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CLINICAL OUTCOME IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS PATIENTS IS NOT INFLUENCED BY HIGH PERITONEAL TRANSPORT STATUS

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♦♦ ***Objectives:*** **We undertook this study to examine the influence of demographics, peritoneal membrane transport characteristics, nutrition indices, dialysis adequacy, and comorbid diseases on patient survival on continuous ambulatory peritoneal dialysis (CAPD), and to identify whether high peritoneal membrane transport is an independent risk factor for mortality on CAPD.**

♦♦ ***Design:*** **Our retrospective study was carried out in CAPD patients in a large tertiary care teaching hospital.**

♦♦ ***Methods:*** **Until December 2000, we followed 212 patients who started CAPD between 1994 and 1997 and who underwent a peritoneal equilibration test (PET) within 3 months of CAPD initiation.**

♦♦ ***Results:*** **By univariate analysis, comorbid diseases, old age, high peritoneal transport, and serum albumin predicted patient mortality. Independent predictors of mortality as determined by the Cox proportional hazard model included diabetes mellitus, cardiovascular disease, serum albumin, and old age. High peritoneal transport failed to independently influence mortality in our CAPD patients.**

KEY WORDS: Comorbid disease; peritoneal transport; patient survival.

Age and comorbidity are the principal determinants of survival in continuous ambulatory peritoneal dialysis (CAPD) patients (1–5). Several studies incorporating multivariate analysis have indicated that major comorbidity categories such as cardiovascular disease (CVD) and diabetes mellitus (DM) have a strong influence on mortality (3). Hypoalbuminemia, malnutrition, and dialysis adequacy parameters are also well-known risk factors for mortality in CAPD patients (6). Recently, the role of peritoneal membrane function—especially small-solute transport—has been extensively studied in regard to patient outcome. Data from both the CANUSA study (7) and the Stoke PD study (8) reported that patients with high solute transport have a greater probability of death as compared with patients of other transport types. The predictive value of peritoneal solute transport in CAPD patients is believed to depend on the type of comorbidity present (9). Diabetes especially was reported to be the most important risk factor for mortality (10).

The purpose of the present study was to examine the influence of peritoneal function on patient survival—alone, and in association with demographic factors, comorbid diseases, and nutrition parameters—and to identify whether high peritoneal transport is an independent risk factor for mortality in this sample of CAPD patients.

PATIENTS AND METHODS

A total of 212 patients (115 men and 97 women) who started CAPD at Yonsei Medical Center, Seoul, Korea, from January 1994 to December 1997 were included in the study. Patients were evaluated by PET within 3 months of commencing CAPD. All subjects were given a standard PET as described by Twardowski *et al* (11). Using reference values for the dialysate-to-plasma ratio of creatinine (D/P_{Cr}), patients were classified into one of the four peritoneal transport types: high, high average, low average, and low. The day before the PET, 24-hour urine (when diuresis was present) and drained dialysate were collected to calculate the weekly standardized creatinine clearance (SC_{Cr}) and Kt/V. The protein catabolic rate (PCR) was calculated using the formula of Bergström *et al* (12).

At the end of the study (December 2000), the patient's status was recorded as living, dead, or lost to follow-up. Data for patients who had transferred to hemodialysis or who had undergone renal transplantation were censored.

Comparisons between the various peritoneal transport types were performed by analysis of variance (ANOVA), and comparisons between proportions were done using the chi-square test. Survival analysis was

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done by the Kaplan–Meier method, and survival comparisons by factors and strata were done using the log-rank test. Mortality risk was analyzed using the Cox proportional hazard model, in which we included all of the significant variables from the univariate analysis.

RESULTS

CLINICAL CHARACTERISTICS

Among the 212 patients studied, the causes of end-stage renal disease were chronic glomerulonephritis (*n* = 54, 25.5%), hypertension (*n* = 49, 23.1%), DM type 2 (*n* = 39, 18.4%), unknown (*n* = 53, 25.0%), and other causes (*n* = 17, 8.0%). Table 1 shows the demographic and baseline clinical data according to peritoneal transport type. When patients were grouped by peritoneal membrane transport characteristics, 9.9% were high transporters, 52.8% were high-average transporters, 29.7% were low-average transporters, and 7.5% were low transporters. No statistical differences were seen among the four transport groups with regard to age at the start of PD, body weight, body surface area, serum creatinine, weekly Kt/V and SC_{Cr}, residual renal function (RRF), or nPCR. High transporters had significantly more comorbid diseases, such as diabetes and prior CVD. High transporters were also significantly older as compared with non high transporters. Drained dialysate volume and initial serum albumin was lowest in high transporters, and serum albumin level decreased as D/P_{Cr} increased.

A further analysis was performed, comparing patient survival between patients with and without diabetes (Table 2). Diabetic patients were significantly older; that group also had a higher proportion of patients with high transport characteristics and CVD. Diabetic patients also had lower serum creatinine and albumin levels as compared with non diabetic patients. The survival duration for diabetic patients was significantly shorter than that for non diabetic patients. No differences were seen in weekly Kt/V and SC_{Cr}, or RRF between diabetic and non diabetic patients.

CLINICAL OUTCOME AND SURVIVAL

At December 2000, 109 patients were living on CAPD, 46 had died, 29 had switched to hemodialysis, and 28 had undergone kidney transplantation. The 46 patients who had died represented 38.1% (8/21) of the high transport group, 19.6% (22/112) of the high-average transport group, 22.2% (14/63) of the low-average transport group, and 12.5% (2/16) of the low transport group. When a comparison was made between living and deceased patients, the patients who had died were significantly older, were more likely to be men, and had more associated comorbid diseases (Table 3). Among the 46 patients who had died, 15 had no comorbid disease, 16 had diabetes, and 7 had CVD, and 8 had both diabetes and CVD. Patients who died had significantly lower initial serum albumin and creatinine levels, but no significant differences in weekly Kt/V and SC_{Cr}, nPCR, and RRF.

Figures 1 – 5 show the observed survival stratified by peritoneal membrane transport, age, diabetes status, CVD, and serum albumin computed by the Kaplan–Meier method. Specifically, patients with high transport, older age, DM, CVD, and low initial serum

TABLE 1
Baseline Characteristics of the Patients According to Peritoneal Transport Type

Variable	H (*n*=21)	HA (*n*=112)	LA (*n*=63)	L (*n*=16)	*p* Value
Age	55.8±9.8	49.6±12.3	43.8±14.0	50.6±12.7	NS
Men [*n* (%)]	12 (57)	69 (62)	29 (46)	5 (31)	0.06
Body weight (kg)	59.3±9.0	59.2±11.0	55.5±8.4	53.8±7.1	NS
BSA (m^2)	1.63±0.16	1.63±0.18	1.57±0.15	1.54±0.12	NS
DM [*n* (%)]	9 (42.9)	22 (19.6)	7 (11.1)	1 (6.3)	<0.05
CVD [*n* (%)]	6 (28.6)	10 (8.9)	6 (9.5)	1 (6.3)	<0.05
Serum albumin (g/dL)	3.2±0.6	3.6±0.5	3.7±0.5	3.9±0.4	<0.01
Drained volume (mL)	2266±215	2397±196	2434±305	2495±307	NS
Weekly Kt/V	2.16±0.50	2.14±0.47	2.25±0.56	2.12±0.37	NS
Weekly SC_{Cr} (L/week/1.73 m^2)	81.5±25.1	79.5±29.8	76.7±28.3	74.3±25.1	NS
nPCR (g/day)	0.97±0.19	0.95±0.11	0.99±0.19	1.11±0.29	NS
RRF (mL/min)	1.3±1.4	1.8±2.1	1.7±1.9	2.8±3.8	NS

H = high transport; HA = high-average transport; LA = low-average transport; L = low transport; BSA = body surface area; DM = diabetes mellitus; CVD = cardiovascular disease; Kt/V = dialysis dose, SC_{Cr} = standardized creatinine clearance; nPCR = normalized protein catabolic rate; RRF = residual renal function.

TABLE 2
Comparisons Between Patients With and Without Diabetes Mellitus (DM)

Variable	With DM (*n*=39)	Without DM (*n*=173)	*p* Value
Age (years)	57.1±9.2	46.6±13.0	<0.05
Men [*n* (%)]	26 (66.7)	89 (51.4)	NS
D/P_{Cr}	0.71±0.10	0.66±0.11	<0.05
High transport type [*n* (%)]	9 (23.1)	12 (6.9)	<0.05
CVD [*n* (%)]	14 (35.9)	9 (5.2)	<0.05
Survival duration (months)	38.0±21.4	51.1±16.3	<0.05
Biochemical data			
Blood urea nitrogen (mg/dL)	51.5±17.3	52.6±15.0	NS
Serum albumin (g/dL)	3.2±0.6	3.7±0.5	<0.05
Weekly Kt/V	2.2±0.6	2.2±0.5	NS
Weekly SCCr (L/week/1.73 m^2)	85.4±34.6	78.0±34.1	NS
nPCR (g/kg/day)	0.96±0.16	0.98±0.20	NS
RRF (mL/min)	1.8±2.1	1.8±2.2	NS

DM = diabetes mellitus; D/P_{Cr} = dialysate-to-plasma creatinine ratio; CVD = cardiovascular disease; Kt/V = dialysis dose; SCCr = standardized creatinine clearance; nPCR = normalized protein catabolic rate; RRF = residual renal function.

TABLE 3
Comparisons Between Survivors and Non Survivors

Variable	Survivors (*n*=166)	Non Survivors (*n*=46)	*p* Value
Age (years)	46.2±12.4	56.7±12.0	<0.01
Men [*n* (%)]	81 (48.8)	33 (71.7)	<0.05
DM [*n* (%)]	15 (9.0)	24 (52.2)	<0.01
CVD [*n* (%)]	8 (4.8)	15 (32.6)	<0.01
Biochemical data			
Blood urea nitrogen (mg/dL)	52.6±14.6	52.0±18.6	NS
Serum albumin (g/dL)	3.4±0.5	3.7±0.5	<0.01
Weekly Kt/V	2.18±0.54	2.19±0.48	NS
Weekly SCCr (L/week/1.73 m^2)	79.5±35.3	78.9±30.4	NS
nPCR (g/kg/day)	0.98±0.20	0.95±0.21	NS
RRF (mL/min)	1.9±2.3	1.4±1.8	NS

DM = diabetes mellitus; CVD = cardiovascular disease; SCCr = standardized creatinine clearance; nPCR = normalized protein catabolic rate; RRF = residual renal function.

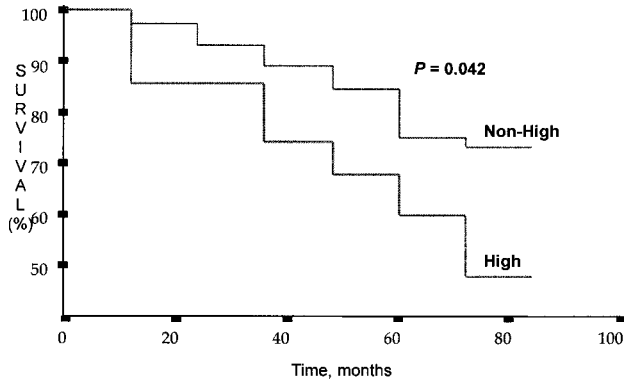

Figure 1 — Survival curves according to peritoneal transport type, by univariate analysis.

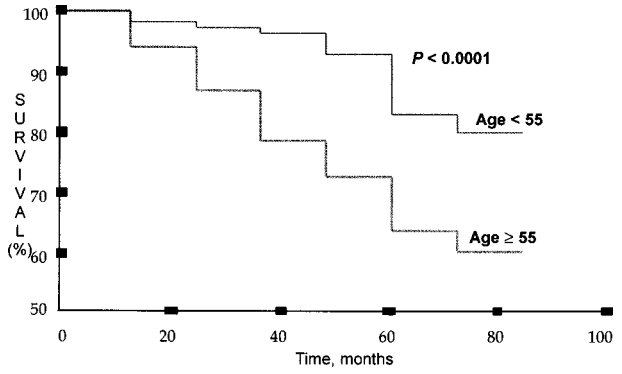

Figure 2 — Survival curves according to age, by univariate analysis.

albumin had a significantly shorter survival (Table 4). Other variables such as weekly Kt/V and SC_{Cr} were not significantly associated with survival in the univariate analysis.

Peritoneal transport rate, DM, CVD, serum albumin, and age significantly predicted patient survival in the univariate analysis. These variables were therefore included in the multivariate analysis. When subjected to a stepwise multivariate analysis using the Cox model, high transport status failed to predict patient survival when the other covariates were included (Table 5).

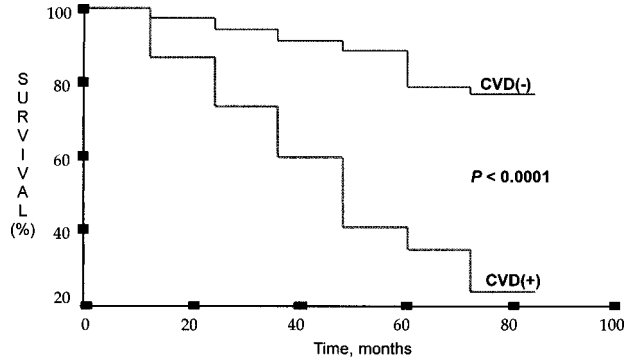

Figure 3 — Survival curves according to cardiovascular disease, by univariate analysis.

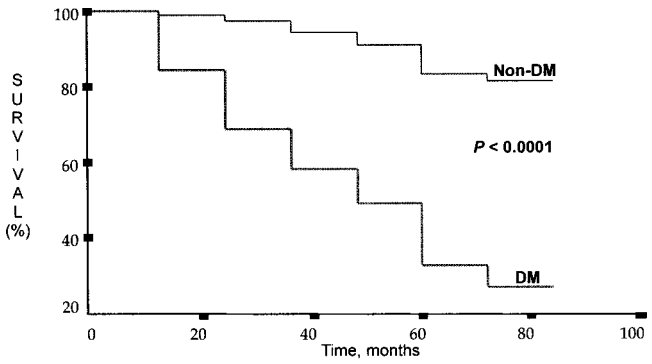

Figure 4 — Survival curves according to diabetes status, by univariate analysis.

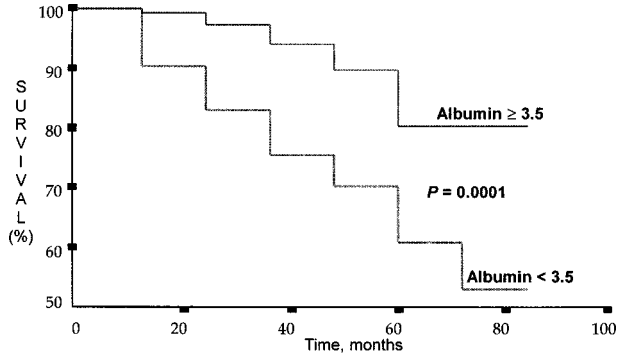

Figure 5 — Survival curves according to serum albumin, by univariate analysis.

DISCUSSION

Many previous studies have demonstrated the profound influence of comorbid disease on mortality in CAPD patients (1–5). The present study provides further evidence that age and comorbid diseases such as DM and CVD are the important factors that predict survival in CAPD patients.

TABLE 4
Prognostic Factors for Patient Survival
(Univariate Analysis)

Variables	Patients *(n)*	Surviving at 5 years (%)
Peritoneal transport type[a]		
High	21	47.9
Non high	191	73.3
Age (years)[a]		
<55	109	82.2
>55	103	49.4
Diabetes mellitus[a]		
Without	173	81.4
With	39	26.7
Cardiovascular disease[a]		
Without	189	76.9
With	23	22.9
Serum albumin (g/dL)[a]		
<3.5	73	53.0
>3.5	139	80.2
Weekly Kt/V		
<2.1	93	62.5
>2.1	112	80.6
Weekly SCCr (L/week/1.73 m^2)		
<70	108	77.2
>70	114	71.1

[a] $p < 0.05$ by *t*-test.
SCCr = standardized creatinine clearance.

TABLE 5
Independent Factors Prognostic of Mortality
(Multivariate Cox Proportional Hazard Model)

Factor	Relative mortality risk	*p* Value
Diabetes mellitus	3.918	<0.001
Cardiovascular disease	2.356	0.028
Serum albumin (<3.5 g/dL vs >3.5 g/dL)	2.222	0.015
Age	1.041	0.008
High peritoneal transport	0.555	0.210

High-average transport (52.8%) was the predominant peritoneal transport type in our study. The proportions of patients with high transport (9.9%) and low transport (7.5%) were lower than the proportions reported for these transport types in previous studies in our population (13,14). The cause of this variation is not clear, but it may be related to the lesser number of diabetic patients included in this study. It is also possible that renal-failure patients who are hypoalbuminemic and therefore more likely to be high transporters are excluded from the dialysis program because of selection criteria for long-term renal replacement therapy.

Peritoneal membrane function is widely believed to have the potential to influence clinical outcome (7,13). It is well established that the CAPD patients with high peritoneal transport do not attain appropriate ultrafiltration, and that they display the lowest serum albumin levels (15–17). Both the CANUSA study (7) and the Stoke PD study (8) have reported the relationship between solute transport and patient and technique survival in detail. The combined information from those studies and from that of Wu *et al* (18) appears to indicate that high peritoneal transport predicts both patient survival and technique failure. However, Wang *et al* (16) found that a high mortality rate with increased peritoneal permeability was related to impaired fluid and small-solute removal in high transporters. Blake suggested that the most likely mechanism underlying the high mortality in high transporters is the effect on cardiovascular status, which is further impaired by fluid overload (19).

By univariate analysis, the high peritoneal transport characteristic was an impressive mortality risk factor in our study. The 5-year cumulative patient survival of high transporters was significantly lower as compared with non high transporters (47.9% vs 73.3%, p = 004). But when other covariates such as DM, CVD, and older age were considered, the high peritoneal transport characteristic lost statistical power. This finding seems to be influenced by the high peritoneal membrane permeability of diabetic patients and the high prevalence of DM in high transporters in the present study. The ultrastructural alterations such as thickening and reduplication of capillary and mesothelial basal membranes observed in diabetic angiopathy have been suggested to increase peritoneal membrane permeability in diabetic patients (20). Also, the increased mortality observed in high transporters in our study could have been influenced by the high prevalence of CVD in that group. Heimbürger *et al* (21) reported that initial D/P_{Cr} was significantly higher in patients with CVD.

The multivariate analysis of our data showed that DM, CVD, older age, and low serum albumin were important mortality risk factors. The most significant risk factor among these was DM, a result that agrees with previous studies reporting the prominent role of this entity as a risk factor for mortality in CAPD patients (1–4,10). In the present study, diabetic patients were significantly older and a higher proportion of them had CVD, which is another well-known cause of mortality in CAPD patients. Cardiovascular disease predicted mortality even after other covariates such as DM and older age were considered. The combined effect of older age and a higher proportion of CVD probably accounted for the high mortality in diabetic patients.

In contrast to previous studies by others (6,22,23), dialysis adequacy parameters such as weekly Kt/V and SC_{Cr} failed to predict patient survival in our study. Davies *et al* (9) reported the predictive value of Kt/V in association with comorbid diseases such as ischemic heart disease and left ventricular dysfunction. The lack of predictive power of the dialysis adequacy variables in our study may be due to the absence of significant differences in weekly Kt/V or SC_{Cr} between peritoneal transport types at the time of the PET. Another factor that could have reduced the significance of Kt/V is the high initial weekly Kt/V reported in our patients. The weekly Kt/V values in the four types of transporters in our study were all above 2.0; in the study by Davies *et al* (9) these values were in the range 1.61 – 2.04.

Serum albumin, although a time-dependent marker, is generally accepted as an independent predictor of survival in CAPD patients (6,24). The present study showed that the non survivors and the diabetic patients had the lowest serum albumin levels. Cueto–Manzano and Correa–Rotter analyzed the interaction of serum albumin with DM and failed to find any predictive power for serum albumin in patient survival (10). In the present study, serum albumin also displayed collinearity with DM, but a serum albumin level below 3.5 g/dL significantly predicted patient mortality even though comorbid diseases and age factors were included in the multivariate analysis. This finding supports the observations of others that serum albumin level correlates with clinical outcome and is a significant predictor of mortality in CAPD patients (6,22–24).

CONCLUSION

Our data suggest that DM is the most important predictive factor for mortality in the present study population. Even though high peritoneal transport type predicted mortality in CAPD patients, its role seemed to be influenced by other comorbid conditions. Cardiovascular disease, hypoalbuminemia, and older age were other important predictors of patient survival.

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