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Relative Contribution of Residual Renal Function and Peritoneal Clearance to Adequacy of Dialysis: A Reanalysis of the CANUSA Study

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Abstract. Studies of the adequacy of peritoneal dialysis and recommendations have assumed that renal and peritoneal clearances are comparable and therefore additive. The CANUSA data were reanalyzed in an effort to address this assumption. Among the 680 patients in the original CANUSA study, 601 had all of the variables of interest for this report. Adequacy of dialysis was estimated from GFR (mean of renal urea and creatinine clearance) and from peritoneal creatinine clearance. The Cox proportional-hazards model was used to evaluate the time-dependent association of these independent variables with patient survival. For each 5 L/wk per 1.73 m^2 increment in GFR, there was a 12% decrease in the relative risk (RR) of death (RR, 0.88; 95% confidence interval [CI], 0.83 to 0.94) but no association with peritoneal creatinine clearance (RR, 1.00; 95% CI, 0.90 to 1.10). Estimates of fluid removal (24-h urine volume, net peritoneal ultrafiltration, and total fluid removal) then were added to the Cox model. For a 250-ml increment in urine volume, there was a 36% decrease in the RR of death (RR, 0.64; 95% CI, 0.51 to 0.80). The association of patient survival with GFR disappeared (RR, 0.99; 95% CI, 0.94 to 1.04). However, neither net peritoneal ultrafiltration nor total fluid removal was associated with patient survival. Although these results may be explained partly, statistically, by less variability in peritoneal clearance than in GFR, the latter seems to be physiologically more important than the former. The assumption of equivalence of peritoneal and renal clearances is not supported by these data. Recommendations for adequate peritoneal dialysis need to be reevaluated in light of these observations.

An association between greater clearance of small molecular weight solutes and better clinical outcomes in patients who are treated by continuous peritoneal dialysis has been reported in prospective cohort studies that have used multivariate statistical analysis (1,2). These and other studies have contributed to the adequacy of peritoneal dialysis recommendations proposed by the Dialysis Outcome Quality Initiative in the United States (3,4). These recommendations assume an equivalence between clearance of small molecules by the native kidneys and by the peritoneal membrane. However, these assumptions have been challenged in several recent publications (5–8). Davies *et al.* (5), from the United Kingdom, reported that for patients who are undergoing continuous ambulatory peritoneal dialysis with similar initial residual renal function, those who died had experienced a more rapid deterioration in renal function compared with survivors. Diaz-Buxo *et al.* (6), in a study from the United States, reported that residual renal function was strongly correlated with survival, whereas peritoneal clearance was not. Szeto *et al.* (7) found a strong association between greater GFR and survival but no association between peritoneal creatinine clearance and patient survival. Finally, Rocco *et al.* (8) reported a 40% decrease in the relative risk (RR) of death associated with a 10 L/wk per 1.73 m^2 greater renal creatinine clearance and a 12% decrease in RR of death associated with a 1-unit greater weekly Kt/V. They found no associations between the RR of death with either peritoneal creatinine or urea clearance. Conversely, in a study of anuric patients who were undergoing peritoneal dialysis (9), there was much better survival among those who had a peritoneal Kt/V greater than 1.85 than for those with lower values.

In the CANUSA study (1), total (renal and peritoneal) solute clearance was found to correlate closely with morbid outcomes and with death. Specifically, an increase of 0.1 unit of Kt/V (peritoneal + renal) per week was associated with a 5% decrease in the RR of death, and an increase of 5 L/1.73 m^2 of creatinine clearance per week (peritoneal + renal) was associated with a 7% decrease in the RR of death. Residual renal function declined over time but was not examined separately as a risk factor for clinical outcomes. The purpose of the current investigation was to analyze the unique contribution of residual renal function to the clinical outcomes reported in the CANUSA study.

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Materials and Methods

The CANUSA study was a prospective cohort study performed in 14 centers in Canada and the United States. The methodology has been reported elsewhere (1).

Residual renal function in the present study was estimated from the GFR as calculated from the mean of urea and creatinine clearances (10). The contribution of peritoneal clearance to adequacy of dialysis was estimated from the peritoneal clearance of urea and of creatinine. Because the results were similar, the peritoneal clearance of creatinine was used in the present analysis.

The contribution of residual renal function to fluid balance was estimated from the 24-h urine volume collected at baseline and at 6-mo intervals. The contribution of peritoneal ultrafiltration was calculated from the net ultrafiltration (dialysate outflow minus prescribed inflow) per 24 h determined at enrollment and at 6 mo. Total fluid removal was the sum of urine volume and net peritoneal ultrafiltration. Other baseline variables that were determined were hemoglobin, serum calcium, phosphorus, CO_2 content, and potassium.

The clinical outcome for this study was patient survival. Statistical analysis of patient mortality used Andersen and Gill's (11) extension to the Cox proportional-hazards model (12), with estimates of nutritional status, GFR, peritoneal clearance, urine volume, net peritoneal ultrafiltration, and total fluid removal as time-dependent covariates (13). Patient deaths were attributed to the level of the time-dependent covariate recorded at the 6-mo evaluation preceding the event. Transplantation, technique failure, and recovery of renal function were treated as censored observations. GFR and peritoneal creatinine clearance then were entered into the baseline model. Baseline variables that might be associated with GFR then were entered separately. Hemoglobin and serum calcium, phosphorus, potassium, and CO_2 content were entered as surrogates for renal endocrine and excretory functions. The 24-h urine volume, 24-h net ultrafiltration, and 24-h total fluid removal then were entered to evaluate the role of fluid removal on patient survival. The likelihood-ratio test was used (14) to determine whether the addition of a variable added significantly to that model. Urine volume, net peritoneal ultrafiltration, and total fluid balance variables then were entered as time-dependent covariates. The validity of the proportional-hazards assumption was considered for all variables that remained in the final models by examination of the Schoenfeld residuals (15).

Results

Among the 680 patients who were enrolled in the original CANUSA report (1), 601 had all variables of interest that address the relative importance of GFR and peritoneal clearance. The mean age was 54.8 yr (SD 15.3); 59.9% were men, and 81.9% were white. The major causes for end-stage renal disease were diabetes mellitus (30.3%), glomerulonephritis (23.3%), and renal vascular disease/nephrosclerosis (20.3%). Among the 183 patients with diabetes mellitus, 83 had type I and 100 had type II. A total of 210 (34.9%) had a history of cardiovascular disease. At the baseline evaluation, 41 (6.8%) had low peritoneal membrane transport, 189 (31.4%) had low average transport, 278 (46.3%) had high average transport, and 93 (15.5%) had high peritoneal transport.

The weekly mean GFR, peritoneal creatinine clearance, 24-h urine volume, 24-h net peritoneal ultrafiltration, and 24-h total fluid removal at baseline and at 6, 12, 18, and 24 mo follow-up are shown in Table 1. The initial GFR was 37.7 L/wk per $1.73m^2$, and this decreased progressively to 14.8 by 24 mo of follow-up. The peritoneal creatinine clearance was 44.3 L/wk per 1.73 m^2 at baseline, and this increased slightly to 47.2 by 24 mo of follow-up. The urine volume decreased from an initial 670 to 335 ml/24 h, whereas the net peritoneal ultrafiltration increased from 958 to 1951 ml/24 h.

The baseline Cox proportional-hazards model demonstrated an association of worse clinical outcomes with increased age, history of cardiovascular disease, lower serum albumin, lower subjective global assessment, and higher peritoneal membrane transport, as has been reported previously (1,16). A 5-L/wk greater total weekly creatinine clearance was associated with a 10% decrease in the RR of death (95% CI, 0.85 to 0.96). The total creatinine clearance was the sum of GFR and peritoneal creatinine clearance. The average of renal urea and creatinine clearance was used to mitigate the effect of renal tubular secretion of creatinine (10). Given that this secretion does not occur across the peritoneal membrane, the two types of clearance are considered to be comparable.

GFR and peritoneal creatinine clearance then were entered as separate time-dependent covariates. The Cox model is shown in Table 2. A 5-L greater weekly GFR is associated with a 12% decrease in the RR of death (95% CI, 0.83 to 0.94). There was no association between the same increase in peritoneal creatinine clearance and the RR of death (RR, 1.00; 95% CI, 0.90 to 1.11). Hemoglobin, serum calcium, serum phosphorus, serum potassium, and serum CO_2 content, entered as surrogates of endocrine and other renal functions, did not add significantly to this statistical model.

Table 1. GFR, peritoneal creatinine clearance, and fluid removal at volumes baseline and at 6, 12, 18, and 24 months of follow-up[a]

Parameter	Baseline	6 Mo	12 Mo	18 Mo	24 Mo
n	601	469	290	147	69
GFR (L/wk)	37.7	28.7	21.4	19.4	14.8
Ccrp (L/wk)	44.3	45.8	46.4	45.3	47.2
Urine volume (ml/24 h)	670	519	428	379	335
Net peritoneal UF (ml/24 h)	958	1478	1807	1677	1951
Total fluid removal (ml/24 h)	1628	1997	2235	2056	2286

[a] Ccrp, peritoneal creatinine clearance; UF, ultrafiltration. GFR and Ccrp are normalized to 1.73 m^2.

Table 2. Cox model of relative risk of death with time-dependent Ccr divided into peritoneal clearance and GFR and entered as time-dependent covariates[a]

Variable	Relative Risk	95% Confidence Limit
Age	1.02	1.005–1.044
CVD	2.42	1.499–3.904
Diabetes mellitus	1.25	0.769–2.036
Serum albumin	0.96	0.912–1.000
LA transport	1.66	0.379–7.218
HA transport	2.33	0.554–9.801
H transport	2.01	0.430–9.357
SGA	0.74	0.647–0.842
Ccrp (5 L/wk per 1.73 m^2 greater)	1.00	0.898–1.105
GFR (5 L/wk per 1.73 m^2 greater)	0.88	0.829–0.943

[a] CVD, cardiovascular disease; LA, low average; HA, high average; H, high; SGA, subjective global assessment.

The effect of adding urine volume is shown in Table 3. Addition of the 24-h urine volume as a time-dependent covariate to this model showed a marked association with the RR of death. For each increase of 250 ml of urine per day, there was a 36% decrease in the RR of death (RR, 0.64; 95% CI, 0.51 to 0.80). Addition of urine volume to this statistical model removed the association of GFR with survival (RR of death, 0.99; Table 3). However, when net peritoneal ultrafiltration per 24 h was added instead of 24-h urine volume, there was no association of this variable with the RR of death (RR, 1.04; 95% CI, 0.99 to 1.08). The peritoneal creatinine clearance remained nonsignificant (RR, 0.96), whereas the GFR again became significant (RR, 0.94; 95% CI, 0.90 to 0.99). Finally, when total fluid removal was used as the volume-related variable, there was no association with the RR of death (RR, 1.02; 95% CI, 0.97 to 1.06). An increase of 5 L/wk per 1.73 m^2 in peritoneal creatinine clearance was not associated with the RR of death (RR, 0.99), whereas the same increase in GFR was associated with a 12% decrease in the RR of death (RR, 0.88).

Table 3. Cox model of relative risk for death with urine volume forced in as a time-dependent covariate

Variable	Relative Risk	95% Confidence Limits
Age (1 yr older)	1.02	1.002–1.041
CVD	2.37	1.465–3.821
Diabetes mellitus	1.31	0.807–2.134
Serum albumin (1 g/L increase)	0.96	0.914–1.003
LA transport	1.84	0.418–8.075
HA transport	2.71	0.631–11.623
H transport	2.46	0.523–11.590
SGA (1 unit greater)	0.78	0.672–0.876
Ccrp (5 L/wk per 1.73 m^2 greater)	0.93	0.795–1.079
GFR (5 L/wk per 1.73 m^2 greater)	0.99	0.943–1.044
Urine volume (250 ml daily greater)	0.64	0.508–0.800

Discussion

In this analysis of the CANUSA data, the separate contributions of peritoneal clearance and renal clearance were evaluated. Previously, we demonstrated that total small solute clearance, both urea and creatinine, was a predictor of mortality in these patients (1). This reanalysis of the CANUSA data indicates that the contribution of residual renal function is much more important than peritoneal clearance.

Prospective studies by Maiorca *et al*. (2) and Davies *et al*. (5) of prevalent and incident patients have identified the important role of residual renal function in the survival of patients who are undergoing peritoneal dialysis. These observations are consistent with the association of more rapid loss of GFR with transfer to hemodialysis or with death, as observed in the CANUSA study (17), compared with those who received a renal transplant or who survived to the end of the study. However, it is possible that "sicker" patients lose residual renal function more rapidly and that this greater mortality occurs because they are sick, not because of the loss of residual renal function *per se*. Moist *et al*. (18) reported predictors of loss of residual renal function among new dialysis patients in the United States. Among the factors associated with an increased rate of loss of GFR in the patients who were undergoing peritoneal dialysis were diabetes mellitus and congestive heart failure, which suggests that patients who have more comorbidity experience a more rapid loss of residual renal function and that the increased risk of death is due to the comorbidity rather than to the loss of GFR. The studies reported from Italy (2) and the United Kingdom (5) do not address the possible confounding effect of these variables on the rate of loss of GFR and poorer patient survival. The studies from the United States by Diaz-Buxo *et al*. (6) and Rocco *et al*. (8) and from Hong Kong by Szeto *et al*. (7) used multivariate statistical analyses and demonstrated the beneficial association between greater GFR and better patient outcomes, adjusted for comorbidity. In a creatinine clearance model, there were worse outcomes associated with increased age and diabetes (6), with duration of dialysis and diabetes (7), and with age and diabetic end-stage renal disease (8). However, these studies were of prevalent patients (6,8) or a mixed prevalent-incident population (7). In two of these studies, there was relatively short follow-up: 1 yr (6) and 7 mo (8), respectively. None of these three studies evaluated change in GFR or peritoneal clearance as a time-dependent covariate, and the hypotheses generated in the discussions were not tested (6–8).

"Incidence-prevalence bias" introduces into observational studies a set of potential methodologic errors (19). Excepting the studies by Davies *et al*. (5) and the present study, all have used a cohort of prevalent (2,6,8) or mixed prevalent-incident patients (7) followed forward in time after cross-sectional ascertainment.

Another potential explanation for the lack of association between peritoneal clearance and patient survival is that higher peritoneal clearance may be associated with higher peritoneal

membrane transport, which is associated with worse patient outcomes (16). These positively correlated variables have opposite associations with patient survival. We have found that the association of peritoneal membrane transport with patient outcome is not significantly changed when peritoneal creatinine clearance is added to the statistical model.

In general, the greater the range and variability of an independent variable (*e.g.,* GFR, peritoneal creatinine clearance), the greater the statistical ability to detect a relationship with a dependent variable (*e.g.,* patient survival). In the study by Diaz-Buxo *et al*. (5), the coefficient of variation of peritoneal clearance at initiation of follow-up of prevalent peritoneal dialysis patients was 29%. The range and variation for GFR were not provided but are described as being much greater than those for peritoneal creatinine clearance. In our study, the coefficient of variation for peritoneal creatinine clearance was 21%, compared with 70% for the GFR. The greater variability in the GFR, compared with that of peritoneal creatinine clearance, may be partly responsible for the detection of an association of GFR but not of peritoneal creatinine clearance with patient survival.

Greater residual renal function might be associated with better preserved renal endocrine function. Addition of baseline hemoglobin as a surrogate for erythropoietin and baseline serum calcium as a surrogate for 1-α hydroxylation of vitamin D3 did not add significantly to the statistical model. Similarly, serum phosphate, potassium, and bicarbonate as estimates of other renal excretory functions showed no association with patient survival.

The advantage conferred by preserved residual renal function may relate to the volume of urine excreted and the maintenance of euvolemic status. Increasing attention is being paid to the role of fluid overload in the precipitation of congestive heart failure. The apparent survival advantage of residual renal function may be due to the volume of urine excreted with mitigation of chronic fluid overload. In this study, when 24-h urine volume was examined as a time-dependent covariate, there was a marked correlation between preserved urine volume and a reduction in the RR of death. For each additional 250 ml of urine excreted per day, the RR of death was decreased by 36% (Table 3). Addition of urine volume to this model caused the association between GFR and survival to become nonsignificant, which suggests that the effect of GFR might be mediated by urine volume. However, if urine volume supersedes GFR, then one would expect that total fluid removal (the sum of urine volume and net peritoneal ultrafiltration) should be even more important. However, neither net peritoneal ultrafiltration nor total fluid removal per 24 h showed an association with mortality. The lack of association of peritoneal ultrafiltration volume with outcome may be confounded by the peritoneal transport status; that is, a low transporter would be expected to have greater volume of peritoneal fluid removal and a better outcome (16). By using both transport status and peritoneal ultrafiltration in the multivariate analysis, we might be obscuring the effect of the latter. However, when transport status is removed as a variable of interest, we were still unable to show that peritoneal ultrafiltration predicted outcome (data not shown). In those statistical models, the GFR became significant once again. Therefore, the beneficial association between GFR and outcome does not seem to be related simply to fluid removal. The failure to identify an association between net peritoneal ultrafiltration and patient survival cannot be explained on the basis of less variability compared with urine volume, because the coefficient of variation was similar for the two (83 *versus* 78%).

The contribution of residual renal function may be biologically more important compared with that of peritoneal clearance, in part because of better clearance of middle and larger molecular weight uremic toxins. As an example, Mamoun *et al*. (20) demonstrated in a rat model that substances with a molecular weight range from 1.0 to 5.0 kD, isolated from uremic plasma, are associated with anorexia. At this molecular weight range, the peritoneal clearance would be poor compared with that achieved by renal excretion.

In the CANUSA study (1), no attempt was made to replace loss of residual renal clearance with increased peritoneal clearance. However, the value of peritoneal clearance has been demonstrated in anuric patients. There is a clinically important but statistically nonsignificant improved patient survival for those with peritoneal Kt/V values greater than 1.85/wk (9). Davies *et al*. (21), in a study of malnourished patients who were undergoing peritoneal dialysis, increased peritoneal Kt/V because of a continued loss of residual renal function. They reported a modest nutritional benefit in patients without comorbidity.

In summary, the original CANUSA data showed an association of total small solute clearance, both urea and creatinine, with patient survival (1). However, when solute clearance is subdivided into that contributed by peritoneal clearance and that from residual renal function, it is the latter that appears to be much more important. This does not seem to be the result of an association of loss of GFR with more severe comorbidity. It may be explained partially by less variability in peritoneal than in renal clearances. The worse patient survival associated with loss of GFR also may be the result of decreased clearance of both small and larger molecular weight uremic toxins and, in part, to loss of renal contribution to the maintenance of euvolemia. When GFR declines, patients should be reviewed very carefully for evidence of uremia, hypervolemia, and malnutrition. The critical GFR level has not been defined but probably is that reached after 2 to 3 yr of peritoneal dialysis treatment, when the survival advantage of peritoneal dialysis over hemodialysis is lost (22).

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