Predictive Factors for Withdrawal from Peritoneal Dialysis: A Retrospective Cohort Study at Two Centers in Japan

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Peritoneal dialysis (PD) is recognized as an excellent method of dialysis because the therapy is gentle, continuous, and cost-effective. However, a large number of patients must unfortunately transfer from PD to hemodialysis because of peritonitis or fluid overload in the early phase after PD initiation. In the present study, we reviewed clinical indicators before PD initiation to try to identify predictive factors for early withdrawal from PD.

For this retrospective cohort study at two hospitals between March 2003 and October 2016, we defined withdrawal from PD as the induction of combination therapy, transfer to hemodialysis, or death. Data about clinical indicators before PD induction—namely age, sex, presence of diabetes mellitus, past history of cardiovascular disease (CVD), body mass index, primary kidney disease, and blood biochemistry—were collected from medical records. The primary outcome was duration of PD until withdrawal.

We analyzed 151 PD patients (median age: 62.5 years; 94 men; 74 with diabetes mellitus; median duration of PD: 30.2 months). Univariate Cox regression analysis showed that the hazard ratio (HR) for withdrawal was 1.08 [95% confidence interval (CI): 1.04 to 1.12; p < 0.001] per 1 mg/L increase in β_2-microglobulin (β_2MG), 0.65 (95% CI: 0.46 to 0.93; p = 0.02) per 1 g/dL decrease in serum albumin, and 1.07 (95% CI: 1.02 to 1.11; p = 0.01) per 1 g per gram creatinine increase in daily urinary protein excretion. Using multivariate Cox regression analysis, β_2MG (HR: 1.08; 95% CI: 1.04 to 1.12; p < 0.001) and past history of CVD (HR: 1.47; 95% CI: 1.02 to 2.13; p = 0.04) were factors predictive for withdrawal from PD. Kaplan–Meier analysis showed that the technique survival rate was significantly different in the two groups defined as having a serum β_2MG level above or below the measured median (p = 0.047).

Serum β_2MG at PD initiation and past history of CVD are high-risk factors for withdrawal from PD. Special focus should be placed on the care and management of patients found to have a high risk of withdrawal at the time of PD induction.

Key words
Withdrawal from PD, cardiovascular disease, β_2-microglobulin

Introduction

Approximately 38,000 incident patients with end-stage kidney disease (ESKD) started dialysis therapy in Japan in 2013 (1). In the entire dialysis patient population, peritoneal dialysis (PD) patients accounted for just 3.0% (2). The low penetration rate of PD is affected not only by the potential for infections such as peritonitis, but also by excessive concerns about the incidence of encapsulating peritoneal sclerosis. However, biocompatible dialysate has been developed in recent years and is being used as standard therapy in Japan. Nakayama *et al.* (3) reported that the incidence of encapsulating peritoneal sclerosis is now lower than it was in past reports.

The low penetration rate of PD in Japan also reflects short technique survival. Various studies about the PD technique survival rate in Japan have been published. Nakamoto *et al.* (4) reported that the 5-year technique survival rate is approximately 70%, and the technique failure rate is approximately 7%

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per year. However, the patients who were reported in the Nakamoto study were those introduced to PD in the 1990s, and patients of that era who continued PD for a long time were not uncommon. A multicenter collaborative research study that registered more than 1300 patients showed that the average duration of PD was 32 months (3). Mizuno *et al.* (5) reported that early withdrawal (defined as withdrawal within 3 years of starting PD) occurred in 40% – 50% of patients. The causes of withdrawal include infectious complications, noninfectious complications, social problems, death, inadequate dialysis, and ultrafiltration failure. However, those factors all become apparent after the introduction of PD. We therefore conducted the present study to look for factors predictive of PD withdrawal at the time of PD start.

Methods

This retrospective cohort study, which included 159 patients more than 18 years of age who selected PD as their first renal replacement therapy, was conducted at two hospitals (St. Marianna University School of Medicine Hospital and Kawasaki Municipal Tama Hospital) between March 2003 and October 2016. Patients who underwent planned renal transplantation within 2 years were excluded. Furthermore, patients for whom data about blood biochemistry were not available were also excluded. The study was approved by the medical ethics committee of Kawasaki Municipal Tama Hospital (no. 3560).

Withdrawal from PD was defined as the induction of combination therapy, transfer to hemodialysis, or death. Data about clinical indicators before PD induction—namely age, sex, presence of diabetes mellitus, past history of cardiovascular disease (CVD), body mass index, primary kidney disease, blood biochemistry (hemoglobin, hematocrit, serum protein, albumin, calcium, phosphorus, intact parathyroid hormone, creatinine), estimated glomerular filtration rate (eGFR), total cholesterol, triglycerides, ferritin, C-reactive protein, β_2-microglobulin (β_2MG), and daily urinary protein excretion—were collected from medical records. The presence of diabetes mellitus was accepted if the patient was using insulin or oral hypoglycemic agents. Cardiovascular disease was defined as the presence of coronary artery disease (history of angina pectoris or history of myocardial infarction), congestive heart failure, peripheral artery disease, or cerebrovascular disease. Measurements of serum β_2MG were performed by each hospital's laboratory using the latex immunoassay method (Eiken Chemical, Tokyo, Japan). The primary outcome was duration of PD until withdrawal.

Continuous variables are presented as medians with interquartile range [IQR (25th – 75th percentile)]. Categorical variables are presented as frequencies or percentages. Cox regression analysis was applied in the analyses to take into account the relative effects of various risk factors. Cox regression analysis was used to calculate hazard ratio (HRs) with 95% confidence intervals (CIs) for withdrawal. Technique survival curves were plotted using the Kaplan–Meier method, and between-group survival was compared using the log-rank test. A p value less than 0.05 was considered statistically significant. Statistical analyses were performed using the IBM SPSS Statistics application for Windows (version 21.0: IBM, Armonk, NY, U.S.A.).

Results

Of the 151 patients studied, 61.6% were men. Median age in the cohort was 62.5 years (IQR: 53.0 – 70.6 years). Approximately half the patients had diabetes mellitus (49.0%), and one third had CVD (37.1%, Table I). The main reason for withdrawal was inadequate dialysis (55%); death was the next major reason (Figure 1). Table II shows the causes of death.

Median duration of PD until withdrawal was 30.2 months (IQR: 17.2 – 49.9 months). Univariate Cox regression analysis showed that the HRs for withdrawal were 1.08 (95% CI: 1.04 to 1.12; $p < 0.001$) per 1 mg/L increase in β_2MG, 0.65 (95% CI: 0.46 to 0.93; $p = 0.02$) per 1 g/dL decrease in serum albumin, and 1.07 (95% CI: 1.02 to 1.11; $p = 0.01$) per 1 g increase per gram creatinine in daily urinary protein excretion (Table III). Although age, body mass index, presence of diabetes mellitus, hemoglobin, C-reactive protein, and eGFR were not associated with duration of PD, past history of CVD seemed to be related to withdrawal (HR: 1.41; 95% CI: 0.98 to 2.02; $p = 0.07$). Using multivariate Cox regression analysis, β_2MG (HR: 1.08; 95% CI: 1.04 to 1.12; $p < 0.001$) and past history of CVD (HR: 1.47; 95% CI: 1.02 to 2.13; $p = 0.04$) were predictors of withdrawal (Table IV). Kaplan–Meier analysis showed that the technique survival rate was significantly different in the two groups defined as having a serum β_2MG level above or below the measured median (log-rank $p = 0.047$, Figure 2). On the other hand, we observed no

TABLE I Characteristics of patients at initiation of peritoneal dialysis

Characteristic	*Value*
Patients (*n*)	151
Age [median (IQR) years]	62.5 (53.0–70.6)
Sex [*n* (%) men]	94 (62.3)
With diabetes mellitus [*n* (%)]	74 (49.0)
Past history of CVD [*n* (%)]	52 (34.4)
Duration of PD [median (IQR) months]	30.2 (17.2–49.9)
Body mass index [median (IQR) kg/m^2]	23.2 (20.9–26.3)
Primary kidney disease [*n* (%)]	
Diabetic nephropathy	65 (43.0)
Chronic glomerulonephritis	32 (21.1)
Nephrosclerosis	26 (17.2)
Other	27 (17.9)
Unknown	1 (0.8)
Laboratory parameters [median (IQR)]	
Hemoglobin (g/dL)	9.5 (8.6–9.5)
Hematocrit (%)	28.9 (25.9–32.3)
Protein (g/dL)	6.5 (6.1–7.0)
Albumin (g/dL)	3.8 (3.4–4.1)
Calcium (mg/dL)	8.7 (8.1–9.1)
Phosphorus (mg/dL)	5.4 (4.8–6.3)
Intact PTH (pg/mL)	280 (177–397)
Creatinine (mg/dL)	7.87 (6.68–9.30)
Estimated GFR (mL/min/1.73 m^2)	5.7 (4.7–6.6)
Total cholesterol (mg/dL)	171 (149–207)
Triglycerides (mg/dL)	120 (90–161)
Ferritin (ng/mL)	131 (64–211)
C-reactive-protein (mg/dL)	0.12 (0.04–0.37)
β_2-microglobulin (mg/L)	17.3 (14.8–21.3)
Daily urinary protein excretion (g/g$_{Cr}$)	3.0 (1.2–4.9)

IQR = interquartile range; CVD = cardiovascular disease; GFR = glomerular filtration rate; Cr = creatinine.

significant difference in the technique survival rate between patients with and without a history of CVD (log-rank $p = 0.063$, Figure 3).

Discussion

Previous studies have reported age, serum albumin, hemoglobin, body mass index, presence of diabetes mellitus, residual renal function, and past history of CVD as predictors for withdrawal from PD (6–10).

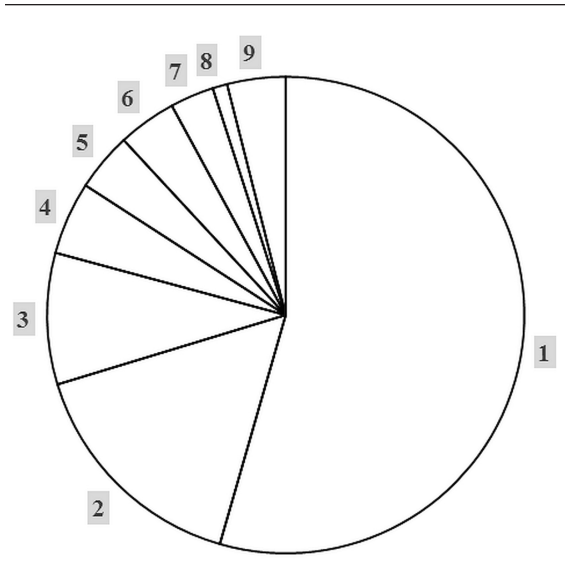

FIGURE 1 Reasons for withdrawal from peritoneal dialysis (PD): (1) inadequate dialysis (55%), (2) death (16%), (3) infection (9%), (4) comorbidity unrelated to peritoneal dialysis (5%), (5) renal transplantation (4%), (6) social problem (4%), (7) catheter problem (3%), (8) encapsulating peritoneal sclerosis (1%), and (9) others (4%).

TABLE II Causes of death in 17 peritoneal dialysis patients

Cause	*Patients*
Cardiovascular death	5
Sudden death	5
Infection	4
Malignant neoplasm	3

However, many of those studies considered predictors of withdrawal because of patient death. In contrast, the present study examined the predictors of withdrawal for all reasons, including death.

A publication examining the technique survival rate in elderly PD patients in Japan (mean age: 75 years; $n = 410$) reported that the 50% technique survival rate was 30.3 months (11), which was almost the same as the rate found by a Japanese multicenter collaborative research study (mean patient age: 62 years) (3). In the present study, we observed no association between age at PD initiation and withdrawal. We hypothesized that frailty, more than patient age,

TABLE III Univariate Cox regression analysis of predictive factors for peritoneal dialysis withdrawal

Factor	p *Value*	*HR*	*95% CI*
Age	0.30	0.99	0.98 to 1.01
Body mass index	0.45	1.02	0.97 to 1.07
Past history of CVD	0.07	1.41	0.98 to 2.02
Presence of diabetes mellitus	0.65	1.08	0.77 to 1.53
Hemoglobin	0.44	0.96	0.85 to 1.07
Serum albumin	0.02	0.65	0.46 to 0.93
C-Reactive protein	0.71	0.96	0.76 to 1.20
β_2-Microglobulin	<0.001	1.08	1.04 to 1.12
Estimated GFR	0.51	0.97	0.88 to 1.06
Urinary protein	0.01	1.07	1.02 to 1.11

HR = hazard ratio; CI = confidence interval; CVD = cardiovascular disease; GFR = glomerular filtration rate.

TABLE IV Multivariate Cox regression analysis of predictive factors for peritoneal dialysis withdrawal

Factor	p *Value*	*HR*	*95% CI*
Past history of CVD	0.04	1.47	1.02 to 2.13
Serum albumin	0.51	0.87	0.59 to 1.30
β_2-Microglobulin	<0.01	1.08	1.04 to 1.12
Urinary protein	0.26	1.03	0.98 to 1.08

HR = hazard ratio; CI = confidence interval; CVD = cardiovascular disease.

would affect PD withdrawal; however, we did not evaluate activities of daily living at the time that this study began.

In a retrospective analysis of 225 patients, Jones *et al.* (12) reported that serum albumin at the start of PD is not a good predictor of the technique survival rate. On the other hand, Gamba *et al.* (6) reported that low albumin levels are associated with a high risk of death. In the present study, univariate analysis showed that serum albumin at the start of PD was significantly associated with PD withdrawal. However, in the multivariate analysis, serum albumin had no effect on PD duration (p = 0.51). Hemoglobin, body mass index, and the presence of diabetes were also not associated with PD withdrawal in the present study. Decline in residual renal function is well known to strongly affect prognosis in PD patients (13). However, the present study found no association between eGFR and PD withdrawal. We considered that those results might possibly be influenced by the small variation of eGFR in our cohort.

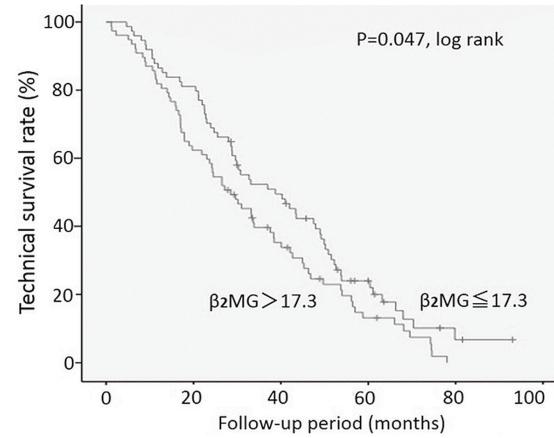

FIGURE 2 Kaplan–Meier analysis of the peritoneal dialysis technique survival rate by median serum β_2-microglobulin (β_2MG) concentration (≤17.3 μg/L or >17.3 μg/L.

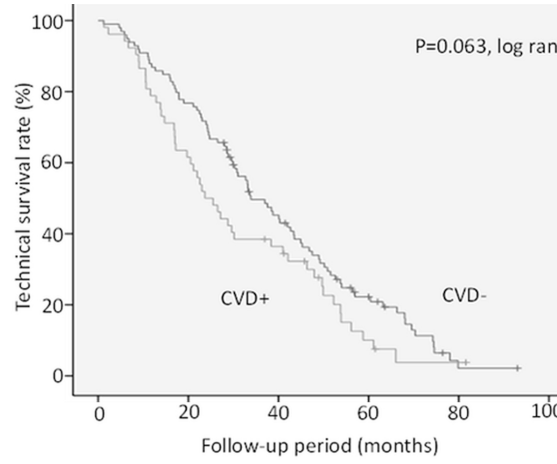

FIGURE 3 Kaplan–Meier analysis of the peritoneal dialysis technique survival rate by history of cardiovascular disease [CVD (yes or no)].

Our observations suggest that β_2MG is significantly associated with the technique survival rate. Serum β_2MG is elevated in chronic inflammation, liver disease, renal failure, acute viral infections, and a number of malignancies. In addition, serum β_2MG is known not only to cause dialysis-related amyloidosis, but also to serve as a useful indicator of residual renal

function (14) and as a predictor of mortality in hemodialysis patients (15). Yokoyama *et al.* (16) reported that, in PD patients, β_2MG is useful as a screening test for the onset of encapsulating peritoneal sclerosis. Recent studies found that higher serum β_2MG predicted mortality in a renal transplantation cohort and in PD patients (17,18). Furthermore, higher serum β_2MG has been independently associated with greater frailty in older adults (19).

As already mentioned, serum β_2MG rises not only based on renal function, but also on inflammation. However, the present study found that eGFR (as an indicator of renal function) and C-reactive protein (as an indicator of inflammation) were not associated with the technique survival rate. We had hypothesized that the synergistic effect of inflammation and declining residual renal function would affect withdrawal from PD.

It is well known that the incidence of CVD is higher in patients with end-stage kidney disease. In recent years, it has become clear that the risk of CVD and all-cause death are related to the decline of renal function in Japanese patients with chronic kidney disease (20). Many patients therefore have complications from CVD at the time of dialysis start. Querido *et al.* (21) reported that the presence of CVD at PD initiation did not affect the rate of PD technique failure. However, the duration of PD was approximately 2 years in that study, and diabetes and older age are present in higher proportions in PD patients with CVD than in those without CVD. In addition, the proportion of patients with CVD at the introduction of PD was lower in the Querido study than in our study (26.8% vs. 34.4%). Deaths attributable to CVD in our study, including sudden deaths, accounted for 60% of all causes of death, and we conjecture that PD in patients with severe left ventricular dysfunction affected the technique survival rate.

The present study had some limitations. First, it was a retrospective observational study, and the sample size was relatively small. Second, there is no definition of inadequate dialysis (the reason that accounted for more than half the withdrawals from PD), and the decision to shift from PD to hemodialysis was made based on the judgment of various doctors. For the future, we are planning a multicenter prospective study to further investigate the factors related to long-term PD technique survival.

Conclusions

Serum β_2MG at PD initiation and past history of CVD are high-risk factors for withdrawal from PD. Patients who are at high risk for withdrawal at the time of PD induction should be managed more carefully.

Disclosures

We understand that *Advances in Peritoneal Dialysis* requires disclosure of any conflicts of interest, and we declare that we have no conflicts to disclose.

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