

## PREDICTORS OF RESIDUAL RENAL FUNCTION DECLINE IN PATIENTS UNDERGOING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

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◆ **Background:** Residual renal function (RRF) is an important prognostic indicator in continuous ambulatory peritoneal dialysis (CAPD) patients. We determined the predictors of RRF loss in a cohort of incident CAPD patients.

◆ **Methods:** We reviewed the record of 645 incident CAPD patients. RRF loss is represented by the slope of decline of residual glomerular filtration rate (GFR) as well as the time to anuria.

◆ **Results:** The average rate of residual GFR decline was  $-0.083 \pm 0.094$  mL/min/month. The rate of residual GFR decline was faster with a higher proteinuria ( $r = -0.506$ ,  $p < 0.0001$ ) and baseline residual GFR ( $r = -0.560$ ,  $p < 0.0001$ ). Multivariate analysis showed that proteinuria, baseline residual GFR, and the use of diuretics were independent predictors of residual GFR decline. Cox proportional hazard model showed that proteinuria, glucose exposure, and the number of peritonitis episodes were independent predictors of progression to anuria, while a higher baseline GFR was protective. Each 1 g/day of proteinuria is associated with a 13.2% increase in the risk of progressing to anuria, each 10 g/day higher glucose exposure is associated with a 2.5% increase in risk, while each peritonitis episode confers a 3.8% increase in risk.

◆ **Conclusions:** Our study shows that factors predicting the loss of residual solute clearance and urine output are different. Proteinuria, baseline residual GFR, and the use of diuretics are independently related to the rate of RRF decline in CAPD patients, while proteinuria, glucose exposure, and the number of peritonitis episodes are independent predictors for the development of anuria. The role of anti-proteinuric therapy and measures to prevent peritonitis episodes in the preservation of RRF should be tested in future studies.

KEY WORDS: Renal failure; survival; cardiovascular disease; peritonitis.

Residual renal function (RRF) is well recognized as an important marker of outcomes in peritoneal dialysis (PD) (1). In dialysis patients, the presence of RRF is associated with easy fluid management, improved nutrition, reduced erythropoietin requirements, better potassium clearance, and improved quality of life (2). Published evidence suggests that a higher level of RRF is independently associated with a better survival in dialysis patients (1,3,4). For example, analysis of the CANUSA study has shown that every 0.5 mL/min higher RRF was associated with a 9% lower risk of death (5). More importantly, the survival benefit conveyed by RRF could not be explained by a better small solute clearance, and is possibly the result of a better preservation of endocrine function of the kidney and the better excretion of uremic toxins of middle molecular weight (6,7).

In recent years, the importance of identifying factors that protect and preserve RRF is increasingly being recognized among dialysis patients. For example, RRF is better preserved with PD than with hemodialysis (8,9), although a more recent study showed no difference in the rate of decline of RRF between PD and hemodialysis patients using biocompatible high flux membranes and ultra-pure water (10). Previous studies also showed that high baseline RRF, high peritoneal transporter, poorly controlled hypertension, persistent proteinuria, prior history of diabetes, congestive heart failure, and peripheral vascular disease are predictors of loss of RRF, while a higher serum calcium level, use of a calcium channel blocker, and use of an angiotensin-converting enzyme inhibitor are independently associated with decreased risk of losing RRF (9,11–15).

Unfortunately, most of the published reports have a small sample size or were conducted in the last century. To complicate the issue, there is increasing evidence of

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dissociation between the loss of residual solute clearance and urine volume (16,17). For example, in the balANZ study, the use of biocompatible PD solution delays the onset of anuria but has no effect on the decline of residual glomerular filtration rate (GFR) (17). In essence, our knowledge of the factors that preserve RRF in CAPD remains limited. We therefore performed a retrospective study to determine the predictors of RRF loss in a large cohort of unselected incident CAPD patients.

## PATIENTS AND METHODS

### PATIENT SELECTION

We studied the clinical record of 645 incident CAPD patients between 1998 and 2009 in our center. We excluded patients who had a failed kidney allograft, planned to have elective living donor transplant or transfer to another renal center within 6 months. We also excluded 122 patients who were treated with machine-assisted PD, and another 118 patients who received more than two weeks of temporary hemodialysis before starting CAPD. The study is approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong, and all study procedures are in adherence to the Declaration of Helsinki.

### COLLECTION OF CLINICAL DATA

Clinical data were recorded by chart review of the whole team. Data collected included age, sex, underlying causes of renal disease, blood pressure, serum chemistry, peritonitis, exposure to aminoglycosides, treatment with angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and diuretics, were recorded. Exposure to ACE inhibitor, ARB, CCB or diuretics was considered to be present when the patients received the corresponding drug for at least six months. The modified Charlson's comorbidity index, which was validated in PD patients (18), was used to calculate a comorbidity score. Dietary protein intake was estimated by the normalized protein nitrogen appearance (NPNA). During the study period, peritonitis episodes were mostly treated according to the recommendations of the International Society for Peritoneal Dialysis (19–21), with empirical antibiotic treatment with cefazolin plus netilmicin or ceftazidime.

### ASSESSMENT OF RRF LOSS

Residual GFR was measured around one month after CAPD and then every six months, or more frequently if

clinically indicated. Residual GFR was calculated as the average of 24-hour urinary urea and creatinine clearances (22). The rate of RRF loss was represented by the rate of residual GFR decline and the time to anuria. The rate of residual GFR decline was computed by the least squares linear regression formula. Anuria was defined as absence of appreciable urine output as in our previous study (23).

### STUDY OF PERITONEAL TRANSPORT

Standard peritoneal permeability test (PET) was performed around one month after CAPD by the method of Twardowski (24). Peritoneal transport characteristic was represented by dialysate-to-plasma ratios of creatinine at four hours (D/P<sub>4</sub>) and mass transfer area coefficients (MTAC) of creatinine as calculated by a formula previously described (25).

### DIALYSIS ADEQUACY AND NUTRITIONAL INDICES

Dialysis adequacy and nutritional status were assessed at least yearly. The method of dialysis adequacy assessment has been described previously (26). Nutritional status was represented by serum albumin level, subjective global assessment (SGA) (27), and comprehensive malnutrition-inflammation score (MIS) (28), which has been validated in PD patients (29,30).

### STATISTICAL ANALYSIS

Statistical analysis was performed by SPSS for Windows software version 15.0 (SPSS Inc., Chicago, IL). Results are expressed as mean  $\pm$  SD unless otherwise specified. For peritoneal transport characteristics, baseline data are used for analysis. For other time-dependent parameters, including blood pressure, serum chemistry, dialysis adequacy and nutritional indices, average values (measured every six months) during the study period are used for analysis. To analyze the relation between era of starting dialysis and the rate of residual GFR decline and anuria, patients were stratified into three groups according to the year PD was started. Comparisons between parameters are performed by chi-square test, Student *t*-test, or Pearson's correlation coefficient as appropriate.

A multiple linear regression model was constructed to determine independent predictors of the slope of residual GFR decline. In addition, we constructed a Cox proportional hazard model to determine independent predictors of time to anuria. In this part of analysis, diabetic status, presence of ischemic heart disease (IHD)

and peripheral vascular disease (PVD), Charlson's comorbidity score, HbA1c level, serum phosphate level, D/P4, dialysis effluent protein level, baseline proteinuria and residual glomerular filtration rate (GFR), the use of ACE inhibitor or ARB therapy, CCB, and diuretics, number of peritonitis episodes, and number of peritonitis episodes that required aminoglycoside therapy, were included as the independent variables. These parameters were selected for the construction of the Cox model because they had substantial association ( $p < 0.1$ ) with the slope of residual GFR decline or time to anuria by univariate analysis, or they were previously reported as predictors of RRF decline. The effects of different medications were analyzed as separate independent variables. Backward stepwise analysis was used to identify independent predictors. Additional linear regression and Cox regression models were constructed for the subgroup analysis of diabetic patients only. Since there was a significant relation between proteinuria and the use of ACE inhibitor or ARB therapy, additional linear regression and Cox models were also constructed without including proteinuria in the model. A  $p$  value of less than 0.05 is considered statistically significant. All probabilities are two-tailed.

## RESULTS

We studied 645 incident CAPD patients. The demographic, clinical and biochemical information are summarized in Table 1 and Table 2, respectively. Patients who received ACE inhibitor or ARB therapy had less proteinuria than those who did not ( $0.98 \pm 1.25$  vs  $1.44 \pm 1.57$  g/day,  $p = 0.001$ ). The anti-proteinuric effect was significant in both diabetic patients ( $1.58 \pm 1.62$  vs  $2.16 \pm 1.83$  g/day,  $p = 0.034$ ) and non-diabetic ones ( $0.63 \pm 0.81$  vs  $0.86 \pm 1.01$  g/day,  $p = 0.047$ ).

### SLOPE OF RESIDUAL RENAL FUNCTION DECLINE

The patients were followed for an average of  $66.3 \pm 34.7$  months. The average rate of residual GFR decline was  $-0.083 \pm 0.094$  mL/min/month. During the study period, there were a total of 1,502 peritonitis episodes, of which 454 episodes received aminoglycosides treatment. The peritonitis rate was one episode per 28.5 patient-months.

The rate of residual GFR decline was faster in patients with diabetes or IHD (Figure 1). Amongst the diabetic patients, the rate of residual GFR decline was

TABLE 1  
Baseline Demographic and Clinical Data

Year starting dialysis	1998–2001	2002–2005	2006–2009	
No. of patients	200	228	217	
Sex (M:F)	99:101	143:85	117:100	$p=0.02$
Age (years)	$57.9 \pm 13.9$	$58.0 \pm 12.3$	$56.5 \pm 12.0$	$p=0.38$
Body height (cm)	$158.8 \pm 9.0$	$160.6 \pm 8.0$	$160.1 \pm 8.3$	$p=0.10$
Body weight (kg)	$58.3 \pm 13.0$	$61.0 \pm 10.9$	$62.0 \pm 12.3$	$p=0.009$
Body mass index (kg/m <sup>2</sup> )	$23.1 \pm 4.5$	$23.6 \pm 3.9$	$24.1 \pm 3.7$	$p=0.04$
Blood pressure (mmHg)				
Systolic	$144.4 \pm 19.1$	$145.0 \pm 17.9$	$140.3 \pm 15.4$	$p=0.014$
Diastolic	$78.2 \pm 11.3$	$76.3 \pm 12.7$	$76.1 \pm 10.5$	$p=0.15$
Renal diagnosis, no. of cases (%)				$p=0.12$
Diabetic nephropathy	74 (37.0%)	72 (31.6%)	66 (30.4%)	
Glomerulonephritis	66 (33.0%)	56 (24.6%)	66 (30.4%)	
Hypertensive nephrosclerosis	12 (6.0%)	25 (11.0%)	17 (7.8%)	
Polycystic kidney	9 (4.5%)	6 (2.6%)	13 (6.0%)	
Obstructive uropathy	7 (3.5%)	15 (6.6%)	12 (5.5%)	
Others/unknown	32 (16.0%)	54 (23.7%)	43 (19.8%)	
Comorbidity, no. of cases (%)				
Diabetes	83 (41.5%)	104 (45.6%)	90 (41.5%)	$p=0.60$
Ischemic heart disease	50 (25.0%)	54 (23.7%)	49 (22.6%)	$p=0.85$
Cerebrovascular disease	52 (26.0%)	56 (24.6%)	49 (22.6%)	$p=0.72$
Peripheral vascular disease	11 (5.5%)	19 (8.3%)	17 (7.8%)	$p=0.49$
Charlson's comorbidity index	$5.73 \pm 2.55$	$5.77 \pm 2.44$	$5.47 \pm 2.69$	$p=0.41$

TABLE 2  
Average Biochemical Data During the Study Period

Year starting dialysis	1998–2001	2002–2005	2006–2009	
No. of patients	200	228	217	
Malnutrition inflammation score	9.1±3.6	7.3±2.8	6.5±3.2	<i>p</i> <0.0001
Subjective Global Assessment	5.4±1.0	5.5±0.7	5.5±0.8	<i>p</i> =0.13
NPNA (g/kg/day)	1.07±0.25	1.11±0.25	1.13±0.31	<i>p</i> =0.11
Hemoglobin (g/dL)	9.3±1.5	9.3±1.6	9.2±1.5	<i>p</i> =0.60
Hemoglobin A1c (%)	6.45±0.97	6.46±1.29	6.38±1.74	<i>p</i> =0.91
Serum biochemistry				
Albumin (g/L)	29.1±4.7	33.2±5.3	33.5±5.3	<i>p</i> <0.0001
Calcium (mmol/L)	2.24±0.17	2.27±0.16	2.26±0.16	<i>p</i> =0.43
Phosphate (mmol/L)	1.58±0.36	1.80±0.38	1.76±0.39	<i>p</i> <0.0001
Baseline peritoneal transport character				
D/P4	0.611±0.136	0.662±0.130	0.558±0.131	<i>p</i> <0.0001
MTAC creatinine (mL/min/1.73 m <sup>2</sup> )	9.06±4.45	10.43±5.15	7.10±3.59	<i>p</i> <0.0001
Baseline residual GFR (mL/min/1.73 m <sup>2</sup> )	3.37±2.07	3.94±2.07	3.73±2.74	<i>p</i> =0.04
Baseline proteinuria (g/day)	1.20±1.42	1.21±1.31	1.43±1.68	<i>p</i> =0.22
Weekly total Kt/V	2.17±0.56	2.24±0.49	2.19±0.72	<i>p</i> =0.42
Glucose exposure (g/day)	132.6±69.5	135.6±44.7	119.9±42.7	<i>p</i> =0.005
Total glucose load (kg)	280.1±267.5	265.6±152.9	238.5±196.9	<i>p</i> =0.13
Medications, no. of cases (%)				
ACE inhibitor or ARB	77 (38.5%)	63 (27.6%)	66 (30.4%)	<i>p</i> =0.046
Calcium channel blocker	77 (38.5%)	133 (58.3%)	152 (70%)	<i>p</i> <0.0001
Diuretics	21 (10.5%)	100 (43.9%)	128 (59.0%)	<i>p</i> <0.0001

NPNA = normalized protein nitrogen appearance; D/P4 = dialysate-to-plasma concentration ratio of creatinine at 4 hours; MTAC = mass transfer area coefficient; GFR = glomerular filtration rate; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

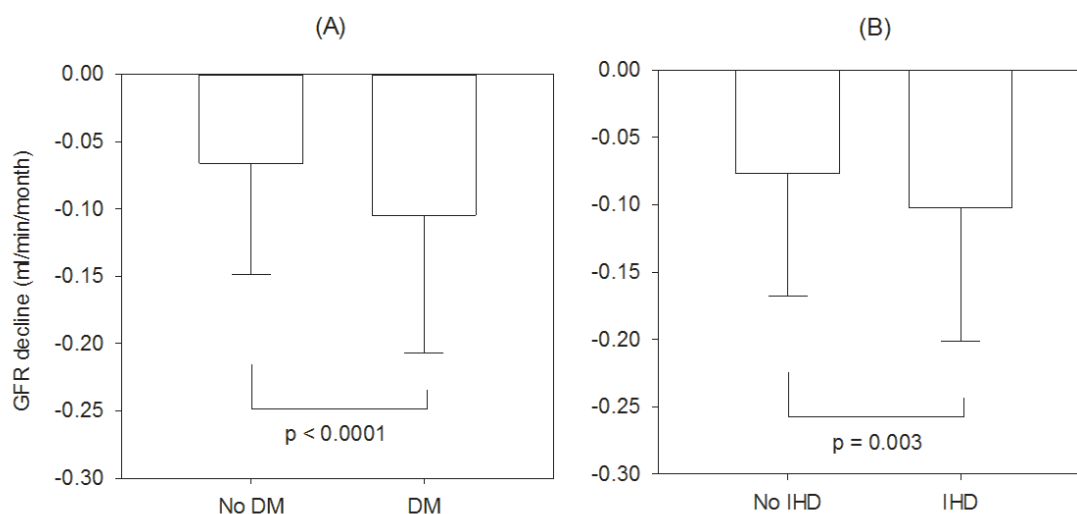


Figure 1 — Comparison of the rate of residual glomerular filtration rate (GFR) decline between (A) patients with and without diabetes (DM); and (B) patients with and without ischemic heart disease (IHD). Data are compared using unpaired Student *t*-test.

also modestly but statistically faster amongst patients with a high HbA1c during the observation period ( $r = -0.163$ ,  $p = 0.003$ ). In contrast, the rate of residual renal function decline was similar between patients with and

without peripheral artery disease or cardiovascular disease (details not shown). There was no significant relation between the year of starting PD and the rate of residual GFR decline ( $-0.076 \pm 0.099$ ,  $-0.091 \pm 0.090$  and

-0.081 ± 0.091 mL/min/month for patients who started dialysis in 1998 – 2001, 2002 – 2005 and 2006 – 2009, respectively,  $p = 0.2$ ).

The rate of residual renal function decline had significant correlation with the proteinuria ( $r = -0.506$ ,  $p < 0.0001$ ) and baseline residual GFR ( $r = -0.560$ ,  $p < 0.0001$ ). The rate of residual GFR decline was also faster in patients with higher body mass index ( $r = -0.160$ ,  $p < 0.0001$ ), Charlson’s score ( $r = -0.174$ ,  $p < 0.0001$ ), D/P4 ( $r = -0.100$ ,  $p = 0.014$ ), dialysis effluent protein level ( $r = -0.129$ ,  $p = 0.005$ ), serum phosphate level ( $r = -0.168$ ,  $p < 0.0001$ ), and dietary protein intake ( $r = -0.293$ ,  $p < 0.0001$ ). In contrast, the rate of residual GFR decline did not correlate with the mean arterial blood pressure ( $r = -0.053$ ,  $p = 0.2$ ), glucose exposure ( $r = -0.020$ ,  $p = 0.6$ ), number of peritonitis episodes ( $r = 0.033$ ,  $p = 0.4$ ), or number of peritonitis episodes treated with aminoglycosides ( $r = 0.011$ ,  $p = 0.8$ ) during the study period. The rate of residual GFR decline did not correlate with any nutritional index or MIS score (details not shown). The rate of decline of residual GFR was slower in patients who received ACE inhibitor or ARB, but faster in those who received CCB or diuretic therapy (Figure 2).

We went on to perform multiple linear regression to identify independent predictors of residual GFR decline. The final model is summarized in Table 3. In essence, proteinuria, baseline residual GFR, the use of diuretics and CCB are independent predictors of rapid residual GFR decline, although the result of CCB usage did not reach statistical significance. In this model, each 1 g/day of proteinuria is associated with an additional 0.22 mL/min decline in residual GFR in one year, and each 1 mL/min higher baseline GFR is associated with an additional 0.14 mL/min decline in residual GFR in one

year. The result of the multiple linear regression model remains similar when only diabetic patients are analyzed; HbA1c does not appear as an independent predictor of the rate of residual GFR decline in diabetic patients (details not shown). Although we noted a significant anti-proteinuric effect of ACE inhibitor or ARB therapy, it is not independently associated with the rate of residual GFR decline even if proteinuria is not added to the linear regression model (details not shown).

PROGRESSION TO ANURIA

During this period, 378 patients (58.6%) progressed to anuria. Another 113 patients died before the development of anuria. During the same period, 42 patients were converted to long-term hemodialysis, 33 had kidney transplantation, 12 were transferred to other dialysis centers, and 1 had recovery of kidney function.

TABLE 3  
Multiple Linear Regression Model for Independent Predictors of RRF Decline

Factor	Adjusted regression coefficient	95% CI	
Proteinuria	-0.018	-0.011 to -0.025	$p < 0.0001$
Baseline residual GFR	-0.012	-0.008 to -0.017	$p < 0.0001$
Use of diuretic	-0.030	-0.002 to -0.058	$p = 0.04$
Use of CCB	-0.028	-0.005 to -0.061	$p = 0.09$
Model constant	0.046	0.006 to 0.085	$p = 0.02$

RRF = residual renal function; CI = confidence interval; GFR = glomerular filtration rate; CCB = calcium channel blocker.

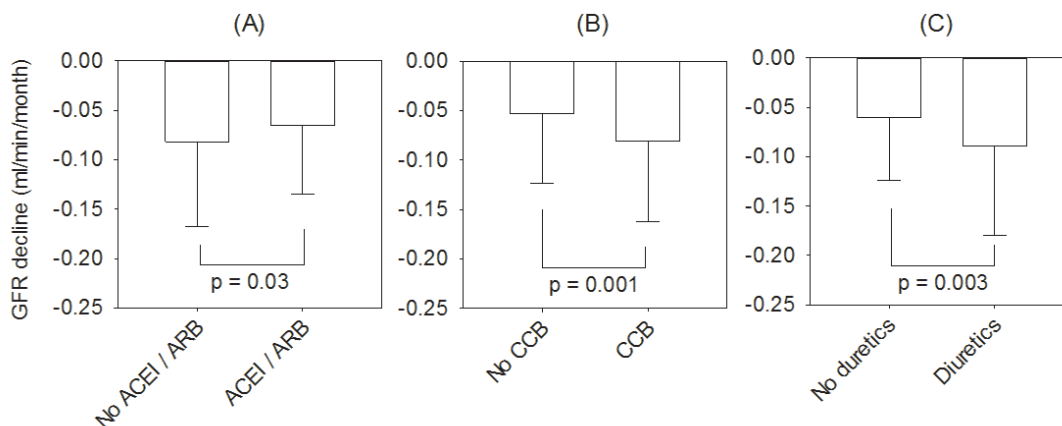


Figure 2 — The effect of drug therapy on the rate of residual glomerular filtration rate (GFR) decline: (A) angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB); (B) calcium channel blockers (CCB); and (C) diuretics. Data are compared using unpaired Student *t*-test.

Univariate Cox analysis for the risk of progressing to anuria is summarized in Table 4. In short, patients with PVD (Figure 3), high body mass index, systolic blood pressure, serum phosphate level, proteinuria, MIS score, glucose exposure, baseline residual GFR, more peritonitis episodes, and a low SGA score were associated with the risk of developing anuria. In contrast, the risk of developing anuria was not related to diabetic status, presence of IHD, Charlson’s score, peritoneal transport status, dietary protein intake, or the use of aminoglycosides, ACE inhibitor or ARB, CCB, or diuretics (details not shown). There was no significant relation between the year of starting PD and the risk of progressing to anuria.

A Cox proportional hazard model was also constructed to determine the independent predictors of time to anuria. The final model is summarized in Table 4. In this model, higher proteinuria, glucose exposure, and number of peritonitis episode were independent predictors of progression to anuria, while a higher baseline residual GFR was protective. In this model, each 1 g/day of proteinuria is associated with a 22.3% increase in the risk of progressing to anuria, each 1 mL/min higher baseline GFR is associated with an 11.3% reduction in the risk, while each episode of peritonitis is associated with a 7.9% increase in the risk. The result of the Cox model remains similar when only diabetic patients are analyzed; HbA1c does not appear as an independent predictor of

TABLE 4  
Cox Proportional Hazard Model for Independent Predictors of Anuria

Factor	Univariate analysis			Multivariate analysis		
	Unadjusted HR	95% CI	<i>p</i>	Adjusted HR	95% CI	<i>p</i>
Body mass index	1.06	1.03–1.09	<i>p</i> =0.0001	--		
PVD	1.71	1.21–2.42	<i>p</i> =0.002	--		
Systolic BP	1.07	1.01–1.14	<i>p</i> =0.02	--		
Serum phosphate	1.38	1.01–1.88	<i>p</i> =0.046	--		
Proteinuria	1.19	1.03–1.37	<i>p</i> =0.02	1.13	1.05–1.22	<i>p</i> =0.001
Glucose exposure <sup>a</sup>	1.02	1.01–1.04	<i>p</i> =0.008	1.03	1.01–1.04	<i>p</i> =0.003
MIS	1.10	1.06–1.15	<i>p</i> <0.0001	--		
Baseline residual GFR	0.89	0.84–0.93	<i>p</i> <0.0001	0.85	0.81–0.91	<i>p</i> <0.0001
Number of peritonitis episodes	1.04	1.02–1.07	<i>p</i> =0.0003	1.04	1.01–1.06	<i>p</i> =0.003

HR = hazard ratio; CI = confidence interval; PVD = peripheral vascular disease; BP = blood pressure; MIS = malnutrition inflammation score; GFR = glomerular filtration rate.

<sup>a</sup> Every 10 g/day increase in exposure.

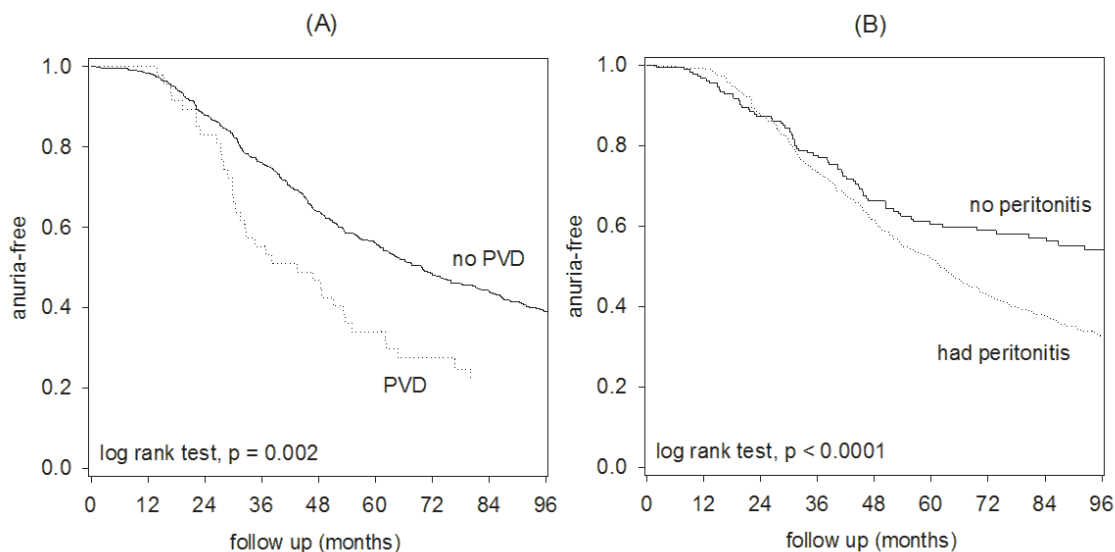


Figure 3 — Kaplan Meier plot of the risk of developing anuria, comparing: (A) patients with and without peripheral vascular disease (PVD); and (B) patients with and without peritonitis episode.

progressing to anuria in diabetic patients (details not shown). Similarly, ACE inhibitor or ARB therapy is not independently associated with the risk of progressing to anuria even if proteinuria is not added to the Cox model (details not shown).

## DISCUSSION

In this observational study, we found that proteinuria, baseline residual GFR, and the use of diuretics are independently related to the rate of decline of residual renal function in Chinese CAPD patients, while proteinuria, baseline residual GFR, glucose exposure, and the number of peritonitis episodes are independent predictors for the development of anuria.

Our results are by and large in line with previous reports. The overall rate of residual renal function decline, in terms of the slope of GFR, is similar to 0.05 to 0.11 mL/min/month as reported in previous reports of other PD patients (12,14). We found that proteinuria accounts for over 25% of the variability of residual GFR decline, and is an independent predictor of progressing to anuria. Similarly, Jansen *et al.* (11) found that a higher urinary protein loss is independently associated with the rate of GFR decline in the first 12 months of dialysis.

We found that a higher baseline residual GFR is independently associated with a high rate of residual renal function decline (as determined by the slope of GFR decline with time) but a *lower* risk of developing anuria. We believe the lower risk of developing anuria in patients with a high baseline residual GFR could readily be explained by the phenomenon of lead time bias. In fact, our observation is similar to previous reports. For example, when the rate of GFR decline is determined by slope calculation, both Liao *et al.* (14) and Liu *et al.* (31) found that a higher baseline GFR is independently associated with faster decline of residual GFR. On the other hand, when time to anuria is used as the end point, Johnson *et al.* (12) reported that a higher baseline GFR is independently associated with a lower risk.

Similar to previous studies (9,14,15,31), we found that patients with diabetes and PVD had more rapid deterioration of residual GFR, although the effect became insignificant after multivariate analysis to adjust for confounding factors. Contrary to the general expectation, we found that the number of total peritonitis episodes, rather than the degree of exposure to aminoglycosides, is related to the risk of progressing to anuria. Similarly, Liao *et al.* (14) found that the episodes of peritonitis independently predicted the decline of residual GFR, while Badve *et al.* (32) reported that the use of aminoglycosides for PD-associated peritonitis does not affect residual renal

function. Although blood pressure and diabetic control are well documented to affect the rate of renal function decline in pre-dialysis patients, we found that systolic blood pressure had only a weak association with the risk of anuria, and HbA1c level had only a modest correlation with the slope of GFR decline. Moreover, the effect of both of them disappeared with multivariate analysis to control for confounding factors. Our observation is consistent with previous reports by Jansen *et al.* (11) and Sung *et al.* (33).

In this study, we found that the slope of GFR decline was slower in patients receiving ACE inhibitor or ARB, and faster in those treated with CCB or diuretics. Our finding is consistent with the result of previous observational studies (9,14) as well as randomized control trials (34,35). The protective effect of renin-angiotensin system blockade, however, disappeared after multivariate analysis to adjust for confounding factors. We believe our results do not disprove the efficacy of such a treatment because a retrospective study like ours is likely biased by the treatment indication. Moreover, there is a strong internal correlation between proteinuria and ACE inhibitor or ARB treatment that could not be reliably adjusted for during multivariate analysis.

In this study, we found that diuretic treatment and high glucose exposure (from hypertonic PD solution) are associated with more rapid decline of residual renal function, but causality could not be established in an observational study. On one hand, excessive volume depletion and glucose toxicity may accelerate the loss of residual renal function. However, it is also possible that diuretics and hypertonic exchange are more likely needed for volume control in patients with rapid loss of residual renal function. In our opinion, diuretic treatment is essentially a non-modifiable risk factor in this situation and, since the detrimental effect of chronic volume overload is well documented in PD patients (36), the use of diuretic treatment should not be discouraged. Since the number of patients treated with glucose-free solutions (e.g., icodextrin) was small, we were unable to analyze the effect of glucose-sparing strategies on the rate of residual GFR decline.

An important observation that we obtained from this study is that the predicting factors for the slope of residual GFR decline are somewhat different from those for the risk of developing anuria. It seems likely that in dialysis patients, residual renal function is lost in two pathways. On one hand, there is a gradual deterioration due to the underlying kidney disease and progressive renal scarring. On the other, a considerable proportion of patients develop anuria suddenly because of acute events (for example, sudden shut down of renal circulation,

acute infection, or exposure to nephrotoxic agents). Our results indicate that clinical research on residual renal function should use both GFR slope and development of anuria as clinical end points.

There are a number of limitations to our study. First, because of the retrospective nature of our study and the practical logistics we used to identify the cases, we omitted patients who had very rapid loss of residual renal function and developed anuria within three months after the initiation of dialysis. For the same reason, we do not have data on all hospital admission or non-peritonitis infections. In our center, aminoglycosides are seldom used in non-peritonitis infections, and this part of our data should be accurate. Unfortunately, we do not have data on the exposure to other nephrotoxic drugs such as non-steroidal anti-inflammatory agents or iodinated contrast, nor do we have data on the use of temporary hemodialysis support during the course of CAPD. In addition, we do not have data on the exact duration of each peritonitis episode; it is possible that the total duration of peritoneal inflammation, rather than the actual number of peritonitis episodes, is the determining factor of residual renal function loss. As mentioned above, any acute infection or cardiac events may precipitate acute irreversible loss of residual renal function, but this hypothesis could not be tested in our present study.

In addition, we only studied CAPD patients from a single center. Although this approach excludes several important confounding factors and makes our study population homogeneous, the validity of our results in other patient populations (for example, patients from other countries or those on hemodialysis or machine-assisted PD) is uncertain. Since hemodialysis and machine-assisted PD have both been reported to cause a more rapid decline of residual renal function as compared to CAPD (9,16), we could not exclude the possibility that the effect of dialysis modality on residual renal function decline may overwhelm other clinical factors that we identify.

Taken together, our results indicate that baseline residual GFR, proteinuria, diuretic treatment, glucose exposure, and peritonitis are major factors affecting the rate of RRF decline. We consider proteinuria and peritonitis are possibly reversible factors, and the role of anti-proteinuric therapy and measures to prevent peritonitis episodes in the preservation of RRF should be tested in future studies.

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## DISCLOSURES

The authors declare no conflict of interest.

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