RISK FACTORS FOR MORTALITY IN CHINESE PATIENTS ON CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

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♦ **Objective:** The intent of this study was to evaluate the clinical outcome and risk factors affecting mortality of the continuous ambulatory peritoneal dialysis (CAPD) patients in a single peritoneal dialysis (PD) center over a period of 10 years.

♦ **Patients and methods:** We retrospectively analyzed patients on PD from June 2001 to June 2011. The clinical and biochemical data were collected from the medical records. Clinical variables included gender, age at the start of PD, smoking status, body mass index (BMI), cause of end-stage renal disease (ESRD), presence of diabetes mellitus and blood pressure. Biochemical variables included hemoglobin, urine volume, residual renal function (RRF), serum albumin, blood urea nitrogen (BUN), creatinine, total cholesterol, triglyceride, comorbidities, and outcomes. Survival curves were made by the Kaplan-Meier method. Univariate and multivariate analyses to identify mortality risk factors were performed using the Cox proportional hazard regression model.

♦ **Results:** A total of 421 patients were enrolled, 269 of whom were male (63.9%). The mean age at the start of PD was 57.9 ± 14.8 years. Chronic glomerulonephritis was the most common cause of ESRD (39.4%). Estimation of patient survival by Kaplan-Meier was 92.5%, 80.2%, 74.4%, and 55.7% at 1, 3, 5, and 10 years, respectively. Patient survival was associated with age (hazard ratio [HR]: 1.641 [1.027 – 2.622], $p = 0.038$), cardiovascular disease (HR: 1.731 [1.08 – 2.774], $p = 0.023$), hypertriglyceridemia (HR: 1.782 [1.11 – 2.858], $p = 0.017$) in the Cox proportional hazards model analysis. Estimation of technique survival by Kaplan-Meier was 86.7%, 68.8%, 55.7%, and 37.4% at 1, 3, 5, and 10 years, respectively.

In the Cox proportional hazards model analysis, age (HR: 1.672 [1.176 – 2.377], $p = 0.004$) and hypertriglyceridemia (HR: 1.511 [1.050 – 2.174], $p = 0.026$) predicted technique failure.

♦ **Conclusion:** The PD patients in our center exhibited comparable or even superior patient survival and technical survival rates, compared with reports from other centers in China and other countries.

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KEY WORDS: Clinical outcome; patient survival; technique survival; mortality; peritoneal dialysis; risk factors; Cox proportional hazards model; dialysis patients.

Peritoneal dialysis (PD) is an established treatment modality in end-stage renal disease (ESRD) patients. Peritoneal dialysis was first described as a renal replacement therapy in the late 1970s (1) and its use has increased considerably worldwide in the past decades (2,3). The home-based nature of this modality gives it an advantage over in-center hemodialysis in many parts of the world. Furthermore, PD treatment more effectively promotes hemodynamic stability, volume regulation and the preservation of residual renal function (RRF) compared with hemodialysis (HD) (4). Through technological advances in catheters and transfer delivery systems, the outcomes of PD patients have steadily improved (5). In spite of the extensive use of continuous ambulatory peritoneal dialysis (CAPD) worldwide (6), there is some information regarding patient survival and risk factors associated with mortality (5,8), but few single-center reports have involved a sufficient number of patients and extended follow-up periods.

Here, we briefly discuss our long-term clinical experience, particularly with respect to survival rates

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and mortality risk factors in a large single-center CAPD program.

PATIENTS AND METHODS

A total of 592 patients with ESRD who underwent surgical PD catheter placement at the Second Xiangya Hospital of Central South University between June 2001 and June 2011 were enrolled and assessed for eligibility. One hundred and seventy-one patients were excluded due to the following reasons: age below 14 years at the start of PD, survived less than 3 months following the initiation of PD, recovered renal function and no longer required dialysis, missing data, a history of HD or kidney transplant before the start of CAPD, or attended other PD unit for follow-up. Finally, 421 patients remained in the final data set. Of the 421 CAPD patients in the study, 269 (63.9%) were males. The mean age of the patient population at the start of CAPD was 57.9 ± 14.8 years. The study terminated in December 2012. Each subject signed an agreement of participation in this study that was approved by the ethics committee of the hospital.

PRESCRIPTION

Peritoneal dialysis catheter insertions were undertaken by trained nephrologists. All patients were treated with CAPD using conventional lactate-buffered glucose-based PD solutions (Baxter Healthcare, Guangzhou, China) via a straight Tenckhoff catheter and Baxter's double-bag system. Continuous ambulatory PD was prescribed in 2-L exchanges either 3 or 4 times daily, depending on the patient's body size and level of RRF. The dialysate glucose concentration varied depending on the individual patient's requirements for ultrafiltration.

DATA COLLECTION

Clinical and biochemical data before the initiation of PD were collected from the medical records. The data included gender, age at the start of PD, smoking status, body mass index (BMI), cause of ESRD, presence of diabetes mellitus, duration of dialysis, blood pressure, hemoglobin level, urine volume, RRF, serum albumin, blood urea nitrogen (BUN), creatinine, total cholesterol, triglyceride, comorbid disease, and outcomes. Blood pressure was measured at a resting state. For laboratory analyses, fasting blood samples were taken from CAPD patients before PD. Body mass index was calculated as the weight (kg) divided by the square of height in metres ($\text{BMI} = \text{kg}/\text{m}^2$). The residual glomerular filtration rate (GFR) was calculated from the mean of creatinine

and urea clearance, and adjusted for body surface area ($\text{mL}/\text{min}/1.73 \text{ m}^2$) (Tables 1 and 2).

The GFR was estimated using the modified MDRD (Modification of Diet in Renal Disease) equation, which has been proven to be applicable in predicting the mean GFR of

TABLE 1
Baseline Demographic and Clinical Characteristics of CAPD patients

Factor	N
N	421
Peritoneal dialysis duration (months)	33.3 ± 24.2
Diabetes (%)	28.7%
Cardiovascular disease (%)	30%
Lifelong non-smokers (%)	87%
Age (years)	57.9 ± 14.8
≤ 65	265 (62.9%)
> 65	156 (37.1%)
Gender	
Male	269 (63.9%)
Female	152 (36.1%)
Renal disease	
Chronic glomerulonephritis	166 (39.4%)
Diabetes mellitus	113 (26.8%)
Hypertension	80 (19.0%)
Polycystic kidney disease	14 (3.3%)
Obstructive uropathy	17 (4.0%)
Systemic lupus erythematosus	4 (1.0%)
Other	27 (6.4%)
MAP (mmHg)	109.2 ± 17.2
BMI (kg/m^2)	22.4 ± 4.0

CAPD = continuous ambulatory peritoneal dialysis; MAP = mean arterial pressure; BMI = body mass index.

TABLE 2
Baseline Biochemical Parameters of CAPD Patients

Parameters	Median $\pm$ quartile range	Minimum	Maximum
BUN (mmol/L)	22.2 ± 13.7	5.5	22.3
Creatinine ($\mu\text{mol}/\text{L}$)	819.3 ± 329.3	317	2400
Triglyceride (mmol/L)	1.2 ± 1.0	0.29	9.0
RRF ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	6.2 ± 3.12	1.18	25.3
Hemoglobin (g/L)	79.4 ± 16.8	41	149
Serum albumin (g/L)	32.8 ± 5.8	13.8	51.6
Total cholesterol (mmol/L)	4.40 ± 1.39	1.60	13.37

CAPD = continuous ambulatory peritoneal dialysis; UV = urinary volume; BUN = blood urea nitrogen; RRF = residual renal function.

Chinese patients with chronic kidney disease (CKD) (9): $\text{GFR (mL/min/1.73 m}^2\text{)} = 175 \times \text{creatinine (mg/dL)} - 1.234 \times \text{age} - 0.179 \times 0.79$ (if female).

We recorded their comorbidities, including diabetes mellitus, cardiovascular disease, and peritonitis. Cardiovascular disease included coronary artery disease, congestive heart failure, and myocardial infarction. Diabetes mellitus was defined by physician diagnosis, the use of diabetes medication, fasting glucose > 7 mmol/L, or non-fasting glucose > 11.1 mmol/L. Peritonitis was diagnosed if at least 2 of the following criteria were fulfilled (10): abdominal pain, cloudy dialysate with a leukocyte count $\geq 100/\text{L}$ and at least 50% polymorphonuclear cells, or a positive dialysate culture. Refractory peritonitis was defined as peritonitis that did not respond to antibiotic therapy and resulted in PD catheter removal. The peritonitis rate was calculated by dividing the months of PD by the number of episodes of peritonitis.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Quantitative data are reported as the mean $\pm$ standard deviation (SD) or as median and quartiles, as appropriate, and qualitative variables are reported as proportions. Death was used as the end point for the analysis of patient survival; patients who were alive at the end of the study, transferred to hemodialysis, underwent renal transplantation or were lost to follow-up were considered censored data. When analyzing technique survival, transferring to hemodialysis and drop-out due to death were considered final events; functional dialysis at the end of the study, renal transplantation and loss to follow-up were considered censored data. Both patient and technique survival were analyzed using the Kaplan-Meier method. The risk factors for mortality and technique failure risks were analyzed with a multivariate Cox's proportional-hazard model in which we included all the significant variables from the univariate analysis, and those variables considered clinically relevant according to the current literature. Differences were considered statistically significant for p values less than 0.05.

RESULTS

Of the 421 CAPD patients in the study, 269 (63.9%) were males. The mean duration of PD was 33.3 ± 24.2 months. The mean age at the start of PD was 57.9 ± 14.8 years. Chronic glomerulonephritis was the most common cause of ESRD (39.4%), followed by diabetes mellitus (26.8%), hypertension (19.0%), polycystic

kidney disease (3.3%), obstructive nephropathy (4.0%), systemic lupus erythematosus (1.0%), and other causes (6.4%). The maximum and minimum value for RRF were $25.3 \text{ mL/min/1.73 m}^2$, and $1.18 \text{ mL/min/1.73 m}^2$, respectively. The mean RRF at the start of PD was $6.2 \text{ mL/min/1.73 m}^2$. Two hundred and fifty-two patients were in high RRF ($\geq 5 \text{ mL/min/1.73 m}^2$) whereas 169 patients were in low RRF ($< 5 \text{ mL/min/1.73 m}^2$).

PATIENT OUTCOMES

By the end of follow-up, 72 (17.1%) patients died, and 349 (82.9%) patients were alive. Of the living patients, 21 (5.0%) patients underwent kidney transplantation, 50 (11.9%) patients switched to hemodialysis, 17 (4.0%) patients were lost to follow-up, 261 (62.0%) patients continued undergoing PD. The annual mortality of PD patients at 1, 2, and 3 years was 7.1%, 5.2%, and 3.3%, respectively. Patient survival at 1, 3, 5, and 10 years was 92.5%, 80.2%, 74.4%, and 55.7%, respectively. Technique survival at 1, 3, 5, and 10 years was 86.7%, 68.8%, 55.7%, and 37.4%, respectively (Figure 1). Patient and technique survival of PD patients in our center was similar or even superior to that reported in other large series (5,7). Among the 72 patients who died, the causes of death were as follows: 29 (40.3%) cardiovascular disease, 25 (34.7%) peritonitis, 2 (2.8%) malignancy, and 16 (22.2%) unknown causes or other causes. The reasons for transfer to HD included 30 (60.0%) peritonitis, 5 (10.0%) hernia, 5 (10.0%) inadequate dialysis, 7 (14.0%) mechanical malfunction, 1 (2.0%) pleura-abdominal fistula and 2 (4.0%) transfers secondary to patient's choice. During the study period, a total of 223 episodes of peritonitis were recorded. The incidence of peritonitis was 1/62.9 patient-month. In the patients with PD-related peritonitis, PD fluid culture was negative in 47.5%, followed by gram-positive bacteria in 21.1%, gram-negative bacteria in 18.4% and fungi in 13.0%. In our center, most of the patients with peritonitis were initiated on a combination of intra-peritoneal gentamicin or vancomycin and intravenous cephalosporins pending culture results, and the regimen was changed based on the culture results. The overall outcome was 75.3% antibiotic cure rate, 13.5% Tenckhoff catheter removal because of fungal and refractory peritonitis, and 11.2% mortality from peritonitis-related complications.

RISK ANALYSES FOR PATIENT AND TECHNIQUE SURVIVAL

In univariate analysis, we reconfirmed that advanced age, cardiovascular comorbidity and hypertriglyceridemia, all of which are well-known risk factors, were

Figure 1 — (A) Patient survival and (B) technique survival analysis of PD patients. PD = peritoneal dialysis.

predictors of mortality and technique failure in PD patients (Table 3).

The multivariate Cox proportional hazards regression model was subsequently applied to identify those factors significantly affecting mortality and technique failure. We included all the significant variables from the univariate analysis, as well as those variables considered to be clinically relevant according to the current literature. Our results revealed that advanced age (HR: 1.641 [1.027 – 2.622], $p = 0.038$), comorbid cardiovascular disease (HR: 1.731 [1.08 – 2.774], $p = 0.023$), and hypertriglyceridemia (HR: 1.782 [1.11 – 2.858], $p = 0.017$) were all significantly associated with an increased risk of death, whereas advanced age (HR: 1.672 [1.176 – 2.377], $p = 0.004$) and hypertriglyceridemia (HR: 1.511 [1.050 – 2.174], $p = 0.026$) were associated with a higher CAPD technique failure (Table 3).

DISCUSSION

This study was a retrospective single-center study with a large enough number of stable patients to perform adequate statistical analyses.

The PD patients in our center exhibited comparable or superior patient survival and technique survival rates, when compared with reports from other centers in China or other countries (5,7,10–12). The reasons underlying the difference may be multifactorial. In general, the survival rates of PD patients were higher in Asian countries than in Western countries. Suzuki *et al.* (11) from Japan reported a 5-year PD patient survival of 67.5%, and in a Korean study, the 5-year survival rate was 69.8% (5). In our study, it is 74.4% and Yang *et al.* (13) reported that

the 5-year survival rate of patients without diabetes was 73%. In contrast, the survival rates reported from Mexico and Turkey were relatively lower (7,10,12). This difference may be partly explained by the various inherent patient factors including genetic factors, dietary habits, life-style differences and cultural background. Furthermore, the percentage of patients with diabetes may have affected the survival rates since diabetes was one of the most important risk factor affecting survival in PD patients in other reports (13,14). The presence of diabetes in the aforementioned studies from Mexico and Turkey was 37% and 35.2%, respectively (7,12) while the rate was only 28.7% in our center. Additionally, well-trained professional PD nephrologists and nurses, as well as the continuous improvement of knowledge and techniques, are important factors to ensure the quality of life of PD patients.

In the Cox proportional hazard model, advanced age at initiation of PD, comorbid cardiovascular disease and hypertriglyceridemia were found to be poor predictors of patient survival in our study. Additionally, age at PD initiation, and hypertriglyceridemia were the strongest predictive factors for technique survival. Advanced age represents an important predictor of poor outcomes in diabetic patients on CAPD (13). Chang *et al.* (15) reported a higher risk in elderly patients on PD. However, Taveras *et al.* (16) suggest that among 235 patients 75 years of age and older who started PD, technique failure rates at 12 months were not significantly different with patients less than 75 years of age and mortality rates were significantly higher in elderly patients. Therefore, whether PD is the best treatment option for elderly patients with ESRD remains controversial.

TABLE 3
Patient Survival and Technique Survival by Univariate and Multivariate Cox Proportional Hazards Analysis

Variable	Univariate HR (95% CI)	<i>p</i>	Multivariate HR (95% CI)	<i>p</i>
Patient Survival				
Age (years)	2.04 (1.317–3.161)	0.001 ^a	1.641 (1.027–2.622)	0.038 ^a
Comorbidity				
Peritonitis	0.762 (0.434–1.336)	0.343	0.803 (0.449–1.433)	0.457
CVD	1.996 (1.289–3.09)	0.002 ^a	1.731 (1.08–2.774)	0.023 ^a
Hemoglobin (g/L)	0.915 (0.552–1.518)	0.732	0.823 (0.478–1.417)	0.482
RRF (mL/min/1.73m ²)	1.17 (0.745–1.837)	0.495	0.977 (0.601–1.587)	0.924
Albumin (g/L)	0.732 (0.454–1.181)	0.202	0.724 (0.439–1.193)	0.205
Total cholesterol (mmol/L)	1.333 (0.721–2.464)	0.359	1.034 (0.538–1.987)	0.919
Triglyceride (mmol/L)	1.935 (1.244–3.008)	0.003 ^a	1.782 (1.11–2.858)	0.017 ^a
Technique Survival				
Age (years)	1.815 (1.307–2.521)	0.000 ^a	1.672 (1.176–2.377)	0.004 ^a
Comorbidity				
Peritonitis	1.123 (0.769–1.64)	0.548	1.101 (0.745–1.629)	0.628
CVD	1.271 (0.902–1.791)	0.17	1.098 (0.758–1.591)	0.622
Hemoglobin (g/L)	0.756 (0.505–1.132)	0.175	0.694 (0.454–1.061)	0.092
RRF (mL/min/1.73m ²)	1.108 (0.791–1.552)	0.551	1.001 (0.698–1.431)	0.999
Albumin (g/L)	0.996 (0.708–1.402)	0.982	1.075 (0.751–1.537)	0.693
Total cholesterol (mmol/L)	1.242 (0.773–1.994)	0.370	1.122 (0.679–1.853)	0.653
Triglyceride (mmol/L)	1.541 (1.098–2.164)	0.012 ^a	1.511 (1.050–2.174)	0.026 ^a

HR = hazard ratio; CI = confidence interval; CVD = cardiovascular disease; RRF = residual renal function.

^a *p* < 0.05.

Cardiovascular disease (CVD) is prevalent in patients with chronic renal failure and is the most important cause of hospitalization and death in PD patients. Recent studies suggest that CVD, perhaps even more so than peritonitis, is one of the most common causes of death and technique failure outcomes of PD patients. In addition to the high prevalence of traditional CVD risk factors in PD patients, chronic renal disease alone is currently considered a coronary heart disease risk that could account in part for the high prevalence of CVD in these patients. Additionally, chronic inflammation and malnutrition are risk factors specifically related to ESRD patients on chronic PD and play a pivotal role in the development of CVD (17). Our study revealed that the patient survival rate of patients with comorbid CVD was lower than patients without comorbid CVD. We also found that CVD was the most frequent cause of death. Therefore, the management of CVD is one of the primary goals in treating patients with ESRD on PD (18).

Hyperlipidemia is frequently encountered in uremic patients and can be exacerbated by dialysis, especially CAPD (19). Cheng *et al.* (20) demonstrated that patients became hypertriglyceridemic after undergoing

CAPD treatments for more than 1 year. Indeed, with a prevalence of 70%, hypertriglyceridemia was the most frequent lipid abnormality (20). The causes of the abnormalities in PD patients may be multifactorial and several mechanisms have been postulated, including a high peritoneal glucose load that results in glucose absorption, peritoneal protein loss, weight gain, and insulin resistance. As dyslipidemia negatively impacts cardiovascular profiles by increasing atherogenesis, hypertriglyceridemia may contribute to the high cardiovascular mortality of PD patients.

Residual renal function is crucial in maintaining the adequacy of CAPD for most patients. Now many other benefits of intrinsic renal function to the health of dialysis patients have been highlighted, including improved nutrition, hemoglobin, and fluid balance, as well as a reduced reliance on dietary and fluid. In a prospective study of 68 CAPD and 34 HD patients, Maiorca *et al.* (21) demonstrated that the persistence of RRF significantly improved survival. Bargman *et al.* (22), in the reanalysis of CANUSA data, showed that for each 5 L/week/1.73 m² increment in the GFR, there was a 12% decrease in the relative risk of death. Thus,

additional studies are needed to develop strategies for preserving RRF in dialysis patients and improving patient quality of life.

Peritonitis is also a major complication of PD. However, comorbid peritonitis exhibited no predictive power in our study. It would be more likely related to a decrease in the rate of peritonitis. The patients in our center experienced a very low rate of peritonitis with a mean of 1/62.9 patient-months. All patients in our center employed the double-bag system which has been demonstrated to contribute greatly to the reduction in the peritonitis rate (23). Better teaching techniques at our center also partly contributed to this improvement. Despite the decrease in the rate of peritonitis, it continues to be the most devastating complication of PD treatment and the leading cause of technique failure in the PD population (24).

Albuminemia was not identified as a significant predictive factor for mortality in our study but the effect of hypoalbuminemia should not be neglected or underestimated. In patients undergoing maintenance dialysis, serum albumin is closely related to malnutrition, inflammation and CVD, and this cluster of symptoms has therefore been referred to as malnutrition-inflammation atherosclerosis (MIA) syndrome (25). In addition to strengthened nutrition support, further new treatment strategies are needed for PD patients suffering malnutrition associated with MIA syndrome.

At the same time, we do recognize that our study has several limitations. First, our study was not a multicenter study, and therefore might be insufficient to reflect survival rate and risk factors of PD patients in other centers. Second, only baseline characteristics, not the changing trend in variables, were analyzed and non-inclusion of some variables could influence mortality analysis. In spite of these limitations, we believe that the results of this study are worthy of further investigation with a prospective randomized study. Ours is one of the largest single-center studies of CAPD patients with 10 years' experience. The size and length of the present study are clear strengths.

CONCLUSION

The PD patients in our center exhibited comparable or even superior patient survival and technical survival rates, compared with reports from other centers in China and other countries. Our study demonstrated that age, RRF and CVD were the most significant predictors of PD patient mortality. Although our study was not a multicenter study, our results are encouraging in an era of improvements in the quality of life of PD patients.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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