

Higher Peritoneal Transport Status Is Associated with Higher Mortality and Technique Failure in the Australian and New Zealand Peritoneal Dialysis Patient Populations

Markus Rumpsfeld,^{*†} Stephen P. McDonald,^{*} and David W. Johnson^{*‡}

^{*}Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia; [†]Department of Renal Medicine, University of North Norway, Tromsø, Norway; and [‡]Department of Renal Medicine, University of Queensland at Princess Alexandra Hospital, Brisbane, Australia

Although early studies observed that peritoneal membrane transport characteristics were determinants of morbidity and mortality in peritoneal dialysis (PD) patients, more recent investigations, such as the Ademex trial, have refuted these findings. The aim of this study was to determine whether baseline peritoneal transport status predicted subsequent survival in Australian and New Zealand PD patients. The study included all adult patients in Australia and New Zealand who commenced PD between April 1, 1999, and March 31, 2004, and had a peritoneal equilibration test (PET) performed within 6 mo of PD commencement. Times to death and death-censored technique failure were examined by Kaplan-Meier analyses and multivariate Cox proportional hazards models. PET measurements were available in 3702 (72%) of the 5170 individuals who began PD treatment in Australia or New Zealand during the study period. In these patients, high transporter status was found to be a significant, independent predictor of death-censored technique failure (adjusted hazard ratio [AHR] 1.23; 95% confidence interval [CI] 1.02 to 1.49; $P = 0.03$) and mortality (AHR 1.34; 95% CI 1.05 to 1.79, $P = 0.02$) compared with low-average transport status. High-average transport class was also associated with mortality (AHR 1.21; 95% CI 1.00 to 1.48; $P = 0.047$) but not death-censored technique failure (AHR 1.04; 95% CI 0.90 to 1.21) compared with low-average transport status. When transport status was alternatively analyzed as a continuous variable, dialysate:plasma creatinine ratio at 4 h was independently predictive of both death-censored technique failure (AHR 1.07; 95% CI 1.01 to 1.295; $P = 0.031$) and death (AHR 1.09; 95% CI 1.01 to 1.373; $P = 0.036$ per 0.1 change in dialysate:plasma creatinine). Peritoneal transport rate is a highly significant risk factor for both mortality and death-censored technique failure in the Australian and New Zealand incident PD patient populations.

J Am Soc Nephrol 17: 271–278, 2006. doi: 10.1681/ASN.2005050566

Peritoneal permeability, as assessed by the dialysate:plasma creatinine ratio from a peritoneal equilibration test (PET) (1), varies widely between peritoneal dialysis (PD) patients and has been found to differ significantly between distinct populations (2,3). Higher peritoneal transport status has been shown to be associated with a number of mortality and technique failure risk factors, including age, racial origin, body mass index, comorbid illness burden, hypoalbuminemia, and elevated inflammatory markers (2,4–6). However, it is presently unclear whether peritoneal transport status *per se* is an independent risk factor for morbidity and mortality in PD patients. Although early studies observed that peritoneal membrane transport characteristics were important determinants of morbidity and mortality in PD patients (6–17), more recent investigations, such as the Ademex trial (18), have not confirmed these findings (18–21). The reasons for these

conflicting observations are not clear, although many of the published studies to date have suffered from a number of serious limitations, including small sample sizes, relatively short follow-up durations, low numbers of events, restriction of observations to single centers, highly selected patient populations, or the inclusion of prevalent patients (thereby potentially introducing informative censoring bias). The aim of our study was to determine whether baseline peritoneal transport status predicted subsequent survival in a large cohort of Australian and New Zealand PD patients using PET data obtained from the Australian and New Zealand Dialysis and Transplant Association (ANZDATA) Registry.

Materials and Methods

Study Population

Our analysis included all patients in Australia and New Zealand who commenced PD between April 1, 1999, and March 31, 2004; were older than 18 yr; and had a PET performed within the first 6 mo of PD commencement. These patients were followed until cessation of PD; death; or March 31, 2004.

Full details regarding the structure and the methods of the ANZDATA Registry are reported elsewhere (22). In summary, the collection is complete from the first renal replacement therapy in Australasia in

Received May 30, 2005. Accepted October 5, 2005.

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Prof. David Johnson, Department of Renal Medicine, Level 2, Ambulatory Renal and Transplant Services Building, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane Qld 4102, Australia. Phone: +61-7-3240-5080; Fax: +61-7-3240-5480; E-mail: david_johnson@health.qld.gov.au

Table 1. Comparison of the baseline characteristics of incident Australian and New Zealand PD patients who did or did not have D:P Cr 4 h measurements performed in the first 6 mo of dialysis onset^a

Variable	No D:P Cr 4 H Available (n = 1468)	D:P Cr 4 H Available (n = 3702)	P Value
Male gender	787 (53.6%)	1966 (53.1%)	0.842
White race	1066 (72.6%)	2603 (70.3%)	0.100
Age (yr)	61.0 ± 15.2	59.4 ± 14.8	0.001
Smoking (current or former)	203 (13.9%)	479 (13.0%)	0.412
Hypertension	1297 (88.4%)	3329 (89.9%)	0.192
Lung disease	183 (12.5%)	346 (9.3%)	0.001
Coronary disease	503 (34.3%)	1098 (29.7%)	< 0.001
Peripheral vascular disease	340 (23.2%)	662 (17.9%)	< 0.001
Cerebrovascular disease	201 (13.7%)	386 (10.4%)	< 0.001
Diabetes	615 (41.9%)	1410 (38.1%)	< 0.001
BMI (kg/m ²)	26.1 ± 5.4	26.3 ± 5.2	0.188
Residual renal function (L/wk per 1.73 m ²)	18.9 ± 35.2	22.1 ± 35.0	0.081
Weekly peritoneal Kt/V	2.03 ± 0.72	2.12 ± 0.72	0.013

^aResults are expressed as mean ± SD or n (%). PD, peritoneal dialysis; D:P Cr 4 h, dialysate:plasma creatinine ratio at 4 h.

1963 and includes all patients from all renal units in both countries. The data collected consist of information about the underlying cause of ESRD, demographic details, a limited range of comorbidities (the presence of coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, hypertension, and smoking), the type and dose of dialysis treatment, details about renal transplantation and measurements of height and (from 1 April 1999) dialysate:plasma creatinine ratio at 4 h (D:P Cr 4 h).

Peritoneal transport status was considered both as a continuous variable (D:P Cr 4 h) and as a categorical variable, according to the four groupings of D:P Cr 4 h values defined by Twardowski (low <0.50, low-average 0.50 to 0.64, high-average 0.65 to 0.80, and high ≥0.81) (1). Baseline D:P Cr, weekly peritoneal Kt/V, and residual renal function were collected once for each patient within the first 6 mo of PD commencement (usually at 1 mo). For potentially related comorbidities, “suspected” was combined with “yes” for analyses. Body mass index (BMI) was calculated from the height and dry weight (empty of dialysis fluid) at commencement of PD and analyzed as either a categorical variable according to World Health Organization criteria (obese ≥30 kg/m², overweight 25 to 30 kg/m², normal weight 18.5 to 24.99 kg/m², and underweight <18.5 kg/m²) or as a continuous variable, where indicated.

Statistical Analyses

Results are expressed as mean ± SD for continuous data and as frequencies and percentages for categorical data. Differences in D:P Cr 4 h between PD patient subgroups were evaluated by unpaired *t* test or ANOVA. The distributions of categorical variables across each of the four transport groups were compared using the χ^2 test. Survival curves, survival probabilities, and estimated mean survival times were generated according to the Kaplan-Meier method. Survival analyses were also performed using univariate and multivariate Cox proportional hazards models using enter method and backward stepwise elimination based on the likelihood ratio. The covariates included in the Cox models were peritoneal transport category; age; gender; racial origin; smoking status; BMI category; weekly peritoneal Kt/V; residual renal function; vintage year; PD modality; and the presence or absence of hypertension, chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and diabetes. Data were cen-

sored at the time of renal transplantation; March 31, 2004; or 60 d after transfer to hemodialysis for the overall survival analyses, whereas the death-censored technique analyses were censored at the time of renal transplantation; death; or March 31, 2004. Adjusted survival curves were estimated using the Cox average covariate method, which calculates predicted survival probabilities at the mean levels of the covariates. Proportional hazards assumptions were checked by Schoenfeld residuals and scaled Schoenfeld residuals, examined by formal hypothesis test and graphically. First-order interaction terms between the significant covariates were examined for all models. Additional subgroup survival analyses were performed in the automated peritoneal dialysis (APD) and continuous ambulatory PD (CAPD) populations. Data were analyzed using the software package SPSS for Windows release 11.5 (SPSS Inc., North Sydney, Australia). *P* < 0.05 were considered statistically significant.

Results

Baseline Characteristics

Baseline D:P Cr 4 h measurements were available in 3702 (72%) of the 5170 individuals who began PD treatment in Australia or New Zealand between April 1, 1999, and March 31, 2004. Compared with the 1468 patients who did not have a D:P Cr 4 h measurement available for study, those who did were significantly younger and had a higher mean weekly peritoneal Kt/V but were less likely to have lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, and diabetes (Table 1). Only those people with D:P Cr 4 h measurements were considered for further analysis of the impact of baseline peritoneal transport characteristics on PD outcomes.

The main baseline demographic and clinical characteristics of the study population are presented in Table 2 (mean ± SD age 59.4 ± 14.8 yr, 54% male, 38% diabetic, 70% white). The mean D:P Cr 4 h was 0.69 ± 0.12, and the numbers of high, high-average, low-average, and low transporters were 614 (16.6%), 1848 (49.9%), 1055 (28.5%), and 185 (5.0%), respectively (Figure 1). Compared with low and low-average transporters, high and

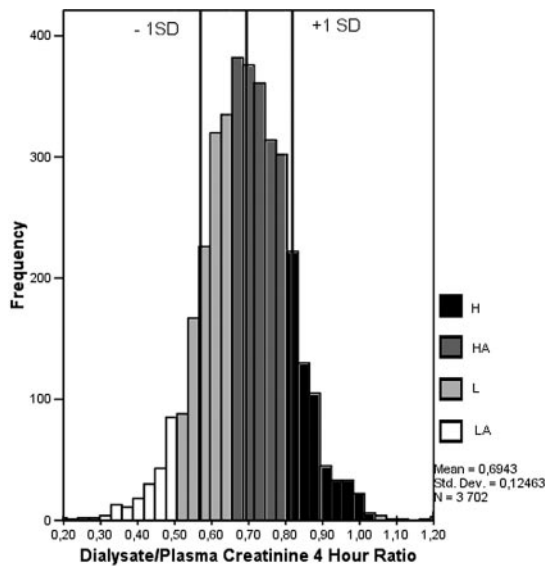


Figure 1. Distribution of baseline peritoneal equilibration test (PET) measurements in the study population. The mean \pm SD dialysate:plasma creatinine ratio at 4 h (D:P Cr 4 h) was 0.69 ± 0.12 . L, low; LA, low-average; HA, high-average; H, high transport classes according to the definitions by Twardowski.

high-average transport categories had lower mean BMI, were more likely to be male, and were more likely to be treated with APD (Table 2). Racial origin varied significantly between each of the peritoneal transport groups; in particular, Asians seemed to have a lower peritoneal transport status.

By the end of the study, 1632 (44.1%) patients were alive on PD, 1074 (29.0%) transferred to hemodialysis, 298 (8.0%) had received a transplant, 36 (1.0%) spontaneously recovered renal function and ceased dialysis, four (0.1%) were lost to follow-up, and 688 (18.6%) had died. A total of 1231 (33.3%) individuals received APD treatment at some point during the study period.

Death-Censored Technique Survival

The median actuarial death-censored technique survival for the overall population was 3.7 yr (95% confidence interval [CI] 3.4 to 4.0 yr). The causes of technique failure among the study cohort were reported as patient preference (35%), followed by inadequate solute clearance (19%), acute peritonitis (11%), recurrent peritonitis (9%), and inadequate fluid clearance (9%). Transport class was not significantly associated with death-censored technique survival on either univariate Cox regression analysis (Table 3) or Kaplan-Meier analysis (log rank 5.49; $P = 0.14$). However, after multivariate Cox proportional haz-

Table 2. Baseline characteristics of the study population ($n = 3702$)^a

Variable	Total Population ($n = 3702$)	Breakdown by Transport Category				Crude P Value
		Low ($n = 185$)	Low-Average ($n = 1055$)	High Average ($n = 1848$)	High ($n = 614$)	
Male gender	1996 (53.9%)	82 (44.3%)	518 (49.1%)	1050 (56.8%)	46 (56.4%)	< 0.001
Racial origin						
white	2603 (70.3%)	128 (69.2%)	749 (71.0%)	1297 (70.2%)	429 (69.9%)	
Aboriginal/TSI	197 (5.3%)	9 (4.9%)	62 (5.9%)	83 (4.5%)	43 (7.0%)	
< Maori/PI	510 (13.8%)	24 (13.0%)	128 (12.1%)	259 (14.0%)	99 (16.1%)	
Asian	331 (8.9%)	22 (11.9%)	95 (9.0%)	179 (9.7%)	35 (5.7%)	
other	61 (1.6%)	2 (1.1%)	21 (2.0%)	30 (1.6%)	8 (1.3%)	0.029
Age (yr)	59.4 ± 14.8	57.5 ± 14.0	59.4 ± 14.9	59.3 ± 14.8	59.3 ± 14.6	0.447
Smoking						
current	479 (12.9%)	26 (14.1%)	114 (10.8%)	243 (13.1%)	96 (15.6%)	
former	1441 (38.9%)	60 (32.4%)	412 (39.1%)	725 (39.2%)	244 (39.7%)	
never	1782 (48.1%)	99 (53.5%)	529 (50.1%)	880 (47.6%)	274 (44.6%)	0.040
Hypertension	3329 (89.9%)	162 (87.6%)	949 (90.0%)	1663 (90.0%)	555 (90.4%)	0.731
Lung disease	471 (12.7%)	28 (15.1%)	126 (11.9%)	234 (12.7%)	83 (13.5%)	0.593
Coronary disease	1421 (38.4%)	72 (38.9%)	385 (36.5%)	722 (39.1%)	242 (39.4%)	0.520
Peripheral vascular disease	945 (25.5%)	41 (22.2%)	266 (25.2%)	481 (26.0%)	157 (25.6%)	0.705
Cerebrovascular disease	522 (14.1%)	20 (10.8%)	129 (12.2%)	277 (15.0%)	96 (15.6%)	0.069
Diabetes	1410 (38.1%)	69 (37.3%)	399 (37.8%)	690 (37.3%)	252 (41.0%)	0.424
BMI (kg/m^2)	26.3 ± 5.2	26.7 ± 5.2	26.9 ± 5.3	26.2 ± 5.1	25.6 ± 5.2	< 0.001
BMI category						
<18.5 kg/m^2	123 (3.4%)	6 (3.2%)	34 (3.2%)	59 (3.2%)	24 (3.9%)	
18.5 to 24.9 kg/m^2	1528 (41.8%)	65 (35.1%)	391 (37.1%)	780 (42.2%)	292 (47.6%)	
25 to 30 kg/m^2	1230 (33.7%)	65 (35.1%)	394 (37.3%)	582 (31.5%)	189 (30.8%)	
>30 kg/m^2	773 (21.2%)	48 (25.9%)	226 (21.4%)	399 (21.6%)	100 (16.3%)	< 0.001
Residual renal function (L/wk per 1.73 m^2)	22.1 ± 35.5	19.8 ± 30.6	22.6 ± 34.2	22.4 ± 35.6	21.1 ± 38.6	0.689
Weekly peritoneal Kt/V	2.1 ± 0.7	2.1 ± 0.7	2.1 ± 0.7	2.1 ± 0.7	2.2 ± 0.8	0.162
Received APD	1231 (33.3%)	52 (28.1%)	295 (28.0%)	641 (34.7%)	243 (39.6%)	< 0.001
D:P Cr 4 h	0.69 ± 0.12	0.42 ± 0.08	0.59 ± 0.04	0.72 ± 0.05	0.88 ± 0.08	< 0.001

^aResults are expressed as mean \pm SD or n (%). Differences between transport categories were assessed by χ^2 test or ANOVA, depending on data type. TSI, Torres Strait Islanders; PI, Pacific Islanders; APD, ambulatory peritoneal dialysis.

Table 3. Predictors of death-censored technique survival in 3702 incident PD patients in Australia and New Zealand, based on the results of univariate and multivariate Cox regression analyses^a

Characteristic (<i>n</i> = 998 Events)	Univariate		Multivariate	
	HR	<i>P</i>	HR	<i>P</i>
PET classes				
low	0.82 (0.60 to 1.13)	0.228	0.82 (0.59 to 1.13)	0.225
low-average	Ref		Ref	Ref
high average	0.99 (0.87 to 1.15)	0.988	1.04 (0.90 to 1.21)	0.605
high	1.16 (0.96 to 1.39)	0.115	1.23 (1.01 to 1.49)	0.036
Age (per decade)	0.98 (0.94 to 1.03)	0.425	0.97 (0.92 to 1.02)	0.177
Male gender	1.15 (0.99 to 1.26)	0.080	1.03 (0.90 to 1.17)	0.691
Race				
white	Ref		Ref	
Aboriginal/TSI	1.48 (1.18 to 1.86)	0.01	1.32 (1.02 to 1.71)	0.035
Maori/PI	0.88 (0.73 to 1.05)	0.159	0.80 (0.65 to 0.97)	0.027
Asian	0.61 (0.47 to 0.78)	< 0.001	0.66 (0.51 to 0.86)	0.002
other	0.71 (0.42 to 1.20)	0.196	0.74 (0.42 to 1.27)	0.273
Smoking				
current smoker	0.94 (0.79 to 1.13)		0.89 (0.74 to 1.09)	
former or never smoker	Ref	0.521	Ref	0.259
Treated hypertension	1.18 (0.95 to 1.47)	0.136	1.16 (0.93 to 1.46)	0.195
Chronic lung disease	0.98 (0.81 to 1.18)	0.82	1.02 (0.84 to 1.24)	0.833
Coronary artery disease	1.05 (0.93 to 1.19)	0.464	1.09 (0.94 to 1.27)	0.248
Peripheral vascular disease	1.02 (0.89 to 1.17)	0.796	0.99 (0.83 to 1.17)	0.888
Cerebrovascular disease	0.89 (0.74 to 1.07)	0.221	0.89 (0.73 to 1.10)	0.288
Diabetes	1.01 (0.89 to 1.14)	0.91	0.96 (0.82 to 1.11)	0.552
BMI category				
<18.5 kg/m ²	0.75 (0.50 to 1.12)	0.161	0.76 (0.51 to 1.15)	0.196
18.5 to 25 kg/m ²	Ref		Ref	
25 to 30 kg/m ²	1.19 (1.03 to 1.37)	0.016	1.18 (1.02 to 1.37)	0.031
>30 kg/m ²	1.35 (1.15 to 1.59)	< 0.001	1.37 (1.16 to 1.64)	< 0.001
Weekly peritoneal Kt/V (per 0.1 unit)	0.98 (0.97 to 0.99)	< 0.001	0.98 (0.97 to 0.99)	< 0.001
Residual renal function (per L/wk per 1.73 m ²)	0.99 (0.99 to 1.00)	0.007	0.99 (0.99 to 1.00)	0.004
Vintage year				
April 1999 to March 2000	Ref		Ref	
April 2000 to March 2001	0.81 (0.69 to 0.95)	0.011	0.82 (0.69 to 0.97)	0.023
April 2001 to March 2002	0.85 (0.72 to 1.01)	0.071	0.92 (0.77 to 1.11)	0.408
April 2002 to March 2003	0.90 (0.74 to 1.09)	0.286	0.96 (0.78 to 1.20)	0.720
April 2003 to March 2004	0.73 (0.51 to 1.05)	0.088	0.79 (0.55 to 1.15)	0.227

^aHR, hazard ratio.

ards model analysis, high transporter status was a significant, independent predictor of death-censored technique failure (Table 3, Figure 2). The other independent predictors of death-censored technique failure were overweight or obese BMI. Conversely, Maori/Pacific Islander racial origin, Asian racial origin, higher baseline weekly peritoneal Kt/V, and higher baseline residual renal function were associated with improved death-censored technique survival. These results were consistent between the uni- and multivariate analyses. When peritoneal membrane permeability was alternatively analyzed as a continuous variable, D:P Cr 4 h remained a strong, independent predictor of death-censored technique failure (adjusted hazard ratio [HR] 1.08; 95% CI 1.01 to 1.295; *P* = 0.031) per 0.1 change in D:P Cr 4 h. Subgroup analyses according to type of PD therapy prescribed demonstrated that high transporter status was independently predictive of death-censored technique failure for patients who received CAPD (adjusted HR 1.43; 95% CI 1.12 to 1.81; *P* < 0.01) but not for those who received APD

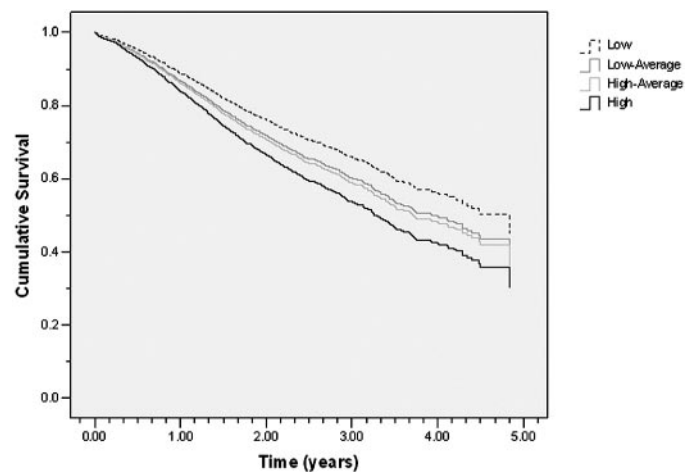


Figure 2. Multivariate Cox-adjusted death-censored technique survival curves for each of the four peritoneal transport classes.

(adjusted HR 0.98; 95% CI 0.71 to 1.36; $P = 0.91$). No significant first-order interactions were identified between peritoneal transport status and other covariates (including BMI).

Overall Survival

A total of 688 (18.6%) patients died during the study period. The causes of death were cardiovascular disease (58%), withdrawal from dialysis (16%), infection (14%), malignancy (4%), cachexia (2%), perforated abdominal viscus (1%), and other (5%). Median actuarial patient survival for the whole study population was 4.3 yr (95% CI 3.9 to 4.6 yr) but was significantly shorter for high transporters (3.6 yr; 95% CI 3.3 to 3.9 yr) than for the remaining three transport classes (log rank 9.56; $P = 0.023$). Compared with low-average transporters, mortality was significantly increased in high transporters (HR 1.43; 95% CI 1.14 to 1.80; $P = 0.002$), with a similar trend in high-average transporters (HR 1.20; 95% CI 0.99 to 1.45; $P = 0.05$) in univariate Cox proportional hazards model analyses (Table 4). After multivariate adjustment, mortality rates were significantly increased in both high-average (adjusted HR 1.21; 95% CI 1.00 to

1.48; $P = 0.05$) and high transport classes (adjusted HR 1.34; 95% CI 1.05 to 1.79; $P = 0.02$; Table 4, Figure 3). Mortality was also independently predicted by higher age, Aboriginal and Torres Strait Islander racial origin, BMI <18.5 kg/m², coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes, and requirement for antihypertensive treatment. Conversely, Asian racial origin, higher baseline peritoneal Kt/V, and higher baseline residual renal function were associated with enhanced survival. When peritoneal membrane permeability was alternatively analyzed as a continuous variable, D:P Cr 4 h remained a strong, independent predictor of mortality (adjusted HR 1.098; 95% CI 1.01 to 1.373; $P = 0.036$) per 0.1 change in D:P Cr 4 h.

Cox multivariate analysis, with backward stepwise elimination based on the likelihood ratio, did not alter the strong associations between peritoneal transport status and death-censored technique survival and overall survival (data not shown). Subgroup analyses according to type of PD therapy prescribed demonstrated that high transporter status was in-

Table 4. Predictors of survival in 3702 incident PD patients in Australia and New Zealand, based on the results of univariate and multivariate Cox regression analyses

Characteristic ($n = 688$ Events)	Univariate		Multivariate	
	HR	P	HR	P
PET classes				
low	1.14 (0.80 to 1.64)	0.473	1.06 (0.72 to 1.55)	0.766
low-average	Ref		Ref	
high average	1.20 (0.99 to 1.45)	0.052	1.22 (1.00 to 1.48)	0.046
high	1.43 (1.14 to 1.80)	0.002	1.34 (1.05 to 1.71)	0.017
Age (per decade)	1.49 (1.40 to 1.59)	< 0.001	1.53 (1.41 to 1.65)	< 0.001
Male gender	0.96 (0.83 to 1.11)	0.576	0.94 (0.79 to 1.10)	0.420
Race				
white	Ref		Ref	
Aboriginal/TSI	1.46 (1.09 to 1.94)	0.011	1.94 (1.39 to 2.70)	< 0.001
Maori/PI	0.96 (0.78 to 1.19)	0.735	1.08 (0.84 to 1.38)	0.560
Asian	0.64 (0.48 to 0.86)	0.003	0.68 (0.50 to 0.93)	0.017
other	0.37 (0.15 to 0.89)	0.027	0.48 (0.20 to 1.17)	0.106
Smoking				
current smoker	1.12 (0.95 to 1.51)		1.00 (0.78 to 1.28)	
former or never smoker	Ref	0.128		0.997
Treated hypertension	1.20 (0.66 to 1.05)	0.126	0.72 (0.56 to 0.92)	0.008
Chronic lung disease	1.49 (1.22 to 1.81)	< 0.001	1.05 (0.85 to 1.30)	0.665
Coronary artery disease	2.53 (2.17 to 2.95)	< 0.001	1.45 (1.21 to 1.74)	< 0.001
Peripheral vascular disease	2.41 (2.07 to 2.80)	< 0.001	1.50 (1.29 to 1.80)	< 0.001
Cerebrovascular disease	2.06 (1.73 to 2.45)	< 0.001	1.24 (1.02 to 1.51)	0.033
Diabetes	1.64 (1.41 to 1.90)	< 0.001	1.62 (1.35 to 1.95)	< 0.001
BMI category				
<18.5 kg/m ²	1.25 (0.85 to 1.81)	0.25	1.61 (1.09 to 2.36)	0.017
18.5 to 25 kg/m ²	Ref		Ref	
25 to 30 kg/m ²	1.04 (0.87 to 1.23)	0.71	0.90 (0.75 to 1.09)	0.287
>30 kg/m ²	1.20 (0.98 to 1.46)	0.08	1.11 (0.89 to 1.38)	0.362
Weekly peritoneal Kt/V (per 0.1 unit)	0.98 (0.97 to 0.99)	< 0.001	0.98 (0.97 to 0.99)	0.002
Residual renal function (per 1 L/wk per 1.73 m ²)	0.997 (0.99 to 1.00)	0.038	0.99 (0.99 to 1.00)	0.034
Vintage year				
April 1999 to March 2000	Ref		Ref	
April 2000 to March 2001	1.07 (0.87 to 1.30)	0.52	1.08 (0.88 to 1.37)	0.478
April 2001 to March 2002	1.04 (0.83 to 1.30)	0.74	1.04 (0.82 to 1.33)	0.748
April 2002 to March 2003	1.06 (0.81 to 1.39)	0.68	1.15 (0.85 to 1.56)	0.365
April 2003 to March 2004	1.39 (0.87 to 2.21)	0.174	1.50 (0.90 to 2.51)	0.124

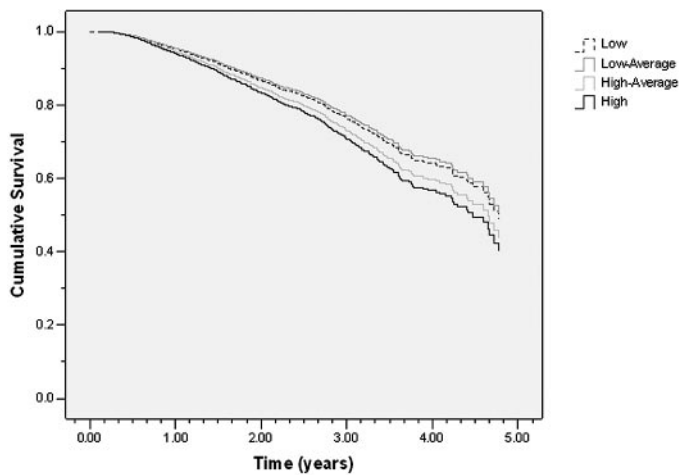


Figure 3. Multivariate Cox-adjusted survival curves for each of the four peritoneal transport classes.

dependently predictive of mortality for patients who received CAPD (adjusted HR 1.44; 95% CI 1.08 to 1.93; $P = 0.01$) but not for those who received APD (adjusted HR 1.39; 95% CI 0.87 to 2.21; $P = 0.16$). No significant first-order interactions were identified between peritoneal transport status and other covariates (including BMI).

Discussion

This study demonstrated that peritoneal transport status is a highly significant risk factor for both mortality and death-censored technique failure in the Australian and New Zealand incident PD patient populations. This risk is independent of demographic characteristics, BMI, comorbid clinical illnesses, peritoneal small solute clearances, and residual renal function. Moreover, peritoneal permeability remains a risk factor for adverse PD outcomes regardless of whether it is analyzed as a continuous or a categorical variable.

Our study is by far the largest examination to date of the relationship between peritoneal transport rate and PD outcomes. Its findings are in keeping with those of a number of earlier investigations (6–17). For example, in an analysis of the CANUSA data, Churchill *et al.* (7) demonstrated that the relative risk of either technique failure or death was increased by 19% (95% CI 5 to 34%) for each 0.1 increase in D:P Cr 4 h. Two-year survival probabilities of high, high-average, low-average, and low transporters were 70.5, 72.4, 80.4, and 90.9%, respectively ($P = 0.11$). The 2-yr probabilities of both patient and technique survival were 48, 52, 61, and 86%, respectively ($P = 0.006$). These results were observed despite that small solute clearances were greater (although not significantly) with higher transport status. Fried *et al.* (10) similarly demonstrated in a prospective study of 123 PD patients that the respective 3-yr survival probabilities of high, high-average, low-average, and low transporters were 70.5, 90.9, 88.9, and 100% ($P < 0.05$), despite no significant differences observed in small solute clearance between the groups. Davies *et al.* (11) prospectively analyzed survival in 210 and subsequently 303 (6) consecutive PD

patients using Cox proportional hazards models and identified that a high D:P Cr 4 h was an independent predictor of death. Similar results were reported by Wu *et al.* (17), Wang *et al.* (8), Hung *et al.* (13), and Cueto-Manzano *et al.* (16) in population sizes ranging between 46 and 171.

More recent studies, however, have failed to observe an independent relationship between peritoneal permeability and PD outcomes (18–21). The largest and best known of these investigations was the ADEMEX trial (18), which observed no significant effect of baseline peritoneal transport characteristics (as determined by the dialysis adequacy and transport test) on the survival of 965 PD patients. The apparent disparity in findings may be explained by the fact that the ADEMEX trial assessed peritoneal transport status by the dialysis adequacy and transport test (which may have given different results compared with PET) and predominantly included prevalent patients, thereby potentially introducing informative censoring bias. For example, if high transport status is associated with a higher technique failure rate, then this group may have been underrepresented in a study of prevalent PD patients. Moreover, in contrast to our study, which examined the vast majority of Australian and New Zealand PD patients, the ADEMEX trial included only a fraction of the total PD population of 24 dialysis centers in Mexico, thereby raising the possibility of ascertainment and selection biases.

Similarly, the prospective, multicenter European Automated PD Outcome Study found that baseline D:P Cr 4 h had no effect on overall or technique survival in 177 patients (19). However, the results may have been adversely affected by the preferential selection of anuric, prevalent automated PD patients and by the relatively low number ($n = 31$) of deaths (thereby making a possible type 2 statistical error likely). Other negative studies (12,20,21) likewise have been limited by small sample sizes (≤ 213 patients), short follow-up times, low event rates, and restriction to single-center observations.

A significant change in the use of automated PD was observed in our study during the data collection period between April 1999 and March 2004. In 1999, 11.4% of all patients who were treated with PD in Australia and New Zealand received automated PD treatment. By 2003, the percentage had risen to 27.7%. However, when the proportion of patients who were being treated with automated PD and the year in which patients received PD were included as covariates in the Cox regression analyses, strong associations were still observed between peritoneal transport status and both death-censored technique survival and overall survival. When subgroup analyses were performed according to the type of PD therapy prescribed, high transporter status was independently predictive of death-censored technique failure and mortality for patients who were receiving CAPD but not for those who were receiving APD. Although a type 2 statistical error in the APD subgroup analysis could not be excluded, it is also possible that APD therapy abrogated the deleterious clinical consequences of high peritoneal transport rate.

There is also a possibility that racial differences influenced the relationship between peritoneal transport and outcomes.

For example, a recent study by Chung *et al.* (9) observed that D:P Cr 4 h was an independent predictor of mortality in 136 Korean PD patients but not in 106 Swedish PD patients. These differences, however, also may have been attributable to differential access to icodextrin therapy, center effects (because they involved only one center in Korea and another in Sweden), differences in PET protocols (4.25 versus 2.27% glucose solutions), informative censoring bias as a result of a much higher transplantation rate in the Swedish center, and inadequate statistical power.

The exact mechanisms for the poorer survival of high and high-average transporters in our study remain unclear but may relate at least partially to impaired ultrafiltration and fluid overload (8,12,21,23,24). High peritoneal transport is associated with a more rapid absorption of glucose and hence dissipation of the osmotic gradient required for sustained ultrafiltration. There is evidence that patients with symptomatic fluid retention are 3.7 times more likely to be high than low transporters (25). The finding in our study that high peritoneal transport status was not associated with death-censored technique survival and overall survival in the subgroup of patients who were receiving APD therapy may have reflected better fluid control with this PD modality. It has also been argued that the increased mortality of high transporters is primarily due to an association between D:P Cr 4 h and comorbid illness burden (6). Chung *et al.* (15) reported that high transport status was an independent risk factor for mortality in patients with comorbid disease but not in those without comorbidity. However, this may have been due to a low event rate (and therefore inadequate statistical power) in the latter group, because our study did not replicate these findings and because we have previously reported a lack of significant association between D:P Cr 4 h and comorbid disease (2).

Malnutrition may also have contributed to the excess mortality in high transporters, because such patients have a higher prevalence of hypoalbuminemia (5,7,8,16,26–29). A low serum albumin correlates with other markers of malnutrition, such as normalized protein catabolic rate and subjective global assessment (30), and is strongly predictive of PD patient death (31,32). Nolph *et al.* (33) and Kang *et al.* (27) demonstrated that high peritoneal permeability was associated with a reduced normalized protein catabolic rate and composite nutritional index, but these associations were not confirmed by the CANUSA study (7). The greater prevalence of hypoalbuminemia in high transporters may also arise from hemodilution secondary to suboptimal ultrafiltration (34) or from excessive peritoneal protein losses (28). Alternatively, hypoalbuminemia in high transporters may reflect a greater incidence of underlying chronic inflammation (12,35), although other studies have not observed a significant correlation between D:P Cr 4 h and various inflammatory markers, such as C-reactive protein (4,36).

The strengths of this study included its very large sample size and the robustness of its findings across different statistical methods. Because we included all centers across both countries, the external validity of our findings was greatly enhanced. Moreover, our cohort consisted solely of incident patients,

thereby avoiding the potentially confounding factor of survivor bias associated with prevalent population studies.

Nevertheless, the use of registry data in this article also carried significant limitations. Because of the retrospective nature of the analysis and that only 72% of the entire cohort had baseline PET results, the potentials for both recall and selection biases were present. As shown in Table 1, patients with certain characteristics were more likely to have undergone a D:P Cr 4 h measurement during the study period. Although these differences were statistically significant, the actual sizes of the differences were generally minor. Furthermore, ANZDATA does not collect information on drain volume, nutritional markers (*e.g.*, albumin), inflammatory markers, icodextrin therapy, or the severity of comorbidities, so residual confounding or unidentified associations could not be excluded entirely. In common with other registries, ANZDATA is a voluntary registry, and there is no external audit of data accuracy.

In conclusion, high peritoneal transport status is a highly significant, independent risk factor for both mortality and death-censored technique failure in the Australian and New Zealand incident PD patient populations. Further studies are required to determine whether the adverse prognosis of high transporters can be improved by various therapeutic strategies, such as automated PD, icodextrin, nutritional supplementation, anti-inflammatory therapies, or early conversion to hemodialysis.

Acknowledgments

We gratefully acknowledge the substantial contributions of the entire Australia and New Zealand nephrology community (physicians, surgeons, database managers, nurses, renal operators, and patients) in providing information for and maintaining the ANZDATA Registry database.

References

1. Twardowski ZJ, Nolph KD, Khanna R: Peritoneal equilibration test. *Perit Dial Bull* 7: 138–147, 1987
2. Rumpfeld M, McDonald SP, Purdie DM, Collins J, Johnson DW: Predictors of baseline peritoneal transport status in Australian and New Zealand peritoneal dialysis patients. *Am J Kidney Dis* 43: 492–501, 2004
3. Voinescu CG, Khanna R, Nolph KD: High peritoneal transport: A blessing or curse? *Adv Perit Dial* 18: 106–111, 2002
4. Wang T, Heimburger O, Cheng HH, Bergstrom J, Lindholm B: Does a high peritoneal transport rate reflect a state of chronic inflammation? *Perit Dial Int* 19: 17–22, 1999
5. Margetts PJ, McMullin JP, Rabbat CG, Churchill DN: Peritoneal membrane transport and hypoalbuminemia: Cause or effect? *Perit Dial Int* 20: 14–18, 2000
6. Davies SJ, Phillips L, Naish PF, Russell GI: Quantifying comorbidity in peritoneal dialysis patients and its relationship to other predictors of survival. *Nephrol Dial Transplant* 17: 1085–1092, 2002
7. Churchill DN, Thorpe KE, Nolph KD, Keshaviah PR, Oreopoulos DG, Page D: Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. The

- Canada-USA (CANUSA) Peritoneal Dialysis Study Group. *J Am Soc Nephrol* 9: 1285–1292, 1998
8. Wang T, Heimbürger O, Waniewski J, Bergström J, Lindholm B: Increased peritoneal permeability is associated with decreased fluid and small-solute removal and higher mortality in CAPD patients. *Nephrol Dial Transplant* 13: 1242–1249, 1998
 9. Chung SH, Heimbürger O, Lindholm B, Lee HB: Peritoneal dialysis patient survival: A comparison between a Swedish and a Korean centre. *Nephrol Dial Transplant* 20: 1207–1213, 2005
 10. Fried L: Higher membrane permeability predicts poorer patient survival. *Perit Dial Int* 17: 387–389, 1997
 11. Davies SJ, Phillips L, Russell GI: Peritoneal solute transport predicts survival on CAPD independently of residual renal function. *Nephrol Dial Transplant* 13: 962–968, 1998
 12. Chung SH, Heimbürger O, Stenvinkel P, Qureshi AR, Lindholm B: Association between residual renal function, inflammation and patient survival in new peritoneal dialysis patients. *Nephrol Dial Transplant* 18: 590–597, 2003
 13. Hung KY, Lin TJ, Tsai TJ, Chen WY: Impact of peritoneal membrane transport on technique failure and patient survival in a population on automated peritoneal dialysis. *ASAIO J* 45: 568–573, 1999
 14. Wiggins KJ, Blizzard S, Arndt M, O'Shea A, Watt R, Hamilton J, Cottingham S, Campbell SB, Isbel NM, Johnson DW: Increases in peritoneal small solute transport in the first month of peritoneal dialysis predict technique survival. *Nephrology (Carlton)* 9: 341–347, 2004
 15. Chung SH, Chu WS, Lee HA, Kim YH, Lee IS, Lindholm B, Lee HB: Peritoneal transport characteristics, comorbid diseases and survival in CAPD patients. *Perit Dial Int* 20: 541–547, 2000
 16. Cueto-Manzano AM, Correa-Rotter R: Is high peritoneal transport rate an independent risk factor for CAPD mortality? *Kidney Int* 57: 314–320, 2000
 17. Wu CH, Huang CC, Huang JY, Wu MS, Leu ML: High flux peritoneal membrane is a risk factor in survival of CAPD treatment. *Adv Perit Dial* 12: 105–109, 1996
 18. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, Mujais S: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 13: 1307–1320, 2002
 19. Brown EA, Davies SJ, Rutherford P, Meeus F, Borrás M, Riegel W, Divino Filho JC, Vonesh E, van Bree M: Survival of functionally anuric patients on automated peritoneal dialysis: The European APD Outcome Study. *J Am Soc Nephrol* 14: 2948–2957, 2003
 20. Park HC, Kang SW, Choi KH, Ha SK, Han DS, Lee HY: Clinical outcome in continuous ambulatory peritoneal dialysis patients is not influenced by high peritoneal transport status. *Perit Dial Int* 21[Suppl 3]: S80–S85, 2001
 21. Chung SH, Heimbürger O, Stenvinkel P, Wang T, Lindholm B: Influence of peritoneal transport rate, inflammation, and fluid removal on nutritional status and clinical outcome in prevalent peritoneal dialysis patients. *Perit Dial Int* 23: 174–183, 2003
 22. Russ GR: The ANZDATA Registry. In: *The Twenty-Fourth Annual Report of the ANZDATA Registry*, Adelaide, South Australia, ANZDATA Registry, 2001
 23. Blake PG: What is the problem with high transporters? *Perit Dial Int* 17: 317–320, 1997
 24. Ates K, Nergizoglu G, Keven K, Sen A, Kutlay S, Erturk S, Duman N, Karatan O, Ertug AE: Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. *Kidney Int* 60: 767–776, 2001
 25. Tzamaloukas AH, Saddler MC, Murata GH: Symptomatic fluid retention in patients on continuous peritoneal dialysis. *J Am Soc Nephrol* 6: 198–206, 1995
 26. Burkart JM: Effect of peritoneal dialysis prescription and peritoneal membrane transport characteristics on nutritional status. *Perit Dial Int* 15: S20–S35, 1995
 27. Kang DH, Yoon KI, Choi KB, Lee R, Lee HY, Han DS, Cho EY, Lee JH: Relationship of peritoneal membrane transport characteristics to the nutritional status in CAPD patients. *Nephrol Dial Transplant* 14: 1715–1722, 1999
 28. Kagan A, Bar Khayim Y: Role of peritoneal loss of albumin in the hypoalbuminemia of continuous ambulatory peritoneal dialysis patients: Relationship to peritoneal transport of solutes. *Nephron* 71: 314–320, 1995
 29. Diaz Alvarenga A, Abasta Jimenez M, Bravo B, Gamba G, Correa Rotter R: Serum albumin and body surface area are the strongest predictors of the peritoneal transport type. *Adv Perit Dial* 10: 47–51, 1994
 30. Han DS, Lee SW, Kang SW, Choi KH, Lee HY, Cho EY, Lee JH: Factors affecting low values of serum albumin in CAPD patients. *Adv Perit Dial* 12: 288–292, 1996
 31. Fung L, Pollock CA, Caterson RJ, Mahony JF, Waugh DA, Macadam C, Ibels LS: Dialysis adequacy and nutrition determine prognosis in continuous ambulatory peritoneal dialysis patients. *J Am Soc Nephrol* 7: 737–744, 1996
 32. Struijk DG, Krediet RT, Koomen GC, Boeschoten EW, Hoek FJ, Arisz L: A prospective study of peritoneal transport in CAPD patients. *Kidney Int* 45: 1739–1744, 1994
 33. Nolph KD, Moore HL, Prowant B, Twardowski ZJ, Khanna R, Gamboa S, Keshaviah P: Continuous ambulatory peritoneal dialysis with a high flux membrane. *ASAIO J* 39: 904–909, 1993
 34. Harty JC, Boulton H, Venning MC, Gokal R: Is peritoneal permeability an adverse risk factor for malnutrition in CAPD patients? *Miner Electrolyte Metab* 22: 97–101, 1996
 35. Breborowicz a, Oreopoulos DG: Evidence for the presence of chronic inflammation during peritoneal dialysis: Therapeutic implications. *Perit Dial Int* 17: S37–S41, 1997
 36. Herzig KA, Purdie DM, Brown AM, Chang W, Hawley CM, Isbel NM, Campbell SB, Nicol DL, Johnson DW: Is C-reactive protein a useful prognostic marker in peritoneal dialysis patients? *J Am Soc Nephrol* 12: 814–821, 2001