Associates of Mortality Among Peritoneal Dialysis Patients With Special Reference to Peritoneal Transport Rates and Solute Clearance

Jose A. Diaz-Buxo, MD, Edmund G. Lowrie, MD, Nancy L. Lew, S.M. Hongyuan Zhang, Xiaofei Zhu, and J. Michael Lazarus, MD

• **The current report describes the distributions of selected demographic and biochemical parameters, clearance, and other transport values among patients undergoing peritoneal dialysis (PD) and evaluates the associates of mortality using those values, with and without clearance and peritoneal equilibration test (PET) data. All patients receiving PD on January 1, 1994 were selected (n = 2,686). Patients who switched to another form of dialysis during the study period were removed from the study at the time of therapy change. Working files were constructed from the clinical database to include demographic, laboratory, and outcome data. Laboratory data were available in only 1,603 patients and were used to evaluate the biochemical associates of mortality after merging the biochemical, demographic, and outcome data. Patients with clearance data or PET studies underwent a second analysis to assess the effects of peritoneal and renal clearance on survival. The analysis of demographic and laboratory data confirmed the importance of age and serum albumin concentration as predictors of death. Residual renal function (RRF) was strongly correlated with survival, but peritoneal clearance was not. Several possible explanations for the lack of correlation between peritoneal clearance and survival are discussed. The data suggest that RRF and peritoneal clearance may be separate and not equivalent quantities. Substantial work is required to confirm or refute these findings, because the information is essential to establish the adequate dose of PD in patients with various degrees of RRF.**

INDEX WORDS: Peritoneal dialysis; mortality; peritoneal transport; peritoneal clearance; residual renal function.

WE HAVE previously reported on the associates of mortality among peritoneal dialysis (PD) patients, based on Fresenius Medical Care's clinical database, the Patient Statistical Profile (PSP), a system that supports ongoing quality enhancement activities.[1,2] The findings were consistent with our previous observations for hemodialysis patients, showing that age, serum albumin concentrations (SACs), serum creatinine, and metabolic acidosis were the main measured associates of death risk.[3] Unfortunately, neither residual renal nor peritoneal clearance data were available at the time. Since then, we have accumulated enough data from peritoneal equilibration tests (PETs) and 24-hour urine and peritoneal effluent collections among our clinics to be able to also correlate the renal and peritoneal contributions to clearance with clinical outcome.

The current report was performed to (1) describe the distributions of selected demographic and biochemical parameters, clearance, and other solute transport values among patients undergoing PD and (2) evaluate the associates of mortality among PD patients using those values, with and without the clearance and PET data. The first analysis was performed without the PET or peritoneal and renal clearance data to achieve a larger sample size. The second analysis correlated the PET values and clearance data with mortal risk, using a smaller sample.

PATIENTS AND METHODS

All patients receiving PD on January 1, 1994 were selected for the first analysis. Only patients undergoing continuous ambulatory peritoneal dialysis (CAPD) and continuous cyclic PD were included (n= 2,686). Patients who switched to another form of dialysis therapy during the study period were removed from the study at the time of therapy change. Working files were constructed from the PSP database as previously described, to include demographic, laboratory, and outcome data.[2] Laboratory data included SAC, creatinine, hemoglobin, white blood cell (WBC) count, anion gap, calcium, phosphorus, alkaline phosphatase, serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, lactate dehydrogenase (LDH), total bilirubin, glucose, cholesterol, and triglycerides. Laboratory data were available from only 1,603 patients and were used to evaluate the biochemical associates of mortality after merging the biochemical, demographic, and outcome data.

Patients with clearance or PET data were used for the

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Address reprint requests to Jose A. Diaz-Buxo, MD, Fresenius Medical Care North America, 1051 Morehead St, Suite 250, Charlotte, NC 28204. E-mail: pdserve@bellsouth.net

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second analysis. Those data were merged with PSP files that included survival data. Survival was measured for 1 year from the date of clearance and PETs. Other laboratory data such as SAC and serum creatinine concentration were taken as the average of all measurements for 3 months preceding the clearance/PETs.

All samples for PET studies were analyzed by LifeChem Laboratories (Rochleigh, NJ) using standard autoanalyzer techniques for serum and dialysate. The PETs were performed and the serum and dialysate samples collected by the nurses at the patients' individual centers using standard methodology as previously published by Twardowski et al.[4] Renal (Kr_{cr}) and peritoneal (Kp_{cr}) creatinine clearances and renal urea clearances (Kr_{urea}) were measured from 24-hour urine and dialysate collections, the recorded respective volume, and a simultaneous serum creatinine and blood urea nitrogen determination obtained during the collection period. Clearance was calculated using the formula: $K = CV/P$, where K is solute clearance, C is the solute concentration in urine or dialysate, and P is solute plasma concentration. There were 1,738 Kr_{cr} determinations and 1,891 Kp_{cr} determinations. Both values were available for 1,301 patients. There were 1,668 Kr_{urea} determinations, and 1,352 patients had both Kr_{cr} and Kr_{urea}. All values were adjusted to body surface area of 1.73 m^2.

Results are presented as means ± standard deviations (SD). Statistical significance was defined as a probability less than 0.05. The analytical logic has been described previously.[2,5] Differences between means were evaluated by Student's *t*-test. Frequency differences of categorical counts between groups were evaluated by chi-square (χ^2) tests. Odds of death was evaluated by logistic regression analysis,[6] as previously described.[2,3,5]

RESULTS

Analysis of Demographic and Laboratory Data

Table 1 describes the base population of 2,686 patients. The mean age was 54.8 ± 15.2 years. The gender distribution was essentially equal for males and females; 37.4% were nonwhite and 38% diabetics. Table 2 shows the results of the logistic analysis of base demographic variables. The odds ratio for death (OR) increased approximately 3.5% per year of advancing age. White patients experienced greater OR than nonwhites (OR = 1.427, $P = 0.002$) and diabetics greater odds than nondiabetics (OR = 1.692, $P < 0.001$). Additional analyses showed no interactions between gender and race, gender and diabetes, or race and diabetes.

Table 3 summarizes the univariate analysis of demographic and laboratory variables screened for possible association with survival. The χ^2, its associated *P* value, and the OR are shown if $P \leq 0.05$. Age, SAC, WBC count, serum creatinine concentration, and diabetes were most closely associated with OR before adjustment for other variables in this data set.

Table 1. Peritoneal Dialysis Patients

Variable	Statistic
No. of patients	2,886
Age (yr)	
Mean	54.8
SD	15.2
25th percentile	43.3
Median	55.4
75th percentile	67.2
Sex (%)	
Male	50.1
Race and ethnicity (% total)	
White	62.6
Hispanic	7.2
Non-Hispanic	54.8
Not specified	0.6
Nonwhite	37.4
Hispanic	5.5
Non-Hispanic	31.1
Not specified	0.8
Diabetics (%)	38.4

Figure 1 charts the development of the final statistical model. Age was selected first, followed by SAC, LDH, anion gap, WBC count, calcium, phosphorus, creatinine, and sex, based on χ^2 statistics. Adjustment of creatinine for its association with SAC reduced the independent strength of the creatinine association with OR. Adjustment of anion gap for SAC and creatinine concentrations increases the strength of its association with OR from negligible to significant. Table 4 describes the final model. The ranking of χ^2 values in the final model (Table 4) is not the same as the order in which variables are added to it (Fig 1), because the final χ^2 reflect statistical adjustment of each for the others. The figure

Table 2. Analysis of Demographic Variables

Variable	χ^2	*P*	OR	95% CI
Age	83.3	<0.001	1.035	1.028-1.043
Sex (ref = male)	0.1	NS	0.976	0.794-1.198
Race (ref = nonwhite)	9.6	0.002	1.427	1.139-1.788
Diabetes (ref = nondiabetic)	25.4	<0.001	1.692	1.379-2.076

NOTE. χ^2 = the χ^2 statistic; *P* = probability of H_o; 95% CI = the 95% confidence interval of the OR.

Abbreviation: OR, odds ratio for death.

Table 3. Logistic Regression of Death on Variables During 1994

Variable*	χ^2	*P*	OR
Age	70.3	<0.001	1.037
Albumin	46.6	<0.001	0.526
WBC	28.2	<0.001	1.142
Creatinine	25.4	<0.001	0.92
Diabetes (ref = no)	22.4	<0.001	1.727
LDH	19.2	<0.001	1.004
Glucose	13.4	<0.001	1.002
Alkaline phosphatase	8.4	0.004	1.002
Race (ref = nonwhite)	5.2	0.023	1.665
Bilirubin	4.1	0.042	1.787
ALT GPT	4	0.044	0.989
Anion gap	2.3	NS	NA

NOTE. Statistics shown are before adjustments. χ^2 = the chi-square statistic; *P* = probability of H_o; 95% CI = the 95% confidence interval of the OR.

*Listed in decreasing order of χ^2. Other variables evaluated but not significantly associated with death odds included anion gap, uric acid, gender, triglycerides, calcium, cholesterol, hemoglobin, phosphorus, and GOT (in decreasing order of χ^2).

Abbreviation: OR, odds ratio for death.

reflects progression of the model, and measures are adjusted as they are entered only for those variables already selected.[6]

Age and SAC were most closely associated with OR; advancing age and lower SAC were associated with higher OR. Each 0.1 U/mL higher LDH was associated with a 0.4% higher OR, and each 1,000 higher WBC per microliter was associated with a 9.2% higher OR.

Figures 2 through 5 show in greater detail the associations between several variables and OR.

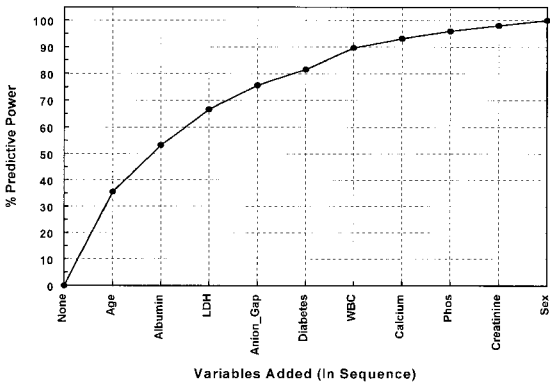

Fig 1. Development of the final logistic model. Variables are added in the order of the changing strengths of their associations with odds of death. 1994 data; N = 1,603; predictive power = % final χ^2; R^2 = 13.14%.

Table 4. Logistic Regression of Death on Variables During 1994: Final Model

Variable	χ^2	*P*	OR	95% CI
Age	55.1	<0.001	1.043	0.032-1.055
Sex (ref = male)	4	0.045	0.752	0.569-0.993
Diabetes (ref = no)	6.5	0.011	1.442	1.089-1.909
Albumin	53.4	<0.001	0.331	0.246-0.445
Anion gap	9.4	0.002	1.063	1.022-1.105
Calcium	10.2	0.001	1.306	1.109-1.539
Creatinine	6.1	0.013	0.946	0.905-0.989
LDH	21.3	<0.001	1.004	1.003-1.006
Phosphorus	8.8	0.003	1.165	1.053-1.288
WBC	11.1	<0.001	1.092	1.037-1.149

NOTE. χ^2 = the chi-square statistic; *P* = the probability of "no association" under the null hypothesis; OR = the odds ratio for death; 95% CI = the 95% confidence interval of the OR.

Patients in the groups with SAC below 3.5 g/dL experienced significantly higher OR than patients in groups exceeding that threshold (Fig 2). Higher OR was seen in patients with WBC counts above 9,000/μL, even when many of those patients had WBC counts in the normal range (Fig 3). The OR increased progressively when LDH exceeded 250 U/L (Fig 4). Figure 5 shows the risk profile for serum calcium concentration. The difference of risk profile between the case mix only adjusted model and the case mix and laboratory values model likely evolves from statistical adjustment of serum calcium concentration for SAC with which it was correlated (r = 0.48; $P < 0.001$). Thus, the finding can be interpreted to suggest that higher ionized serum calcium concentration is associated with increasing OR.

Analysis of Solute Clearance and PET Data

Figure 6 shows the total and combined peritoneal and renal creatinine clearance (Kpr_{cr}). The median combined clearance was approximately 76 L/wk (lower quartile [Q_L] = 56; upper quartile [Q_U] = 110). Figure 7 shows the distributions of the Kp_{cr} and Kr_{cr}. The median Kp_{cr} was 41 L/wk (Q_L = 35; Q_U = 48). The median Kr_{cr} was 3.6 mL/min or 36 L/wk (Q_L = 1.4; Q_U = 7.1). Thus, 25% of patients had a Kr_{cr} exceeding 7.1 mL/min or 71 L/wk, and in 10% it exceeded 11.0 mL/min or 110 L/wk, whereas 25% had values less than 1.4 mL/min or 14 L/wk. Comparison of the charts of Fig 7 with each other and

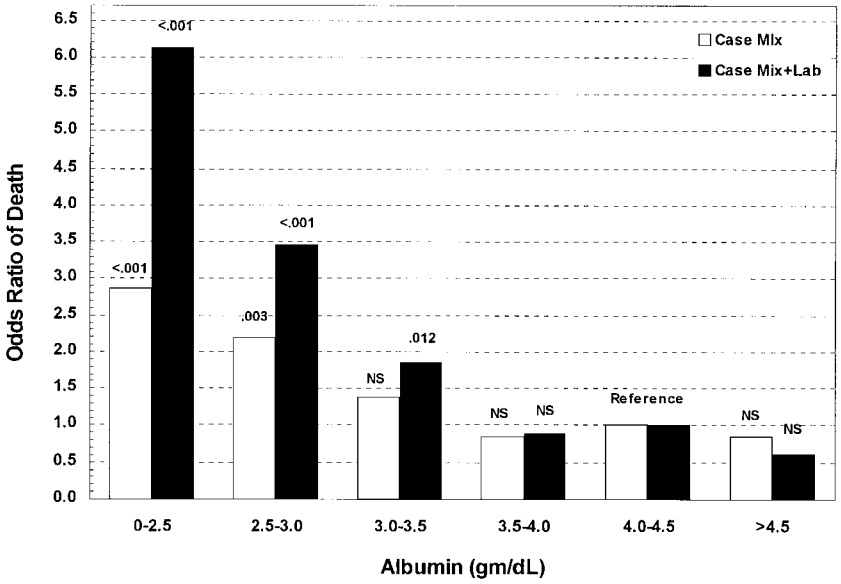

Fig 2. Risk profile for serum albumin concentration.

with Fig 6 suggests that the native kidney and dialysis treatment each contributed approximately half ($Kr_{cr} \sim 47.8\%$) of the total weekly creatinine clearance to these patients at the median.

Figure 8 shows the distributions for the residual Kr_{urea} and average of the Kr_{urea} and Kr_{cr}. The Kr_{cr} was higher than Kr_{urea}, as expected because of renal tubular secretion of creatinine, and the average rests between the two. The median Kr_{urea} was 1.9 mL/min, as opposed to 3.6 for Kr_{cr}, and the average or corrected clearance was 2.8 mL/min or 28 L/wk for the 1,352 patients with both values.

Three logistic models were used to evaluate the association of weekly creatinine clearance with OR (Table 5). The three models evaluated weekly—(1) Kp_{cr}, (2) Kr_{cr}, and (3) Kpr_{cr}—were adjusted to 1.73 m^2 of body surface area and for demographic variables.

Kr_{cr}, but not Kp_{cr}, was associated with risk of death. Each milliliter-per-minute increase of Kr_{cr} (equivalent to 10 L/wk) was associated with a 12% reduction of OR whether or not adjusted for Kp_{cr}. There was no statistical interaction between Kp_{cr} and Kr_{cr}. Evaluating the sum of Kp_{cr} and Kr_{cr}, to calculate total weekly creatinine clearance (Kpr_{cr}: mean = 86.5 L/wk; median =

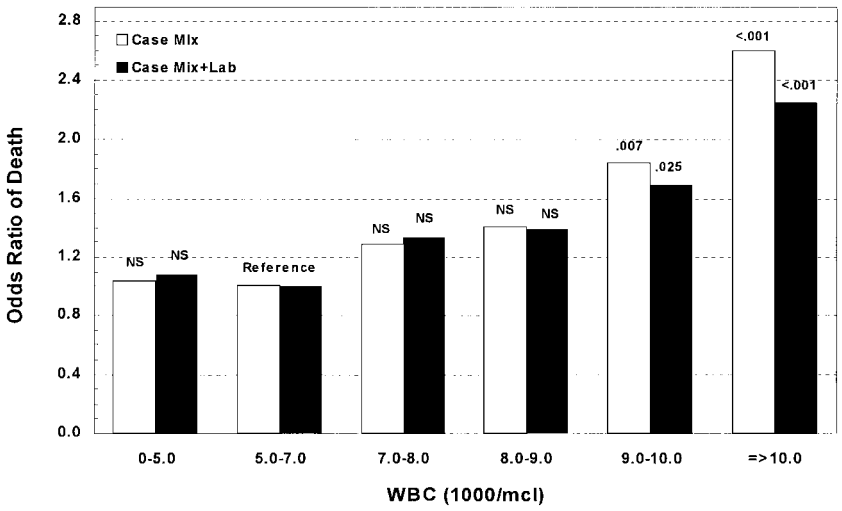

Fig 3. Risk profile for WBC count.

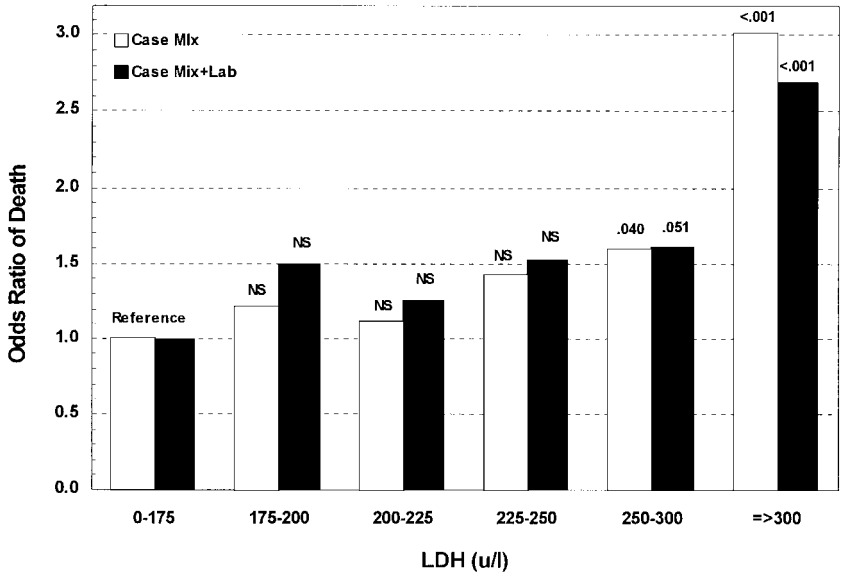

Fig 4. Risk profile for LDH.

76.0 L/wk), gave coefficients for age, sex, race, and diabetes that were similar to those shown in the Kpr_{cr} column. The OR associated with Kpr_{cr} was 0.988 (95% confidence interval [CI] = 0.980 to 0.996; $\chi^2 = 8.7$; $P = 0.003$). Hence, total clearance and renal clearance, but not peritoneal clearance, were associated with death risk.

Similar analyses, restricting the sample to patients with $Kr_{cr} \leq 1.0$ mL/min and also to $Kr_{cr} \leq 2.0$ mL/min, were performed. There was no significant association of Kp_{cr} with OR in either analysis. Statistical models that included SAC, serum creatinine, hemoglobin, anion gap, iron, phosphorus, WBC count, alkaline phosphatase, and serum glutamic-pyruvic transaminase also were used to evaluate the clearance values. Kpr_{cr} was significantly associated with OR (OR = 0.972; $P = 0.010$); so was Kr_{cr} (OR = 0.750; $P = 0.002$); but not Kp_{cr} ($P = 0.128$).

Table 6 shows the results of analyses that

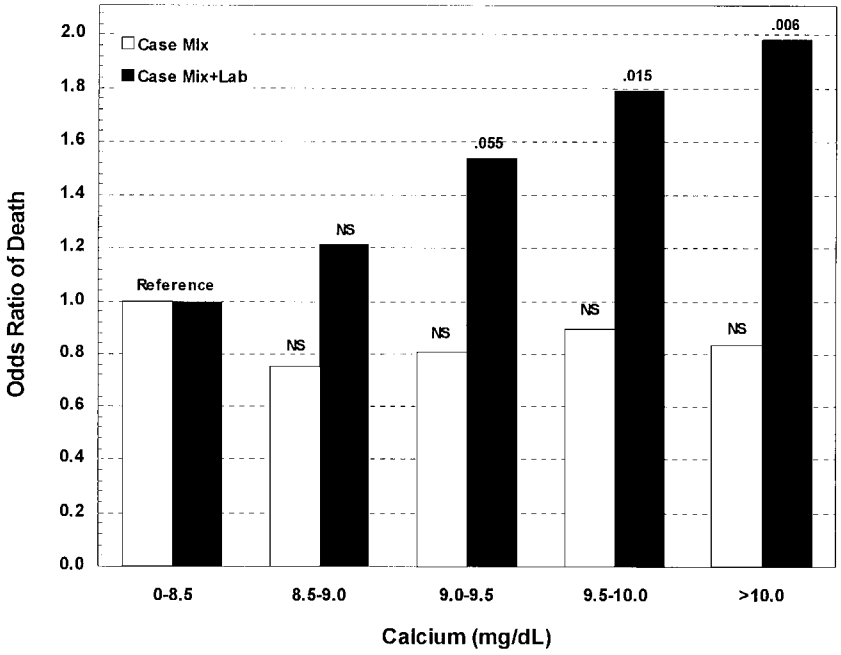

Fig 5. Risk profile for serum calcium concentration.

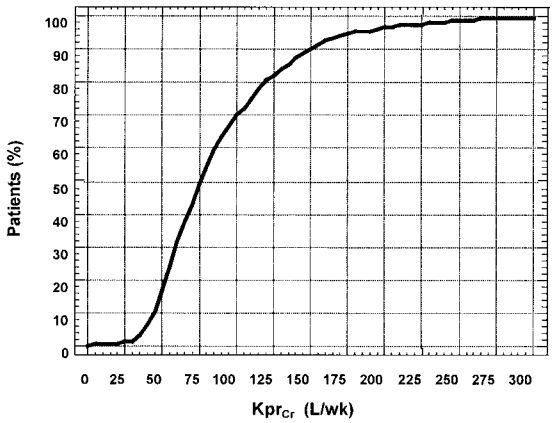

Fig 6. Distributions of total weekly creatinine clearance (Kpr_{cr}).

include either the ratio of dialysate glucose concentration at 4 hours to glucose concentration immediately after infusion (D_4/D_0) or the dialysate-to-plasma ratio of creatinine at 4 hours ($D/P_{cr,4h}$) from the PET with demographic data and the clearance values. The sample sizes of patients with complete data are much smaller. The analyses suggest that Kr_{cr}, but not Kp_{cr}, was associated with OR. Neither D_4/D_0 nor $D/P_{cr,4h}$ were associated with survival. Laboratory value adjustments were not used with those models because of small size of the sample. A similar model, not including Kp_{cr} or Kr_{cr} data, evaluating the D_4/D_0 (n = 504), did not show an association with OR ($\chi^2 = 0.8$; P = not significant [NS]). Similarly, no correlation was observed in a model using $D/P_{cr,4h}$ ($\chi^2 = 0.1$; P = NS).

Figure 9 compares the strong association between Kr_{cr} and the OR with the weak association between OR and Kp_{cr}. The OR at Kp_{cr} equals 43 to 50, 37 to 43, 30 to 37, and 30 L/wk or less were 0.58, 0.63, 0.66, and 0.67 compared with the reference group ($Kp_{cr} > 50$ L/wk). Similar ratios for the case mix plus laboratories model were 1.02, 0.58, 1.25, and 1.49, respectively. No categories were significantly different from the reference group in either model. The model was reevaluated using Kp_{cr} equals 37 to 43 L/wk as reference because that group was associated with the most favorable OR. No group differed from it in either model.

By contrast, the association of Kr_{cr} with survival was robust. Whether case mix adjusted for demographic variables with or without laboratory variables, the relationships were monotonic—ORs become less with each successive increase in Kr_{cr}. Both Kr_{cr} profiles illustrate the trend and are highly significant. Adjustment for laboratory values increased the apparent magnitude of the risk. Hence, it appears that residual Kr_{cr} is associated with survival among patients receiving PD, whereas the association of survival with peritoneal clearance is very weak at best.

DISCUSSION

The analysis of demographic and laboratory data confirms previous findings for patients undergoing hemodialysis and PD.[1,3] The data once again emphasize the importance of age and SAC as predictors of mortality among dialysis patients. The observation of higher odds of death among PD patients with higher WBC counts and LDH concentrations is similar to previous observations among hemodialysis patients.[1] The source of LDH responsible for the higher relative risk of death has not been characterized. Future studies should include evaluation of LDH isoenzymes to determine whether it is caused by increased

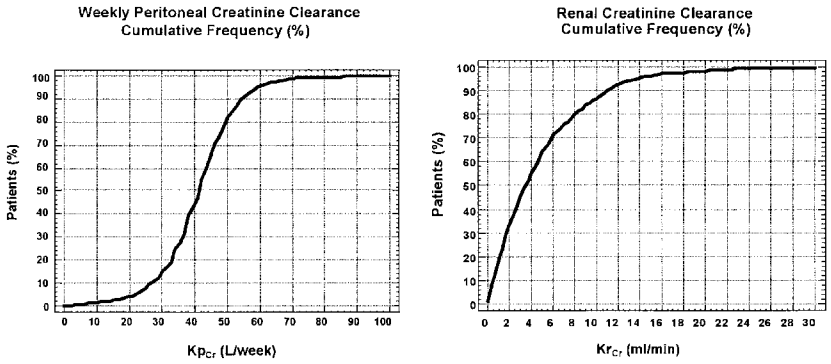

Fig 7. Distributions of peritoneal (Kp_{cr}) and residual renal creatinine clearance (Kr_{cr}).

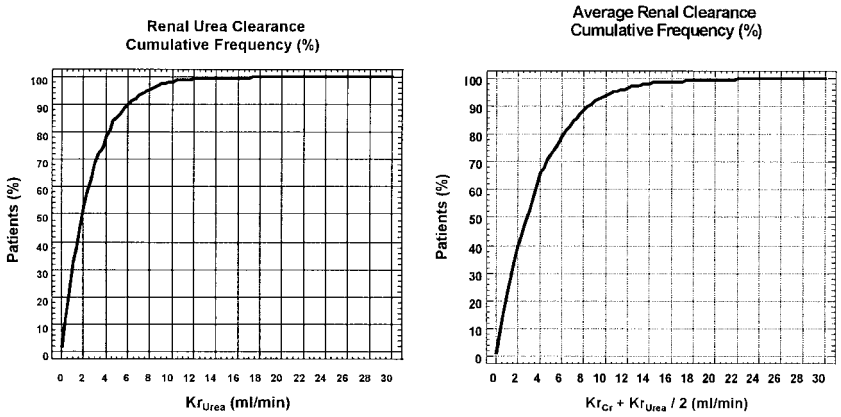

Fig 8. Distributions of residual renal clearance of urea (Kr_{urea}) and the average clearances of urea and creatinine ($[Kr_{cr} + Kr_{urea}]/2$).

blood cell turnover, liver dysfunction, or muscle injury.

We will focus primarily on the findings from the analysis of solute clearance and the contributions of renal and peritoneal clearance to survival. In this analysis, residual renal function was strongly associated with survival among PD patients, but such an association for peritoneal clearance could not be substantiated. This finding is both interesting and disturbing.

We do not interpret these data to mean that PD has no life-sustaining effect. It is well known that, in the absence of dialysis, patients without significant residual renal function die, and those with no residual renal function undergoing PD with certain amounts of Kp survive for variable periods. Most of the long-term survivors of PD (>5 years) in some series were anuric.[7] PD is a common form of renal replacement therapy for patients who have lost their renal transplant or blood access from hemodialysis, many of whom survive for many years despite being essentially anuric. Yet, we were unable to clearly show an association between Kp_{cr} and survival.

We evaluated the association of Kp_{cr} with survival across patients. As such, nothing can be said about higher Kp_{cr}, or increasing the value of Kp_{cr}, in any particular patient. For example, suppose two patients receive a standard 2 L, four exchange per day CAPD treatment protocol. Kp_{cr} could be higher in one patient (patient A) than another (patient B) because he or she has ''better'' peritoneal membrane transport characteristics—a higher D/P_{cr}. Patient A's higher Kp_{cr} may provide little survival advantage to patient A over patient B according to our data. Our data do not permit, however, conclusions about the effect of increasing Kp_{cr} in patient B (by increasing the number or volume of exchanges, for example) on the survival likelihood of patient B relative to either patient A's or patient B's old treatment protocol. Hence, these data should not be interpreted to suggest that increasing PD will have no

Table 5. Association of Weekly Peritoneal (Kp_{cr}) and Residual Renal (Kr_{cr}) Creatinine Clearance With Odds of Death: Three Logistic Models

	Kp_{cr} Only (N = 673)			Kr_{cr} Only (N = 559)			Kpr_{cr} (N = 443)		
Variable	χ^2	*P*	OR	χ^2	*P*	OR	χ^2	*P*	OR
Age (yr)	30.2	<0.001	1.046	26.8	<0.001	1.054	13.2	<0.001	1.042
Sex (male)	1.7	NS	0.750	2.1	NS	0.691	1.7	NS	0.689
Race (nonwhite)	2.5	NS	1.512	3.8	0.050	1.833	2.8	0.092	1.881
Diabetes (no)	11	<0.001	2.023	12.0	<0.001	2.431	14.4	<0.001	2.991
Kp_{cr} (L/wk)	1	**NS**	1.009				0.5	**NS**	1.008
Kr_{cr} (mL/min)				12.7	**<0.001**	**0.876**	8.9	**0.003**	**0.887**

NOTE. N = the number of patients evaluated by the model: χ^2 = the chi-square statistic; *P* = the probability of ''no association'' under the null hypothesis; OR = the odds ratio for death; the designators in brackets indicate the reference group. Bold typeface emphasizes values.

Table 6. Association of 4-Hour D/D_0 (Glucose) and D/P (Creatinine) With Odds of Death: Two Logistic Models

	D/D_o (N = 156)			D/P (N = 198)		
Variable	χ^2	*P*	OR	χ^2	*P*	OR
Age (yr)	6.7	0.009	1.067	6.1	0.013	1.054
Sex (male)	0.5	NS	0.678	0.4	NS	0.732
Race (nonwhite)	0.5	NS	1.628	1.0	NS	1.913
Diabetes (no)	9.4	0.002	6.045	11.6	<0.001	6.519
Kp_{cr} (L/wk)	0.2	**NS**	1.009	0.1	**NS**	0.995
Kr_{cr} (mL/min)	6.2	**0.012**	**0.764**	8.1	**0.004**	**0.754**
D/D_0	1.0	**NS**	19.6			
D/P				0.01	**NS**	1.620

NOTE. N = the number of patients evaluated by the model; χ^2 = the chi-square statistic; *P* = the probability of "no association" under the null hypothesis; OR = the odds ratio for death; the designators in brackets indicate the reference group. Bold typeface emphasizes values.

effect (either favorable or unfavorable) on the probability of survival for an individual patient.

These data may be interpreted in several ways: (1) There are abnormalities/errors in the data themselves, the collection of the data, or the analysis of the data to evaluate the contribution of Kp_{cr} to survival; (2) Kp_{cr} may not be a sensitive marker for survival; (3) other processes are more important to survival than Kp_{cr}; or (4) high Kp, although enhancing solute removal, is also associated with a mortality producing process.

1. *Data errors:* It is possible that measurement of Kp by patients and clinics was so bad as to simply render the data meaningless. If so, the tests on which the physicians and nurses that performed them rely on, were also meaningless, leading, perhaps, to inadequate treatment prescription. That would be a finding in its own right. Peritoneal clearance measures are done when a patient is 100% compliant. Lack of compliance to PD is probably very common in the United States.[8,9] The renal clearance is independent of compliance. The CANUSA results suggest that US CAPD patients do an average of only three of four prescribed exchanges per day.[9] Thus, it is conceivable that the data collected for Kr_{cr} are real, but the Kp_{cr} is grossly overestimated in many patients. The negative results among patients with Kr_{cr} less than 1 mL/min suggest poor compliance. In other words, the Kp_{cr} used for analysis does not reflect the dose delivered on the remaining days of the month.

Similarly, systematic patterns of missing

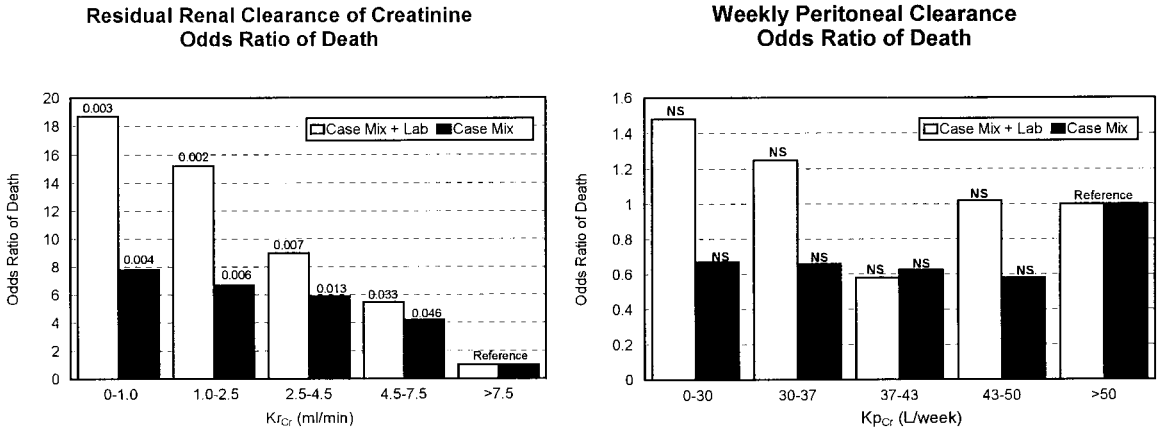

Fig 9. Comparison of the risk profile for residual renal function as estimated by the renal creatinine clearance (Kr_{cr}) with the risk profile for weekly peritoneal clearance (Kp_{cr}). The *P* values over the bars indicate the significance of (no) difference from the reference group for each model: An *NS* denotes no significant difference.

data could bias these results in unforeseen ways. However, there is no evidence for such nonrandom patterns. The case mix and laboratory measures associated with death odds were similar to those found in earlier reports,[1] and several analyses of PET and clearance data gave similar results.

Other data quality and statistical considerations include:

a. *There was an insufficient range of Kp.* The range of Kp was substantial, as the X-axis of Fig 5 suggests. The coefficient of variation of Kp was 29%, against a mean value of 41.5 L/wk (±12.1 SD; 5th to 95th percentile = 22 to 60).
b. *Kp was just too low in these patients to have a meaningful effect.* The usual guidelines for PD adequacy involve total clearance, that is, Kp + Kr. The median total clearance was 76 L/wk. Peritoneal clearance provided approximately half of that value. If a clearance effect is not seen somewhere in this range, then the threshold value for any effect must be extraordinarily high—perhaps not achievable.
c. *The distribution of the magnitude of Kp is much narrower than that for Kr.* The bulk of the Kp values are below 40 L/wk, whereas those for Kr extend to 180 L/wk. What would be the correlation between Kr and clinical outcome if the range of values for Kr and Kp were comparable?
d. *Only one measurement of Kp and Kr is used in these data to characterize therapy.* The use of single measurements of Kp and Kr may not provide adequate control.
e. *Lower Kr could simply be a proxy of greater duration on dialysis.* In other words, Kr could decline over time, and it was longevity that contributed to higher mortality rather than low Kr per se. One could equally argue, however, that any increase of mortality over time results primarily from declining Kr. Furthermore, the lack of association of Kp with death odds persisted when the analytic sample was restricted to patients with Kr_{cr} less than or equal to 1.0 mL/min.

Despite all these considerations, we should strongly consider the possibility that Kp and Kr are not comparable quantities clinically (biologically) speaking. First, the pattern of associations (Kr was associated with survival, but Kp was not) was found in all analyses performed no matter the sample and no matter the statistical adjustments made. This finding was quite robust. Second, we found good internal consistency between the PET and peritoneal clearance measurements during our initial explorations of these data.

The importance of residual renal function on the survival of patients and the superiority over peritoneal clearance is substantiated in a recent analysis from the CANUSA Study.[10] When patients were grouped according to baseline residual renal function, those above the mean glomerular filtration rate (GFR) had improved survival at 24 months compared with those below the mean GFR ($P < 0.02$). Cox multivariate analysis of the OR indicated that each 5 L/wk of residual GFR at baseline conferred a 5% reduction in OR. When residual renal function was analyzed as a time-dependent covariable, each 5 L/wk of GFR was associated with almost a 10% reduction in OR. These data show that the renal contribution to clearance is an important predictor of patient survival and suggest that it may be more important than peritoneal clearance.

2. *Kp_{cr} may not be a sensitive marker for survival.* Several reports have suggested that urea is a better surrogate marker of uremia than creatinine clearance.[11,12] Selgas et al[11] observed good correlation between urea kinetic indices and clinical outcome but found that creatinine kinetics did not show sufficient discriminative capacity. Mehrotra et al[12] found good correlations between protein equivalent of total nitrogen appearance (nPNA) and Kt/V_{urea}, but not with creatinine clearances, suggesting that the toxins that inhibit appetite in uremia are filtered and reabsorbed in the renal tubules, such as urea, but not creatinine.[12] The authors suggested that Kt/V_{urea} may be supe-

rior to creatinine clearance in determining the appropriate timing for initiation of dialysis and in the prevention of malnutrition. The scarcity of data on peritoneal K_{urea} did not allow analysis of the peritoneal contribution to total clearance using urea.

3. *Other processes are more important to survival than Kp.* It is quite possible that the association of PD dose with survival is simply lost in other mortality-associated processes. Support for this hypothesis is found in the difference between the ''case mix only'' and ''case mix plus lab'' models in both the Kp and Kr risk charts (Figs 5 and 6). Statistical adjustment for other measures enhanced the death risk association for both measures.

   Churchill et al have further analyzed the CANUSA data in regards to peritoneal transport rates and clinical outcome.[13,14] The 4-hour D/P_{cr} was added as a time-dependent covariate to a Cox proportional hazards model containing age, insulin-dependent diabetes mellitus (IDDM), cardiovascular disease, SAC, and Kr_{cr}. The OR was 1.12 per 0.10 increase in D/P_{cr} ($P < 0.0001$). Variables associated with technique survival were SAC and Kr_{cr}. The D/P_{cr} added significantly to the model ($P < 0.001$). The 2-year patient survivals for low, low-average, high-average, and high transporters according to D/P_{cr} were 91%, 80%, 72%, and 71%. Thus, the OR increased 12% for every 0.10 increase in D/P_{cr}. The high transporters had a significantly higher OR despite their superior creatinine clearances, suggesting that membrane transport characteristics may be a strong predictor of outcome and perhaps stronger than the quantity of clearance received.

   Fried[15] prospectively studied 123 PD patients and confirmed the CANUSA findings that patient survival was significantly worse for high transporters and that this effect was independent of SAC. The patients were studied with PETs at the start of PD, creatinine clearances, and Kt/V_{urea}. Survivals were significantly different, with the lowest PET groups having better survival than those in the higher groups ($P = 0.043$). The 1-year patient survival for low, low average, high average, and high were 100%, 100%, 95%, and 90%, respectively. The 3-year survivals were 100%, 89%, 91%, and 71%, respectively. The D/P_{cr} was not correlated with age, race, diabetes, sex, or initial SAC. The Cox proportional hazards model showed age ($P = 0.001$), initial albumin ($P = 0.027$), and D/P_{cr} entered as a continuous variable ($P = 0.014$) as predictors for mortality. The Kt/V, creatinine clearance, and residual renal function at 1 year were not statistically different among the groups. Similar findings have been observed by other investigators.[11,16] The possibility of a high D/P_{cr} being responsible for a higher OR and canceling the benefits of a higher Kp cannot be totally excluded, but it is not supported by the model evaluating the association of 4-hour D/P_{cr} or D/D_0 with OR (Table 6).

4. *Higher Kp, while improving solute removal, is associated also with some mortality-enhancing effect(s) or processes.* This hypothesis deserves evaluation in our view. We know that higher peritoneal membrane transport as measured by the 4-hour D/D_0 for glucose or the D/P_{cr} is associated with lower SAC.[1, 17-21] Higher D/P_{cr} is associated with higher Kp all else being equal. It is very difficult to define the interdependence between SAC and high peritoneal transport as adverse predictors in PD patients because the two variables are very strongly correlated.[17] Therefore, processes associated with higher Kp (processes → greater peritoneal membrane permeability) are already known associates of mortality-enhancing processes (processes → low SAC).

   Peritoneal transport rates depend on both effective peritoneal surface area and the intrinsic permeability of peritoneal capillaries. Although the former may be at least partly related to body surface area (BSA), the determinants of the latter are less well understood. Blake[17] offers the possibility that sicker, malnourished patients simply

have more permeable capillaries, as is the case with critically ill patients with adult respiratory distress syndrome. If that is the case, malnutrition and low SAC would be expected to be present before the commencement of PD. Harty et al[22] found no difference in dietary protein intake, protein catabolic rate, serum transferrin levels, or lean body mass and peritoneal transport status. However, Nolph et al[23] reported significantly lower protein catabolic rate and lean body mass by creatinine kinetics in high transporters. Several studies have also shown that a low SAC at the initiation of dialysis persists even among patients receiving adequate dialysis by urea kinetic standards.[24,25] This hypothesis also considers the possibility that both hypoalbuminemia and high peritoneal transport status result from a state of chronic inflammation or increase in cytokine regulation in the uremic patient, as previously supported by Lowrie's data[26] and by Kaysen et al,[27] who showed that SAC in hemodialysis patients is strongly influenced by its role as an inverse acute-phase reactant.

Whatever the pathophysiologies that contribute to these observations, it is clear that residual renal function and peritoneal clearance may be separate quantities in our clinical thinking. One process (peritoneal clearance) simply does not substitute for the other (residual renal clearance) on a one-to-one basis if we are concerned with biological effects and the outcome of clinical care. The presumption of equivalence may be appropriate if the concern were solute removal from the body rather than biological effects on the body. Adding the two clearances to determine whether treatment is adequate may be inappropriate—biologically speaking.

Substantial work is required to confirm or refute these findings. The nature of the trade-off points between peritoneal and renal clearance require clarification because they are not likely to be equivalent. The increased use of automated PD, using cyclers with memory cards to assess compliance with therapy, will probably provide the necessary data to corroborate these findings.

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