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Effect of fluid and sodium removal on mortality in peritoneal dialysis patients

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Background. Adequacy of peritoneal dialysis (PD) traditionally is assessed using Kt/V_{urea} and total creatinine clearance (TCC). However, this approach underestimates the importance of fluid and sodium removal. The aim of this study was to determine the effect of fluid and sodium removal on morbidity and mortality in PD patients.

Methods. One hundred twenty-five PD patients were monitored for three years from the beginning of the treatment. The effects of demographic features, comorbidity, peritonitis rate, blood pressure, medications, blood biochemistry, peritoneal membrane transport characteristics, residual renal function (RRF), Kt/V_{urea}, TCC, normalized protein nitrogen appearance (nPNA), and removal of sodium and fluid on mortality were evaluated. Total and cardiovascular hospitalization rates were also recorded. A Cox proportional hazards model was used to determine factors predicting mortality.

Results. In the Cox model, comorbidity, total sodium and fluid removals, hypertensive status, serum creatinine, and RRF were independent factors affecting survival. In contrast, Kt/V_{urea} or TCC did not affect the adjusted survivals. Total sodium and fluid removal and hypertensive status also significantly influenced the hospitalization rate. Systolic and diastolic blood pressures were negatively correlated with total fluid ($P < 0.001$) and sodium removal ($P < 0.001$).

Conclusions. Together, these findings suggest that removal of sodium and fluid is a predictor of mortality in PD patients, whereas Kt/V_{urea} and TCC are not factors. Adequate fluid and sodium balance is crucial for the management of patients on PD.

Mortality in patients with end-stage renal disease (ESRD) is 10 to 20 times higher than that in the age-matched general population [1, 2], cardiovascular disease being the most frequent cause of death [1–4]. The clinical outcome of peritoneal dialysis (PD) patients is affected by many factors, including age, race, the presence of comorbid conditions such as diabetes mellitus and cardiovascular disease, nutritional status, serum albumin level, small solute clearance, and peritoneal membrane transport property [5–15].

Several groups have studied on the importance of small solute clearance using Kt/V_{urea} and total creatinine clearance (TCC) to predict morbidity and mortality of PD patients. Although there are some conflicting results [16], an association between small solute clearance and clinical outcome has been found in these studies [10–12, 14, 17–21]. These findings have resulted in the prescription of an adequate dose of treatment based on urea and creatinine kinetics. Regarding the studies indicating cardiovascular disease is the most common cause of death in PD patients [1–4], it is difficult to explain the influence of small solute clearance on cardiovascular events. One explanation for this association might be fluid and sodium balance, which might have a direct effect on cardiovascular mortality. Nevertheless, excess fluid and sodium as potential risk factors for patient morbidity and mortality to our knowledge has not been assessed in prognostic studies. It has been suggested that PD permits more effective management of fluid overload and hypertension than hemodialysis (HD) [22]. However, compelling evidence exists that PD patients have a greater fluid overload than HD patients [23, 24]. Therefore, adequate fluid and sodium balance may be crucial for the management of patients on PD with regard to the prevention of cardiovascular disease.

The purpose of this study was to identify the factors that predict mortality in our PD population during a three-year follow-up period. In addition, we tried to determine the effect of adequacy of fluid and sodium removal on clinical outcome.

METHODS

Patients

One hundred twenty-five patients (77 male and 48 female) who survived more than six months on PD were

Key words: end-stage renal disease, dialysis, death, hospitalization, hypertension, serum creatinine, residual renal function, Kt/V_{urea}, creatinine clearance, high peritoneal transport.

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monitored from the day of starting PD therapy for three years. All patients had started their PD treatment between 1992 and 1996. One hundred sixteen of the patients were on CAPD, and the rest were on automatic PD (APD). The mean age at the start of the treatment was 46.3 ± 14.8 years (range 18 to 74 years). The cause of ESRD was chronic tubulointerstitial nephritis in 37 cases, chronic glomerulonephritis in 34, diabetic nephropathy in 13, renal amyloidosis in 11, autosomal dominant polycystic kidney disease in 8, hypertensive nephrosclerosis in 7, and unknown in 15 cases. All were dialyzed with a glucose dialysate containing 132 mmol/L sodium. A prescription of 24-hour dialysate volume was always performed according to the clinical and biochemical status to avoid uremic symptomatology and to achieve an adequate control of extracellular fluid volume. The median instilled dialysate volume on PD was 8.0 L/24 hours (range of 4.0 to 11.2 L/24 hours), with a mean glucose concentration of 2.14%.

After the training period of three weeks, all patients were regularly examined at an outpatient clinic every two months. Data recorded for each patient included demographic features, comorbidity, blood pressure, medications, blood biochemistry, peritoneal membrane transport characteristics, residual renal function (RRF), kinetic indices of dialysis adequacy, and nutritional status such as Kt/V_{urea}, TCC and normalized protein nitrogen appearance (nPNA), renal, dialytic, and total sodium and fluid removals, peritonitis rate, total and cardiovascular hospitalization rates, and mortality.

Comorbid conditions, including diabetes mellitus, amyloidosis, hypertensive nephrosclerosis, cardiovascular disease, and chronic liver disease present at the start of dialysis, were scored. Each disease was given a value of two. If two diseases were present, this value was squared, and if three were present, this value was cubed [17].

Height and weight were measured with the patient wearing indoor clothing before intraperitoneal dialysate at routine visits. Body mass index (BMI) was calculated by the formula of [weight (kg)/height (m^2)]. Body surface area (BSA) was estimated from Du Bois nomograms [25].

Systolic and diastolic blood pressure levels were measured at the routine visits. Hypertension was defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or taking at least two drugs to control blood pressure. The levels of hematocrit, serum albumin, urea nitrogen, creatinine, sodium, total cholesterol, and triglyceride were measured every two months. Serum albumin was determined by bromcresol purple method. The reference value of the local accredited laboratory was 3.2 to 5.5 g/dL. All the values of arterial blood pressure and blood biochemistry during the follow-up were averaged for each patient.

The transport property of peritoneal membrane was determined by the standard peritoneal equilibration test (PET) [26]. Patients were classified as a high transporter when the ratio of dialysate/plasma (D/P) creatinine at the fourth hour was higher than the mean value plus one standard deviation, and as a low transporter when the D/P creatinine ratio was lower than the mean value minus one standard deviation. The 24-hour dialysate and urine samples were collected to calculate RRF, Kt/V_{urea}, TCC, nPNA, and total sodium removal. RRF was defined as the mean of renal urea nitrogen and creatinine clearances. Weekly TCC was determined by adding the RRF to the peritoneal creatinine clearance. Total body water was calculated by the formulae of Watson, Watson and Batt [27]. Protein nitrogen appearance was calculated according to Bergström et al and was normalized to the actual body weight (nPNA) [28]. Total sodium removal was estimated as the sum of the renal and dialytic sodium losses. The amount of daily dialytic sodium removal was calculated by:

$$(V_{dr} \times C_{dr}) - (V_{in} \times C_{in})$$

where V_{dr} represents the volume of the drained dialysate (L/24 hours), C_{dr} the sodium concentration of the drained dialysate (mmol/L), V_{in} is the volume of the instilled dialysate (L/24 hours), and C_{in} is the sodium concentration of the instilled dialysate (mmol/L). RRF, TCC, and total sodium removal were normalized to 1.73 m^2 BSA. The first kinetic analysis was done following the completion of training of CAPD, that is, within 3 months of commencing treatment and then repeated every 6 to 12 months. All measurements obtained during the follow-up were averaged for each patient. Total fluid removal was estimated as urine volume plus peritoneal ultrafiltration, determined as the means of seven daily urine volume and net peritoneal ultrafiltration rates as noted by the patient the week before the routine visits, and was normalized to 1.73 m^2 BSA.

Statistical analysis

Results are given as mean ± SD. Comparison of means and percentages was by the unpaired two-tailed Student *t* test or Mann-Whitney U test, as appropriate, and the chi-square test with Yates correction. Correlations were analyzed using Pearson's or Spearman's correlation coefficient, as appropriate.

Overall patient survival was estimated for each group with the Kaplan-Meier method, and a comparison of these outcomes was based on the log rank test. In the patient's survival analysis, death was considered as the final event, and transplantation or transfer to HD was regarded as censored information. The Cox proportional hazards model was used for the statistical analysis of patient survival. Death was attributed to the average levels of the study parameters during the follow-up period. The likelihood ratio was used to determine whether the addition of a variable to a model added significantly

to that model. Variables significant at a P value less than 0.02 in univariate analysis were included to a Cox proportional hazards model to assess their independent prognostic value for mortality. Only variables significant at a P value of less than 0.05 were kept in the model. Initially, the demographic and comorbidity data (age, diabetes mellitus, comorbidity score) were presented to the model by forward selection (step I). Thereafter, parameters of nutritional status (serum albumin and creatinine, and nPNA), hematocrit, and peritonitis rate were added to the model (step II). Next, high peritoneal status, RRF, and the indices of dialysis adequacy (Kt/V_{urea} and TCC) were presented to the model (step III). Kt/V_{urea} and TCC were each added separately to this model, and their corresponding peritoneal component was also added separately to the model at the same time. Finally, total sodium and fluid removal and hypertensive status were each presented separately to the model (step IV). This procedure was repeated with a backward selection strategy, and the results of both strategies were compared. The independent prognostic values of the variables were expressed as adjusted relative risks (RR) with their 95% confidence intervals (CIs).

Table 1. Mean values of study parameters

Parameters	Mean ± SD
Body mass index *kg/m²*	24.6 ± 4.0
Body surface area *m²*	1.69 ± 0.19
Systolic blood pressure *mm Hg*	131.3 ± 17.5
Diastolic blood pressure *mm Hg*	83.4 ± 9.8
Hematocrit *%*	31.1 ± 4.2
BUN *mg/dL*	52 ± 9
Serum creatinine *mg/dL*	10.1 ± 2.4
Serum albumin *g/dL*	3.5 ± 0.5
Sodium *mmol/L*	138 ± 2
Total cholesterol *mg/dL*	195 ± 41
Triglyceride *mg/dL*	178 ± 75
D/P creatinine	0.66 ± 0.11
RRF *mL/min/1.73 m²*	1.21 ± 1.36
Urine volume *mL/24 h/1.73 m²*	364 ± 525
Dialytic fluid removal *mL/24 h/1.73 m²*	1302 ± 657
Total fluid removal *mL/24 h/1.73 m²*	1666 ± 685
Renal sodium removal *mmol/24 h/1.73 m²*	18 ± 26
Dialytic sodium removal *mmol/24 h/1.73 m²*	167 ± 80
Total sodium removal *mmol/24 h/1.73 m²*	185 ± 78
Weekly total Kt/V_{urea}	2.03 ± 0.33
Weekly dialytic Kt/V_{urea}	1.78 ± 0.29
Total creatinine clearance *L/week/1.73 m²*	62.3 ± 11.9
Dialytic creatinine clearance *L/week/1.73 m²*	51.2 ± 9.3
nPNA *g/kg/24 h*	1.01 ± 0.19
Peritonitis rate *episodes/patient-year*	0.57 ± 0.50
Total hospitalization *days/patient-year*	18.4 ± 20.4
Cardiovascular hospitalization *days/patient-year*	7.2 ± 10.8

Abbreviations are: BUN, blood urea nitrogen; D/P, dialysate/plasma; RRF, residual renal function; nPNA, normalized protein nitrogen appearance.

The averaged value of the study parameters during the follow-up period were used for each patient.

RESULTS

The total follow-up period was 319 patient-years, with a mean of 30.6 months (range, 7 to 40 months). Twenty-two patients died (20.8%) during the three-year follow-up period. Causes of death were cardiovascular disease in 11 patients (50.0%), infection in 6, malnutrition in 2, and gastrointestinal bleeding, colonic perforation, and unknown in 1 patient each. During the follow-up period, 5 patients received a kidney transplant, while 18 patients were transferred to HD, 5 of whom for ultrafiltration failure. Two- and three-year patient survival rates were 86.3 and 79.2%, respectively. Mean values of the study parameters during the follow-up period are shown in Table 1. There was one comorbid condition in 39 patients at the time of the initiation of PD, 2 in 13 patients, and 3 in 1 patient. The mean comorbidity score was 1.1 ± 1.3.

Sodium removal

The mean total sodium removal was 185 ± 78 mmol/24 h/1.73 m^2, and the median value was 181 mmol/24 h/1.73 m^2. The contribution of renal component to total sodium removal was 9.7%. Although dialytic sodium removal was higher in CAPD patients (170 ± 80 mmol/24 h/1.73 m^2) than that of APD patients (130 ± 78 mmol/24 h/1.73 m^2), the difference did not reach a statistically significant level ($P > 0.05$). There was a strong correlation between peritoneal sodium and fluid removal ($r = 0.83$, $P < 0.001$). Total sodium removal was also positively correlated with total Kt/V_{urea} ($r = 0.42$, $P < 0.001$) and TCC ($r = 0.29$, $P = 0.001$), and negatively correlated with high peritoneal transport status ($r = -0.25$, $P < 0.01$).

Both the total and cardiovascular hospitalization rates were significantly higher in patients who had a total sodium removal below the median value than those of the others (24.9 ± 22.4 vs. 11.9 ± 15.8 days/patient-year, respectively, $P < 0.001$ for total hospitalization, and 10.1 ± 12.7 vs. 4.2 ± 7.6 days/patient-year, respectively, $P < 0.01$ for cardiovascular hospitalization).

Patients were classified into four groups according to total sodium removal: group I, total sodium removal below the 25th percentile value (<130 mmol/24 h/1.73 m^2); group II, total sodium removal between the 25th and 50th percentile values (130 to 181 mmol/24 h/1.73 m^2); group III, total sodium removal between 50th and 75th percentile values (181 to 232 mmol/24 h/1.73 m^2); and group IV, total sodium removal above the 75th percentile value (>232 mmol/24 h/1.73 m^2). The three-year patient survival rates were significantly different among these groups (group I, 59.3%; group II, 73.1%; group III, 88.9%; and group IV, 96.1%, $P < 0.01$; Fig. 1).

Fluid removal

The mean renal, dialytic, and total fluid removals were 364 ± 525, 1302 ± 657, and 1666 ± 685 mL/24 h/1.73 m^2, respectively. The contribution of urine volume to total

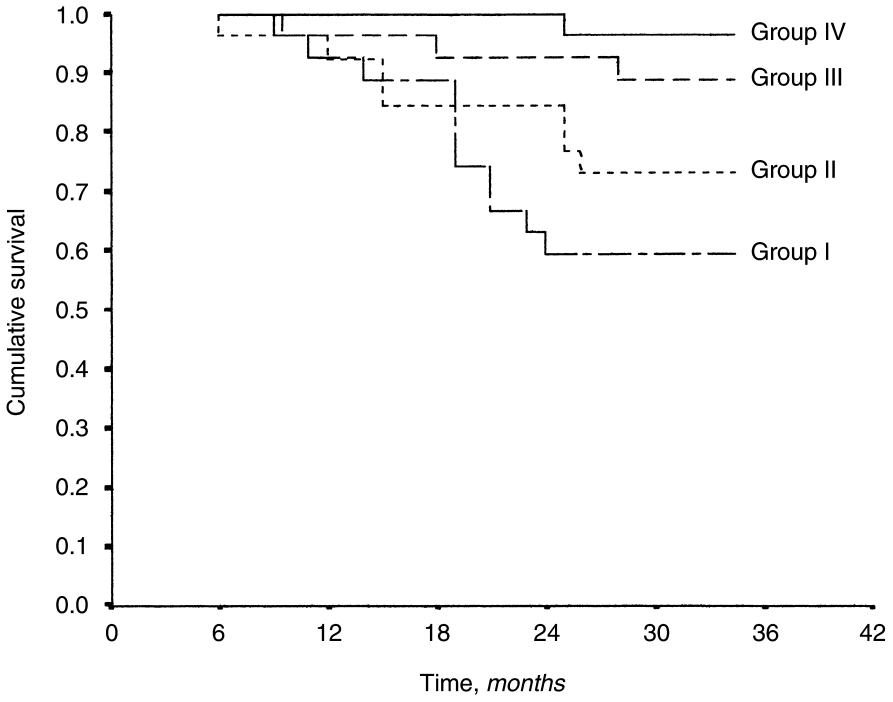

Fig. 1. Three-year patient survival rates in peritoneal dialysis (PD) patients according to the total sodium removal. The four groups are defined as: group I, <130 mmol/24 h/1.73 m^2; group II, 130 to 181 mmol/24 h/1.73 m^2; group III, 181 to 232 mmol/24 h/1.73 m^2; and group IV, >232 mmol/24 h/1.73 m^2.

fluid removal was 21.8%. Total fluid removal was negatively correlated with high transport status ($r = -0.39$, $P < 0.001$). The total and cardiovascular hospitalization rates were significantly higher in patients who had a total fluid removal scores below the median value (<1570 mL/24 h/1.73m^2) than those scoring above the median (25.2 ± 23.4 vs. 11.6 ± 14.0 days/patient year, respectively, $P < 0.001$ for total hospitalization, and 11.4 ± 13.7 vs. 2.9 ± 4.1 days/patient year, respectively, $P < 0.001$ for cardiovascular hospitalization).

Patients were classified into four groups according to total fluid removal: group I, total fluid removal below the 25th percentile (<1265 mL/24 h/1.73 m^2); group II, total fluid removal between the 25th and 50th percentiles (1265 to 1570 mL/24 h/1.73 m^2); group III, total fluid removal between the 50th and 75th percentiles (1570 to 2035 mL/24 h/1.73 m^2); and group IV, total fluid removal above the 75th percentile (>2035 mL/24 h/1.73 m^2). The three-year patient survival rates were different among these groups (group I, 61.5%; group II, 71.4%; group III, 88.0%; and group IV, 96.3%, $P < 0.01$; Fig. 2).

Blood pressure

The mean blood pressure level was 131.3 ± 17.4/83.4 ± 9.8 mm Hg. Forty-nine patients (39.2%) were hypertensive. The three-year patient survival rate was significantly worse in hypertensive patients compared to that of normotensives (60.5 vs. 92.1%, respectively, $P = 0.0001$). The total sodium removal was found to be negatively correlated with systolic ($r = -0.49$, $P < 0.001$), and diastolic blood pressure levels ($r = -0.42$, $P < 0.001$) and the use of antihypertensive drugs ($r = -0.56$, $P < 0.001$). There also were statistically significant correlations between total fluid removal and both systolic ($r = -0.48$, $P < 0.001$), and diastolic blood pressures ($r = -0.39$, $P < 0.001$). Total sodium removal, total fluid removal, urine volume, Kt/V_{urea}, TCC, and serum albumin were significantly lower in hypertensive patients than those in normotensives (Table 2). Total and cardiovascular hospitalization rates were significantly higher in patients with hypertension ($P = 0.001$ and $P < 0.01$, respectively).

Peritoneal transport characteristics

The mean D/P creatinine ratio was 0.66 ± 0.11. Fifteen patients (12.0%) were classified as high transporters, and 19 (15.2%) were classified as low transporters according to the PET scores. Total and peritoneal sodium removal, total and peritoneal fluid removal, Kt/V_{urea}, serum albumin, and creatinine were significantly lower in high transporters than those of the average or low transporters ($P < 0.01$, $P < 0.01$, $P < 0.05$, $P < 0.001$, and $P < 0.05$, respectively; Table 3). The TCC and nPNA were not different between the groups. In high transporters, systolic blood pressure was significantly higher compared to the average or low transporters ($P < 0.05$). Among the high transporters, the prevalence of hypertension was significantly higher than the other groups (66.7 vs. 35.5%, respectively, $P < 0.05$). The rates of total and cardiovascular hospitalization were significantly higher

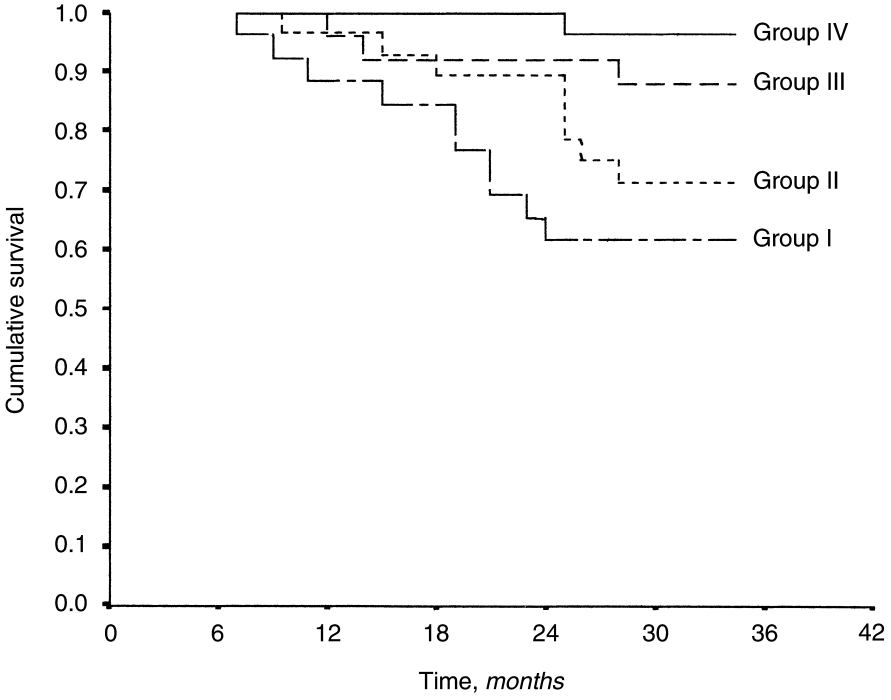

Fig. 2. Three-year patient survival rates in PD patients according to total fluid removal. The four groups are defined as: group I, <1265 mL/24 h/1.73 m^2; group II, 1265 to 1570 mL/24 h/1.73 m^2; group III, 1570 to 2035 mL/24 h/1.73 m^2; and group IV, >2035 mL/24 h/1.73 m^2.

Table 2. Comparison of the study parameters between hypertensive and normotensive patients

	Hypertensives	Normotensives	*P*
Body mass index *kg/m²*	25.1 ± 3.7	23.8 ± 4.3	=0.07
Total sodium removal *mmol/24 h/1.73 m²*	136 ± 60	218 ± 70	<0.001
Total fluid removal *mL/24 h/1.73 m²*	1353 ± 570	1875 ± 679	<0.001
Urine volume *mL/24 h/1.73 m²*	245 ± 420	443 ± 573	<0.05
RRF *mL/min/1.73 m²*	0.93 ± 1.27	1.38 ± 1.40	=0.07
Weekly total Kt/V_{urea}	1.92 ± 0.28	2.10 ± 0.35	<0.01
TCC *L/week/1.73 m²*	59.0 ± 11.9	64.5 ± 11.4	=0.01
nPNA *g/kg/24 h*	0.99 ± 0.17	1.03 ± 0.21	NS
Serum albumin *g/dL*	3.32 ± 0.45	3.64 ± 0.46	<0.001
Total hospitalization *days/patient-year*	25.6 ± 22.6	13.7 ± 17.3	=0.001
Cardiovascular hospitalization *days/patient-year*	10.5 ± 12.4	5.0 ± 9.0	<0.01

Abbreviations are: RRF, residual renal function; TCC, total creatinine clearance; nPNA, normalized protein nitrogen appearance; NS, not significant.

in high transporters than the other groups ($P < 0.01$ and $P < 0.001$, respectively).

Seven of the high transporters died during the follow-up period. The three-year survival rate was significantly worse in high transporters compared with both average and low transporters (46.2, 84.4, and 81.3%, respectively, $P < 0.001$). In the high transporters who died during the follow-up, the baseline comorbidity score was significantly higher than those of the surviving high transporters and patients with other transport status (3.43 ± 0.98, 1.00 ± 1.07, and 0.93 ± 1.26, respectively, $P < 0.01$). These patients had also less RRF (0.73 ± 0.39 vs. 1.24 ± 1.12 mL/min/1.73 m^2), and total (109 ± 55 vs. 154 ± 68 mmol/24 h/1.73 m^2) and dialytic sodium removal (98 ± 51 vs. 133 ± 61 mmol/24 h/1.73 m^2) than those of the survivors, although the differences did not reach statistical significance ($P > 0.05$).

Small solute clearances

The mean values of Kt/V_{urea}, TCC, and nPNA are shown in Table 1. The contribution of renal component on total solute clearance was 12.4% for Kt/V_{urea} and 17.7% for TCC. The three-year survival rate was significantly higher in patients who had a Kt/V_{urea} value above 2.0 (88.5 vs. 70.4%, respectively, $P < 0.05$), a TCC value above 60.0 L/week/1.73m^2 (87.7 vs. 69.4%, respectively, $P < 0.05$), or an nPNA value above 1.0 g/kg/24 h (89.4 vs. 71.2%, respectively, $P < 0.05$) than the other patients with lower values.

Table 3. Comparison of the study parameters according to peritoneal transport characteristics of the patients

	High transporters	Other patients	*P*
BUN *mg/dL*	50 ± 10	53 ± 10	NS
Serum creatinine *mg/dL*	8.7 ± 2.6	10.3 ± 2.4	<0.05
Serum albumin *g/dL*	3.1 ± 0.5	3.6 ± 0.4	<0.001
Systolic blood pressure *mm Hg*	139.9 ± 11.5	130.1 ± 17.2	<0.05
Diastolic blood pressure *mm Hg*	86.4 ± 6.3	83.0 ± 9.4	NS
Dialytic fluid removal *mL/24 h/1.73 m²*	876 ± 730	1361 ± 628	<0.01
Total fluid removal *mL/24 h/1.73 m²*	1186 ± 687	1732 ± 661	<0.01
Dialytic sodium removal *mmol/24 h/1.73 m²*	117 ± 58	174 ± 80	<0.01
Total sodium removal *mmol/24 h/1.73 m²*	133 ± 64	192 ± 77	<0.01
RRF *mL/min/1.73 m²*	1.00 ± 0.82	1.23 ± 1.42	NS
Weekly total Kt/V_{urea}	1.87 ± 0.29	2.05 ± 0.33	<0.05
TCC *L/week/1.73 m²*	64.2 ± 9.1	62.0 ± 12.2	NS
nPNA *g/kg/24 h*	0.96 ± 0.21	1.02 ± 0.19	NS
Total hospitalization *days/patient-year*	31.5 ± 31.2	16.7 ± 17.9	<0.01
Cardiovascular hospitalization *days/patient-year*	17.0 ± 19.3	5.8 ± 8.5	<0.001

Abbreviations are: BUN, blood urea nitrogen; RRF, residual renal function; TCC, total creatinine clearance; nPNA, normalized protein nitrogen appearance; NS, not significant.

Cox proportional hazards model

The relative risks (RRs) of death associated with the study parameters are shown in Table 4. The following variables reached statistically significant levels in univariate analysis and were included in the Cox model: age, diabetes mellitus, comorbidity score, serum creatinine and albumin, nPNA, hematocrit, peritonitis rate, high transporter status, RRF, Kt/V_{urea}, TCC, total sodium removal, total fluid removal, and hypertensive status. Table 5 presents the Cox model at each step until the final model. The final Cox proportional hazards model for patient survival obtained by forward and backward selection was identical. Tables 6, 7, and 8 show the final models containing total sodium removal, total fluid removal, and hypertension, respectively. Comorbidity, serum creatinine, RRF, total sodium removal, total fluid removal, and hypertensive status were the predictors of death. Similar results were obtained when dialytic components were presented to the model instead of total sodium and fluid removals [RR = 0.91 (95% CI, 0.85 to 0.98) per 10 mmol/24 h/1.73 m^2, $P = 0.01$ for peritoneal sodium removal; and RR=0.94 (95% CI, 0.90 to 0.99) per 100 mL/24 h/1.73 m^2, $P < 0.05$ for peritoneal fluid removal]. It was estimated that a 10 mmol/24 h/1.73 m^2 higher value in total sodium removal, and a 100 mL/24 h/1.73 m^2 higher value in total fluid removal was associated with a 10% decrease in the RR of death. In contrast, the total and dialytic components of Kt/V_{urea} and TCC were not predictive for death.

Table 4. Relative risk of death (RR) of study parameters in univariate Cox regression

	RR	95% CI	*P*
Age *1 year*	1.04	1.01–1.07	<0.05
Sex male	1.36	0.58–3.18	NS
Body mass index *1 kg/m²*	1.02	0.88–1.10	NS
Diabetes mellitus *present*	3.54	1.38–9.06	<0.01
Comorbidity score *1 point*	1.97	1.47–2.63	<0.0001
1 comorbid condition	6.01	1.68–21.57	<0.01
2 comorbid conditions	17.64	4.63–67.28	<0.0001
Peritonitis rate *1 episode/patient-year*	3.63	1.54–8.52	<0.01
Systolic blood pressure *10 mm Hg*	1.64	1.22–2.21	<0.01
Diastolic blood pressure *10 mm Hg*	1.70	1.10–2.61	<0.05
Hypertension *present*	6.01	2.21–16.32	<0.001
Use of antihypertensive drugs			
1 drug	4.88	1.63–14.57	<0.01
2 drugs	9.25	3.01–28.47	=0.0001
Hematocrit *1%*	0.86	0.77–0.97	<0.05
BUN *1 mg/dL*	0.95	0.91–1.01	NS
Serum creatinine *1 mg/dL*	0.54	0.41–0.71	<0.0001
Serum albumin *0.1 g/dL*	0.85	0.79–0.92	=0.0001
Total cholesterol *10 mg/dL*	0.90	0.81–1.01	NS
Triglyceride *10 mg/dL*	0.95	0.90–1.01	NS
Instilled dialysate volume *100 mL/24 h/1.73 m²*	1.00	0.97–1.04	NS
RRF *1 mL/min/1.73 m²*	0.59	0.36–0.98	<0.05
High transporter status *present*	4.73	1.92–11.66	<0.001
Kt/V_{urea} *0.1 unit/week*	0.79	0.65–0.96	<0.05
TCC *1 L/week/1.73 m²*	0.94	0.90–0.99	<0.05
nPNA *0.1 g/kg/24 h*	0.67	0.49–0.90	<0.01
Urine output *100 mL/24 h/1.73 m²*	0.97	0.95–0.99	<0.05
Dialytic fluid removal *100 mL/24 h/1.73 m²*	0.89	0.83–0.96	<0.01
Total fluid removal *100 mL/24 h/1.73 m²*	0.88	0.83–0.95	<0.001
Renal sodium removal *1 mmol/24 h/1.73 m²*	0.97	0.95–1.01	NS
Dialytic sodium removal *10 mmol/24 h/1.73 m²*	0.88	0.83–0.94	<0.001
Total sodium removal *10 mmol/24 h/1.73 m²*	0.86	0.80–0.92	<0.0001

Abbreviations are: BUN, blood urea nitrogen; RRF, residual renal function; TCC, total creatinine clearance; nPNA, normalized protein nitrogen appearance; NS, not significant.

DISCUSSION

Dialysis prolongs the life of patients with ESRD by the removal of excess fluid and waste products. Despite this therapy, mortality in this population is 10 to 20 times higher than in the age-matched general population [1, 2]. Several studies have shown that insufficient urea and creatinine clearance in PD is associated with increased mortality and morbidity [10–12, 14, 17–21]. The CANUSA study, a prospective, cohort study of 680 new patients treated by PD, provides further information [12]. In that study, following adjustments for demographic factors such as age, diabetes, cardiovascular disease and serum albumin, both Kt/V_{urea} and TCC were shown to predict survival significantly. These findings have lead to a definition of dialysis adequacy by parameters of small solute removal. However, in view of the finding of many studies that cardiovascular disease is the most common cause of death [1–4], accounting for nearly 50% of mortality,

Table 5. Cox proportional hazards model at each step until final model

	RR	95% CI
Step I		
Age *1 year*	1.01	0.97–1.04
Comorbidity score *1 point*	1.97	1.47–2.62
Diabetes mellitus *present*	0.73	0.25–2.19
Step II		
Comorbidity score *1 point*	1.77	1.31–2.40
Serum albumin *0.1 g/dL*	0.93	0.83–1.05
Serum creatinine *1 mg/dL*	0.68	0.55–0.83
nPNA *0.1 g/kg/24 h*	0.79	0.60–1.04
Hematocrit *1%*	0.90	0.79–1.02
Peritonitis rate *1 episode/patient-year*	0.94	0.62–1.45
Step III		
Comorbidity score *1 point*	1.87	1.36–2.58
Serum creatinine *1 mg/dL*	0.64	0.50–0.79
High transporter status *present*	1.07	0.35–3.26
RRF *1 mL/min/1.73 m²*	0.53	0.31–0.92
Small solute clearance		
Total Kt/V_{urea} *0.1 unit/week*	0.90	0.74–1.10
TCC *1 L/week/1.73 m²*	0.95	0.89–1.01

Abbreviations are: nPNA, normalized protein nitrogen appearance; RRF, residual renal function; TCC, total creatinine clearance; NS, not significant; RR, relative risk of death.

Table 6. Final multivariate Cox proportional hazards model of patient survival using total sodium removal

	RR	95% CI	*P*
Comorbidity score *1 point*	1.65	1.19–2.31	<0.01
Serum creatinine *1 mg/dL*	0.69	0.55–0.87	<0.01
RRF 1 mL/*min/1.73 m²*	0.53	0.31–0.91	<0.05
Total sodium removal *10 mmol/24 h/1.73 m²*	0.90	0.84–0.96	<0.001

Abbreviations are: RR, relative risk of death; RRF, residual renal function.

Table 7. Final multivariate Cox proportional hazards model of patient survival using total fluid removal

	RR	95% CI	*P*
Comorbidity score *1 point*	2.04	1.44–2.90	=0.0001
Serum creatinine *1 mg/dL*	0.69	0.56–0.86	<0.001
RRF *1 mL/min/1.73 m²*	0.41	0.22–0.73	<0.01
Total fluid removal *100 mL/24 h/1.73 m²*	0.90	0.84–0.96	<0.01

Abbreviations are: RR, relative risk of death; RRF, residual renal function.

Table 8. Final multivariate Cox proportional hazards model of patient survival using hypertensive status

	RR	95% CI	*P*
Comorbidity score *1 point*	2.20	1.51–3.23	<0.0001
Serum creatinine *1 mg/dL*	0.74	0.59–0.93	=0.01
RRF *1 mL/min/1.73 m²*	0.45	0.24–0.83	<0.05
Hypertension *present*	5.61	1.97–15.93	=0.001

Abbreviations are: RR, relative risk of death; RRF, residual renal function.

it is logical to assume that failure to achieve targets of adequacy is in some way associated with an increased risk of adverse cardiovascular targets. It is difficult to explain the influence of small solute clearance on cardiovascular disease. Harty, Venning and Gokal suggested that insufficient clearance returns the patients to the predialysis uremic milieu and thus increases the likelihood of cardiac dysfunction [29]. Another possible explanation for the association between small solute clearance and cardiovascular mortality may be the relationship of small solute clearance to fluid and sodium balance, which could have a direct effect on cardiovascular events. Inadequate fluid and sodium removal as potential risk factors for patient morbidity and mortality have not yet been assessed in PD patients. Recently, the Netherlands Cooperative Study on the Adequacy of Dialysis showed that systolic blood pressure, as an indicator of fluid overload, is an independent predictor of mortality [15]. However, in that study, total daily fluid removal was not significantly associated with mortality, and the effect of sodium removal on patient survival has not been examined.

Although the present study was done with a relatively small number of patients, it provides useful data about the prognostic factors in our PD cohort. Particularly, the center effect on prognosis was excluded, as it was a single-center study. Moreover, our patient population was younger and had less comorbid conditions than that in other published studies. The incidence of diabetes in our study population was less than that in the CANUSA study (10.4 vs. 29.7%), indicating that the present study had a few confounding factors. The most remarkable result of this study was the importance of the predictive effect of adequacy of fluid and sodium removal on mortality in PD patients. Both fluid and sodium removal were independent predictors of death in Cox model. A 10 mmol/24 h/1.73 m^2 lower value of total sodium removal and a 100 mL/24 h/1.73 m^2 lower value of total fluid removal was associated with a 10% increase in the RR of death. The survival rate, determined with the Kaplan-Meier survival analysis, increased linearly over the entire range of both fluid or sodium removal. Moreover, decreased fluid and sodium removal was associated with an increased hospitalization rate. Similar to studies of Jager et al [15] and Kemperman et al [30], hypertensive status was found to be a poor prognostic indicator in Cox model. Kaplan-Meier survival analysis revealed that three-year patient survival rate was significantly lower in hypertensive patients compared to normotensives. Although the pathophysiology of hypertension in PD patients is multifactorial, the significant negative correlations between blood pressures and both fluid and sodium removal suggest that retention of fluid and sodium is quite important. The significant association between the use of antihypertensive drugs and mortality in univariate analysis suggests that the antihypertensive medications did not abolish the undesirable effect of the retention of fluid and sodium, and consequently hypertension on prognosis in dialysis patients. Adequate sodium and fluid removal as the treatment for hypertension instead of antihypertensive drugs seems to be a more

logical approach. It is speculated that a high fluid and sodium removal on dialysis is not only an indicator of good volume control, but also may be related to more fluid and sodium intake. However, the negative correlations observed between blood pressures and both sodium and fluid removal in our study suggest that a high fluid and sodium removal can provide good volume control.

The experience from Tassin, France has shown that aggressive blood pressure control and normalization of extracellular volume with long slow HD improved the overall patient outcome [31]. There is no reason to believe that this would be different in PD. Therefore, rigorous control of blood pressure and normalization of the extracellular volume status should be a part of the definition of adequacy in PD patients. Despite some hemodynamic advantages of PD, there is compelling evidence that PD patients have greater fluid overload than HD. Rottembourg monitored pulmonary capillary wedge pressures in CAPD patients and found that they were constantly overhydrated [23]. The overhydration is further demonstrable when CAPD patients are transferred to HD. Within three months after transfer to HD, significant decreases were observed in body weight and blood pressure [24]. Two important conclusions can be derived from these observations: First, the determination of dry weight of PD patients is difficult, unless hemodynamic parameters are obtained. Second, there is a serious problem of achieving a normal fluid and sodium balance in the greater portion of PD patients. Indeed, clinical features of overhydration are evident in approximately one fourth of the patients undergoing PD [32], and latent overhydration also is quite frequent in these patients. Chronic asymptomatic fluid overload would contribute to hypertension, and thus left ventricular hypertrophy, a predictor of mortality in ESRD patients [33, 34], or directly to cardiac dilation. Excess of fluid is generally accompanied by excess extracellular sodium. Adequate fluid and sodium balance therefore is crucial for the management of patients on PD to prevent cardiovascular disease. Restricting oral fluid and sodium intake is frequently not enough, and compliance is often inadequate, to achieve a neutral fluid and sodium balance. RRF may have an important impact on the ability to deliver adequate fluid and sodium balance. However, once the RRF is too low or absent, which generally occurs two years after the initiation of dialysis, control of fluid and sodium retention as well as hypertension becomes more difficult. Therefore, fluid and sodium removal by dialysis may be an important approach to reduce the risk of death in PD patients.

The present study also demonstrates that RRF has a major impact on patient survival. Data from CANUSA demonstrated that the overall outcome was worse for patients who lost their RRF (abstract; Bargman et al, *J Am Soc Nephrol* 8:185A, 1997). Lameire reported that although the prevalence of left ventricular hypertrophy and hypertension decreased significantly in the first three years, after five years, both of these risk factors were found with the same prevalence as at the start of CAPD treatments [35]. This late increase in the frequency of left ventricular hypertrophy and hypertension probably reflects the loss of RRF. The adverse impact of loss of RRF on outcome in PD patients could be partly from a difficulty in managing fluid status, hypertension, and left ventricular hypertrophy, all of which contribute to increased cardiovascular mortality.

In contrast to what has been suggested in other studies [13, 14], a high peritoneal transporter status was found to be associated with patient survival only in the univariate analysis but not in the multivariate analysis. The cause of the lack of association between high transport status and mortality in the multivariate analysis might be that the baseline comorbidity score was significantly higher in those high transporters who died compared to other patients. High transporters have a decreased fluid and sodium removal and a higher blood pressure level. Moreover, the hospitalization rate was found to be significantly higher in high transporters. Therefore, aggressive control of volume status and blood pressure would help to decrease cardiovascular morbidity and mortality in these patients.

The validity of small solute clearance for clinical outcome in PD patients has been debated, with studies favoring [10–12, 14, 17–21] or opposing [15, 16] the theory. We have not found an independent association between mortality and either Kt/V_{urea} or TCC in the Cox model. The clearance concept was developed to characterize the quality of a membrane, but not to completely estimate the removal of waste products. The Kt/V value therefore reflects not only the fractional clearance of urea, but also the peritoneal permeability and the degree of fluid removal. It is recognized that the loss of ultrafiltration due to high peritoneal permeability and declining of RRF leads to a state of chronic fluid overload. In this situation, the measured Kt/V_{urea} is less because the V represents an increased volume of urea distribution caused by increased fluid accumulation. Thus, decreased Kt/V_{urea} may reflect an increase in volume as opposed to inadequate absolute solute removal. The lower values of Kt/V_{urea} and TCC in hypertensive patients compared with normotensives in present study supports this probability. The predictive value of Kt/V_{urea} or TCC on prognosis largely depends upon RRF, but not the dialytic component in most of the relevant studies [12, 20, 21]. Furthermore, no study has shown clearly that a prospective increase in peritoneal clearance leads to improved outcomes.

We found that serum creatinine and comorbid conditions were independent predictors of survival in the Cox model. A 1 mg/dL lower value of serum creatinine was associated with a 30% increase in the RR of death. How-

ever, in contrast to what other studies have suggested [6, 9, 12, 34], serum albumin was not an independent predictor of survival in our multivariate analysis. The relationship between serum albumin and patient survival in univariate analysis may be a consequence of comorbid conditions and decreased fluid removal, which result in hypoalbuminemia. Our findings suggest that serum creatinine may be a better biochemical indicator of prognosis than serum albumin.

In conclusion, adequacy of dialysis should refer to the provision of enough renal replacement therapy to a particular patient, not only to alleviate the uremic symptoms, but also improve the patient's overall well being by reducing morbidity and mortality. The best means of assessing the adequacy of PD remains ill defined. Solute clearance should not be the unique criterion for assessing adequacy in PD patients. The concept of adequate dialysis should include adequate fluid and sodium removal to achieve normal volume homeostasis, control of blood pressure, and adequate nutrition.

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APPENDIX

Abbreviations used in this study are: APD, automatic peritoneal dialysis; BMI, body mass index; BSA, body surface area; CAPD, continuous ambulatory peritoneal dialysis; D/P, dialysate/plasma ratio; ESRD, end-stage renal disease; HD, hemodialysis; Kt/V_{urea}, dialysis dose; nPNA, normalized protein nitrogen appearance; PD, peritoneal dialysis; PET, peritoneal equilibration test; RRF, renal residual renal function; TCC, total creatinine clearance.

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