer for a dwell time of 0–1, 1–4 or 4–8 h with 2L of 1.5% dialysate was 49.8 ± 3.9, 16.1 ±

1.0, 8.3 ± 0.6 mg/h/1.73 m^2, respectively [20]. Similarly, we showed a remarkable decline of UA mass transfer of 72.9 ± 41.1 and 23.9 ± 5.6 mg/h/1.73 m^2 in PD with 2L 2.5% dialysate for 0 and 4 h dwell. In addition, we revealed an average peritoneal UA clearance of 40.2 ± 7.1 L/week/1.73 m^2 in this study. The correlation analysis indicated a negative relationship between the peritoneal UA clearance and SUA level. The further multiple linear regression and logistic regression strongly suggested the indispensable role of peritoneal UA clearance but not the residual kidney removal in SUA control in PD patients. It's speculated that the high SUA level in PD patients was partly caused by the relatively inadequate UA removal by PD modality.

Then the relevant influencing factors associated with the peritoneal UA clearance were further explored. As for the effects of membrane characteristics on peritoneal UA clearance, we found that the peritoneal UA clearance was significantly greater in higher transporters than the lower transporters classified by 4 h D/P creatinine. The 4 h D/P UA was shown to be highly correlated with the 4 h D/P creatinine, and further analysis indicated a similar correlation between the 4 h D/P UA or 4 h D/P creatinine and peritoneal UA clearance. Moreover, the ROC analysis revealed that peritoneal CCL showed best value in predicting peritoneal UA clearance among the widely used solute removal index. All of the results above illustrated that the membrane characteristics based on the creatinine transport can excellently represent the UA transport status. It was mainly because that the UA molecular weight (168 Da) was closer to that of creatinine (113 Da) and few of the circulating UA was bound to the albumin or affected by the electrochemical gradient like serum phosphorus [21]. What worth mentioning in the present study was that evaluating the peritoneal UA clearance merely by the most frequently used indicator of Kt/V for peritoneal adequacy may not be entirely accurate. The peritoneal CCL seemed to be more suitable for reflecting the UA clearance adequacy in PD regimen.

Few studies have focused on the UA removal in PD, among which the average UA clearance in PD was revealed to be positively proportional to the exchange volume and flow rate [13] while inversely proportional to the dwell time [20]. In this study, we found that the higher transporters, lower albumin level and greater peritoneal CCL were independent determinants of continuous peritoneal UA clearance. A dominate linear effect of peritoneal CCL with the UA clearance (β 0.95, 95%CI 0.81, 0.93) was observed which highlight the potential role of peritoneal CCL as a reliable assessing index for UA clearance in PD modality. Since the higher transporters possessed significantly greater peritoneal UA clearance than the lower transporters, adjusting the dialysis prescription for better PD-related UA removal on basis of the peritoneal CCL rather than the widely used Kt/V will be much more appropriate especially for lower transporters with hyperuricemia. In addition, the serum albumin level was revealed to be associated with both the continuous peritoneal UA clearance and higher peritoneal UA clearance category. Previous studies have shown a negative correlation between the peritoneal albumin loss and serum albumin level in PD patients [20, 22]. Furthermore, the peritoneal albumin loss was demonstrated to be positively associated with peritoneal CCL in a cross-sectional study including 351 PD patients [23]. Therefore, the mechanism of the inverse association between the peritoneal UA clearance and serum albumin level may be elucidated as follows: the greater peritoneal UA clearance itself signifying more removal of albumin

from peritoneum caused lower circulating albumin reserves, which was mainly on account of the inadequate albumin synthesis to compensate the peritoneal albumin loss [20]. Therefore, the peritoneal albumin loss should be taken into consideration while optimizing dialysis prescription for efficient solute removal. However, whether there existed a causal relationship between the lower albumin status and greater peritoneal UA clearance or not remained to be explored. Besides, we found that the mGFR was significantly lower in higher peritoneal UA clearance group (2.3 ± 2.3 vs. 3.8 ± 2.4 mL/min/1.73 m^2, P < 0.001), which seemed to show that the worse residual renal function, the greater peritoneal UA removal. Then in the multiple linear regression model, especially after adjusting the peritoneal CCL, the mGFR was shown to positively associated with the peritoneal UA clearance at a near statistical significance (P = 0.07). It was speculated that that the raw negative correlation between the residual renal function and peritoneal UA removal (r=-0.42, P < 0.001) may be aroused by confounding effects of the relatively larger dialysis dose, glucose concentration and peritoneal CCL in the PD patients with worse renal function compensating for insufficient renal solute removal. Larger sample size was requisite for clarifying relationship between the residual renal function and peritoneal UA removal in PD more accurately.

There are some limitations in our study. Firstly, the cross-sectional observational study itself figures out merely the association relationship but not causal relationship. Secondly, we haven't explored the effect of different PD modality such as continuous cyclic peritoneal dialysis (CCPD), automated peritoneal dialysis (APD) or different exchange flow rate on the peritoneal UA clearance. Thirdly, the dialysis vintage of patients enrolled were relatively short which may lead to bias for inadequate and unstable dialysis. In spite of the limitation above, this was the first study systematically exploring the independent influencing factors of peritoneal UA clearance in relatively large PD sample. We collected common small solute removal indicators at the same time period for further comparison and analysis which has significant guiding value in optimizing prescription for better UA control in PD patients. Moreover, we excluded the PD patients with history of taking UA lowering agents to study UA clearance in PD regimen more specifically.

Conclusions

In summary, the UA removal in PD patients was deemed to be more rely on the peritoneal clearance but not the residual kidney function. The peritoneal CCL appears to be optimal indicator for assessing UA removal in PD for its close resemblance of removal process through the dialysis membrane. The lower albumin level, greater peritoneal CCL and higher transporters were revealed to be independently associated with greater peritoneal UA clearance.

Abbreviations

APD:automated peritoneal dialysis; BMI:body mass index; BSA:body surface area; CCL:creatinine clearance; CCPD:continuous cyclic peritoneal dialysis; CI:confidence interval; CKD:chronic kidney disease; CVD:cardiovascular disease; D/P:dialysate to plasm; H:high; HA:high average; HD:hemodialysis; L:low;

LA:low average; mGFR:measured glomerular filtration rate; nPCR:normalized protein catabolic rate; OR:odds ratio; PD:peritoneal dialysis; PET:peritoneal equilibration test; SUA:serum uric acid; UA:uric acid

Declarations

Acknowledgments

We are very grateful to the doctors and nurses in our PD centers for their earnest work of clinical evaluation and data collecting.

Authors' contributions

XY and XY* designed the research, HY and XX conducted the research, CY, JL and YP collected data, XH, MW and HW analyzed the data, HM and XY interpreted the findings, XX and XY* wrote the paper, XY* had the primary responsibility for the whole content and final approval of the version to be published. And all authors read and approved the final manuscript.

Funding

This work was supported by the Natural Science Foundation of China (Grant no. 81774069, 81570614), National Key Research and Development Program (Grant no. 2016YFC0906101), Program of the Ministry of Health of China (201502023), the Guangdong Science Foundation of China (Grant 2017A050503003, 2017B020227006), Foundation of Guangdong Key Laboratory of Nephrology (Grant no. 2017B030314019), and the Guangzhou Committee of Science and Technology, China (201704020167).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study has conformed to the ethical principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University. And all patients had signed informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Nephrology, The First Affiliated Hospital, Sun Yat-Sen University, 58th, Zhongshan Road II, Guangzhou ,510080, China

[2]Key Laboratory of Nephrology, Committee of Health and Guangdong Province, Guangzhou, 510080, China

References

1. Ndrepepa G. Uric acid and cardiovascular disease. Clin Chim Acta. 2018; 484: 150-63.
2. Murea M, Tucker BM. The physiology of uric acid and the impact of end-stage kidney disease and dialysis. Semin Dial. 2019; 32(1): 47-57.
3. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet. 2016; 388(10055):2039-52.
4. Richette P, Bardin T. Gout. Lancet. 2010; 375(9711):318-28.
5. Terkeltaub R, Bushinsky DA, Becker MA. Recent developments in our understanding of the renal basis of hyperuricemia and the development of novel antihyperuricemic therapeutics. Arthritis Res Ther. 2006; 8 Suppl 1:S4.
6. Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009-10.PloS one. 2012; 7(11):e50046.
7. Li PK, Chow KM, Van de Luijtgaarden MW, Johnson DW, Jager KJ, Mehrotra R, et al. Changes in the worldwide epidemiology of peritoneal dialysis. Nat Rev Nephrol. 2017;13(2):90-103.
8. Dousdampanis P, Trigka K, Musso CG, Fourtounas C. Hyperuricemia and chronic kidney disease: an enigma yet to be solved. Ren Fail. 2014; 36(9):1351-9
9. Murea M. Advanced kidney failure and hyperuricemia. Adv Chronic Kidney Dis. 2012;19(6):419-24.
10. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, et al. Relationship of uric acid with progression of kidney disease. Am J Kidney Dis. 2007;50(2):239-47.
11. Silverstein DM, Srivaths PR, Mattison P, Upadhyay K, Midgley L, Moudgil A, et al. Serum uric acid is associated with high blood pressure in pediatric hemodialysis patients. Pediatr Nephrol. 2011; 26(7):1123-8.
12. Xia X, Zhao C, Peng FF, Luo QM, Zhou Q, Lin ZC, et al. Serum uric acid predicts cardiovascular mortality in male peritoneal dialysis patients with diabetes. Nutr Metab Cardiovasc Dis. 2016; 26(1):20-6.
13. Xia X, He F, Wu X, Peng F, Huang F, Yu X. Relationship between serum uric acid and all-cause and cardiovascular mortality in patients treated with peritoneal dialysis. Am J Kidney Dis. 2014; 64(2):257-64.
14. Vargas-Santos AB, Neogi T. Management of Gout and Hyperuricemia in CKD. Am J Kidney Dis. 2017; 70(3):422-39.
15. Robson M, Oreopoulos DG, Izatt S, Ogilvie R, Rapoport A, deVeber GA. Influence of exchange volume and dialysate flow rate on solute clearance in peritoneal dialysis. Kidney Int. 1978; 14(5):486-90.

16. Twardowski ZJ, Nolph KO, Khanna R, Prowant BF, Ryan LP, Moore HL, et al. Peritoneal equilibration test. Perit Dial Int. 1987; 7:138-48.
17. Huang R, Liu Y, Wu H, Guo Q, Yi C, Lin J, et al. Lower plasma visceral protein concentrations are independently associated with higher mortality in patients on peritoneal dialysis. Br J Nutr. 2015; 113(4):627-33.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5):373-83.
19. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989,5(5):303-11.
20. Kagan A, Bar-Khayim Y, Schafer Z, Fainaru M. Kinetics of peritoneal protein loss during CAPD: I. Different characteristics for low and high molecular weight proteins. Kidney Int. 1990; 37(3):971-9.
21. Graff J, Fugleberg S, Brahm J, Fogh-Andersen N. The transport of phosphate between the plasma and dialysate compartments in peritoneal dialysis is influenced by an electric potential difference. Clin Physiol. 1996; 16(3):291-300.
22. Kaysen GA, Schoenfeld PY. Albumin homeostasis in patients undergoing continuous ambulatory peritoneal dialysis. Kidney Int. 1984; 25(1):107-14.
23. Fan J, Ye H, Zhang X, Cao P, Guo Q, Mao H, et al. Association of Lean Body Mass Index and Peritoneal Protein Clearance in Peritoneal Dialysis Patients. Kidney Blood Press Res. 2019; 44(1):94-102.

Figures

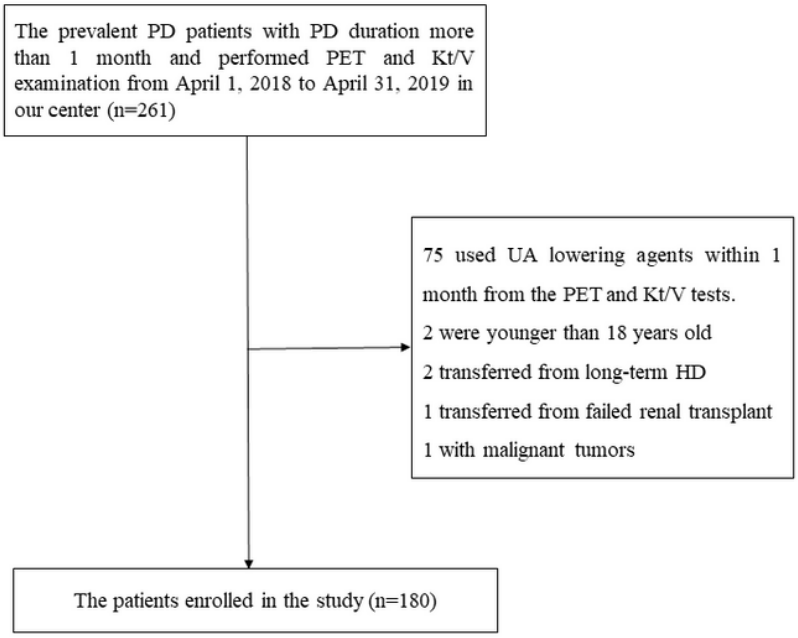


Figure 1. The flow chart for the enrollment process of the PD patients in the study. PD, peritoneal dialysis; PET, peritoneal equilibration test; HD, hemodialysis; UA, uric acid.

Figure 1

The flow chart for enrollment process of the PD patients in the study. HD, hemodialysis; PD, peritoneal dialysis; PET, peritoneal equilibration test; UA, uric acid.

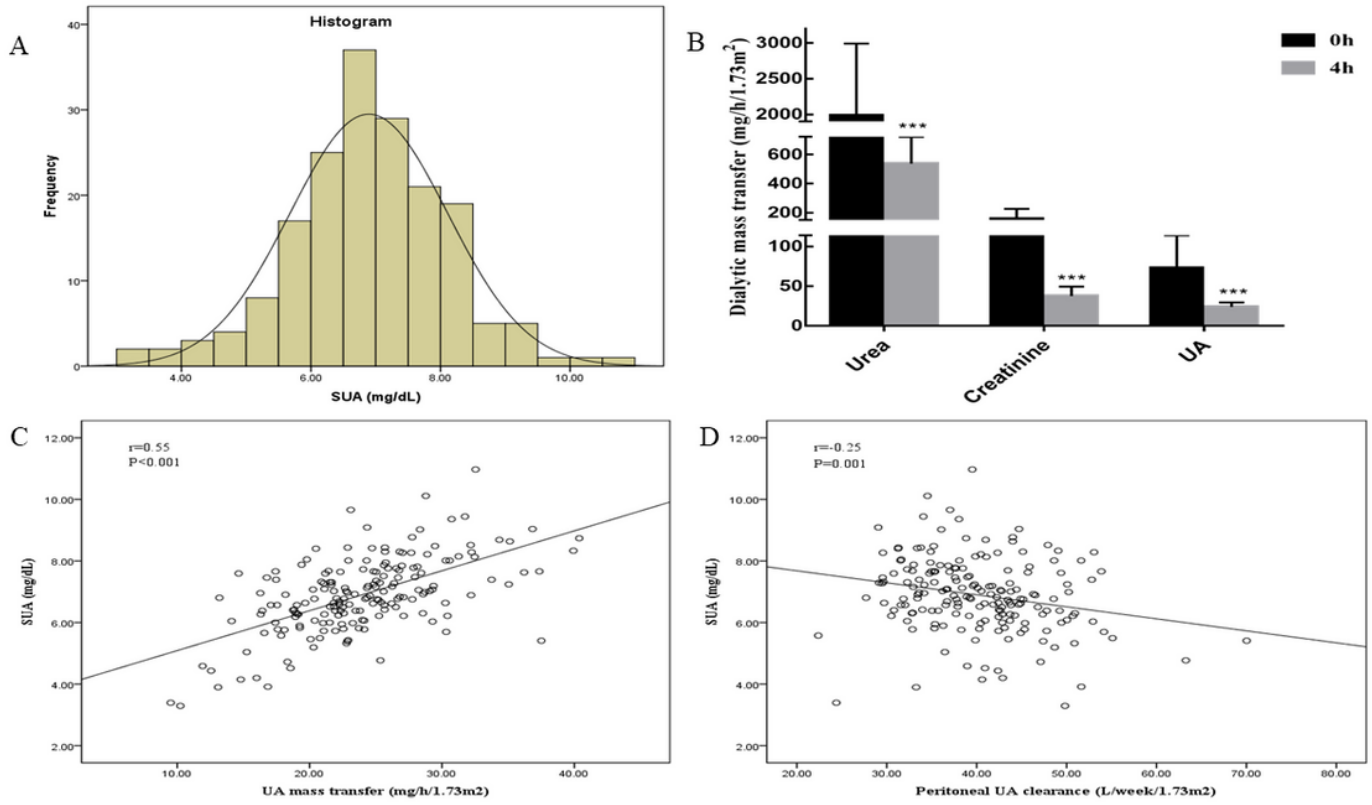


Figure 2

The correlation between SUA and dialytic UA clearance. A. The distribution of SUA in PD patients enrolled. B. The average dialytic mass transfer of urea, creatinine and UA with 2L of 2.5% glucose-based dialysate for a dwell time of 0 or 4 hours. C. and D. showed the correlation between the SUA and UA mass transfer with a dwell time of 4 hours or the peritoneal UA clearance. ***P<0.001, 0h vs 4h. SUA, serum uric acid; UA, uric acid.

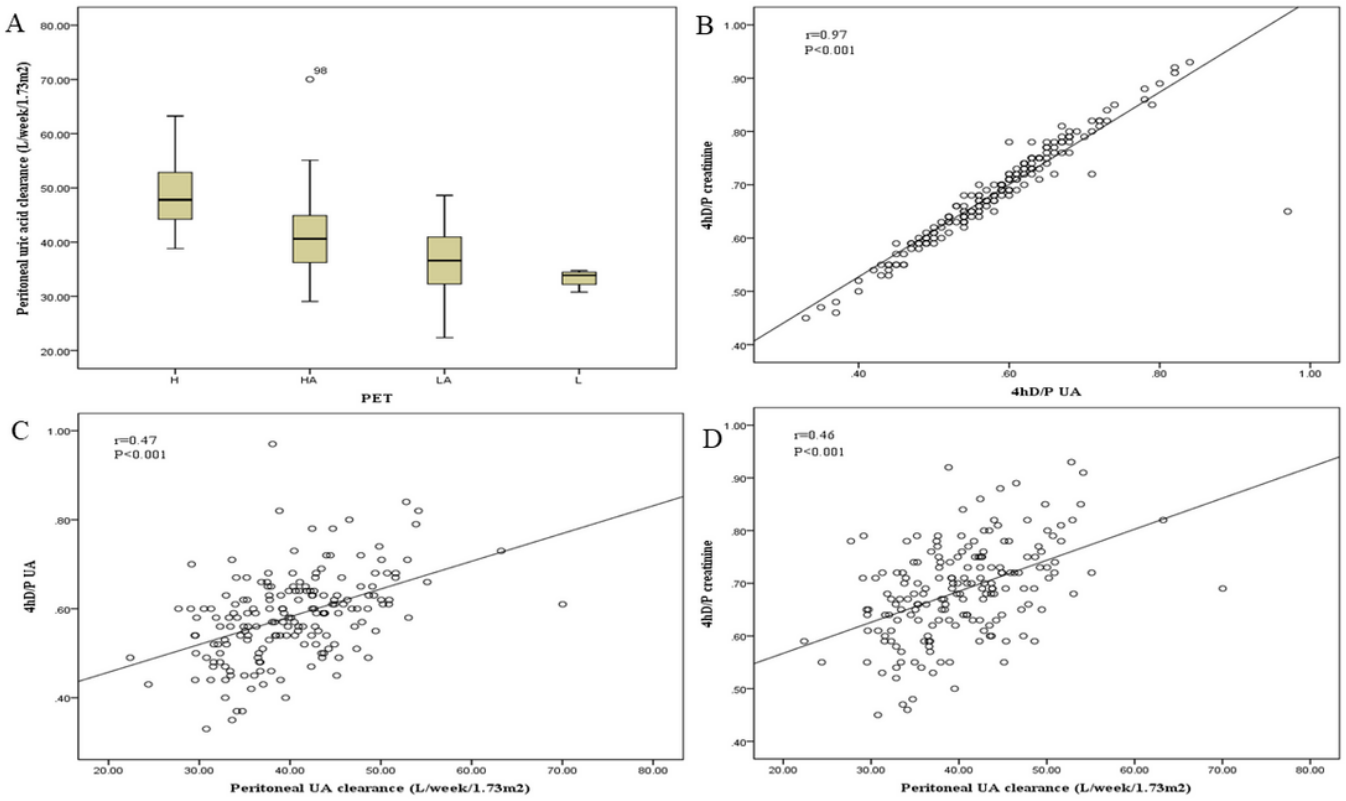
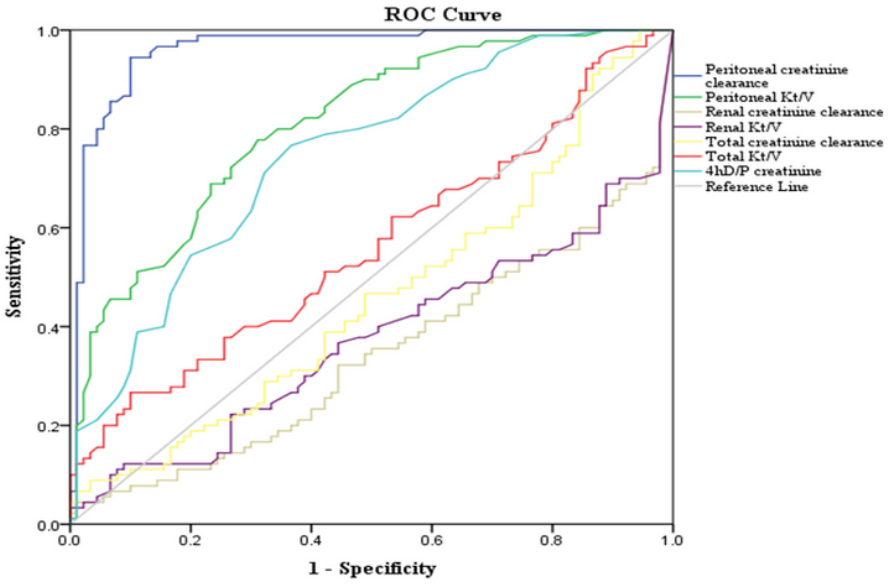


Figure 3

The effects of the peritoneal transport characteristics on peritoneal UA clearance. A. The distribution of the peritoneal UA clearance in different categories of peritoneal transport characteristics. B. The correlation between the 4h D/P creatinine and 4h D/P UA. C. and D. exhibited the comparison between the peritoneal UA clearance and 4h D/P UA or 4h D/P creatinine. D/P, dialysate to plasm; UA, uric acid.



Variables	AUC	SE	*P* value	95%CI
Peritoneal CCL (L/week/1.73m^2)	0.96	0.02	<0.001	0.93-0.99
Peritoneal Kt/V	0.81	0.03	<0.001	0.75-0.87
Residual renal CCL (L/week/1.73m^2)	0.34	0.04	<0.001	0.26-0.42
Residual renal Kt/V	0.37	0.04	0.004	0.29-0.46
CCL (L/week/1.73m^2)	0.46	0.04	0.36	0.38-0.55
Total Kt/V	0.56	0.04	0.15	0.48-0.65
4h D/P creatinine	0.75	0.04	<0.001	0.67-0.82

Figure 4

The performance of different small solute removal indicators for predicting higher peritoneal UA clearance (>39.8 L/week/1.73 m2) in ROC analysis.