Survival predictors in anuric patients on peritoneal dialysis: A prospective, multicenter, propensity score-matched cohort study

Ja-Yong Park[1,2☯], Jang-Hee Cho[1,2☯], Hye Min Jang[1,2], Yon Su Kim[1,3], Shin-Wook Kang[1,4], Chul Woo Yang[1,5], Nam-Ho Kim[1,6], Ji-Young Choi[1,2], Sun-Hee Park[1,2], Chan-Duck Kim[1,2‡]*, Yong-Lim Kim[1,2‡]*

1 Clinical Research Center for End-Stage Renal Disease (CRC for ESRD) in Korea, 2 School of Medicine, Kyungpook National University, Daegu, Korea, 3 Seoul National University College of Medicine, Seoul, Korea, 4 Yonsei University College of Medicine, Seoul, Korea, 5 Catholic University of Korea College of Medicine, Seoul, Korea, 6 Chonnam National University Medical School, Gwangju, Korea

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* drcdkim@knu.ac.kr (CDK); ylkim@knu.ac.kr (YLK)

Abstract

Prevalent anuric peritoneal dialysis (PD) patients usually have higher mortality than PD patients with residual urine volume. We aimed to evaluate the predictors of survival in anuric PD patients. Anuric PD patients (n = 505, <100 mL of daily urine) enrolled in Korean nationwide prospective cohort were analyzed. Survived and non-survived anuric PD patients were compared by propensity score matching analysis with a ratio of two to one. The propensity method was used to adjust for patient age, dialysis duration, and presence of diabetes. Among the total anuric PD patients, non-survived patients showed a significantly older age, higher incidence of diabetes, coronary artery disease, and arrhythmia, and lower serum creatinine and albumin. After propensity score matching, multivariate Cox regression analysis for patient survival showed a decreasing risk as serum albumin increased (HR = 0.347, p = 0.0094). Analysis using the receiver-operating-characteristic (ROC) curve showed that survival could be predicted with a sensitivity of 59.4% and a specificity of 63.2% using a cutoff value of 3.6 g/dL of serum albumin in unmatched total PD patients. The beneficial impact of high albumin level on death was significantly greater for patients with older age (≥50 years), no diabetes, low ultrafiltration (UF) volume (<1000 mL/day), and low levels of serum creatinine (<10 mg/dL), total cholesterol (<177.5 mg/dL), ferritin (<100 ng/mL), and high-sensitivity C-reactive protein (hs-CRP) (<0.1 mg/dL). Survival in anuric PD patients was associated with age, comorbidities, and nutritional factors such as creatinine and albumin. After adjustment by propensity score matching, serum albumin level was an independent predictor for survival in anuric PD patients.

Introduction

Patients with end-stage renal disease (ESRD) show much lower survival rate compared to general population of the same age [1]. Peritoneal dialysis (PD) is an established treatment modality for patients with ESRD. In several retrospective and prospective cohort studies, predictors of outcome in patients treated with PD have been investigated. The survival of patients on PD is associated with various clinical factors such as demographic findings, comorbidities, nutritional markers, and peritoneal clearance [2–5].

For each 1-year increase in age, the risk of death increases by 4%, and patients with diabetes have a 30% increased risk of death compared with non-diabetic patients [6]. Cardiovascular disease accounts for most deaths in dialysis patients (approximately 50%). In addition, malnutrition is a negative predictor of survival in patients with ESRD. Fluid status and volume homeostasis are important in patients on PD, and a number of studies have shown that fluid overload is prevalent in patients on PD. Inadequate fluid removal in this population contributes to hypertension and is associated with an increased risk of cardiovascular disease, hypoalbuminemia, and systemic inflammation [7–9]. However, this effect was found to depend mainly on the contribution of residual glomerular filtration rate (GFR) [5]. Regardless of how long the residual renal function can be maintained in patients on PD, patients will ultimately lose their residual renal function completely.

Prevalent PD patients might have higher mortality rate when they become anuric during dialysis. The purpose of this study was to identify the factors that predict survival in anuric patients on PD.

Materials and methods

Patients and data collection

We conducted a prospective observational cohort study on Korean dialysis patients at the Clinical Research Center for End-Stage Renal Disease (CRC for ERSD, NCT00931970). Patients who were at least 20 years old and who began treatment with maintenance PD because of ESRD within 3 months were included for the study. Patients scheduled to receive kidney transplantation within 3 months were excluded. Between September 2008 and June 2011, 505 anuric patients on continuous ambulatory peritoneal dialysis (CAPD) were recruited into the study with the mean follow-up duration of 21.4±7.9 months. Anuria was defined as a 24-h urine output lower than 100 mL. Demographic variables at enrollment included age, gender, duration of dialysis, primary renal disease, comorbidities, laboratory data, and dialysis information. Comorbid conditions included chronic lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus, congestive heart failure, arrhythmia, connective tissue disease, peptic ulcer disease, mild liver disease, and moderate to severe chronic liver disease. Laboratory data were available for hemoglobin, serum blood urea nitrogen (BUN), creatinine, albumin, total cholesterol, triglyceride, ferritin, and high-sensitivity C-reactive protein (hs-CRP). PD information included membrane transport status, UF volume, weekly dialysate Kt/Vurea, body mass index (BMI), and blood pressure. The erythropoiesis-stimulating agents used in this study were epoetin-α and darbepoetin, using a conventional ratio of 200:1 to convert from epoetin-α to darbepoetin. Comorbidities, laboratory data, and dialysis information were followed at 3 and 6 months after the start of renal replacement therapy, and then at 6-month intervals thereafter. The present study used the data at the recruitment period of anuric PD patients. Patient's death, a primary end point of the study, was reported within 1 month after the event and ascertained by data from Statistics Korea. The study had local ethical committee clearance at all sites. Written informed consent was obtained

from all studied subjects before inclusion. The Institutional Review Board of Kyungpook National University Hospital approved the study protocol, and all clinical investigations were conducted in accordance with the guidelines of the 2008 Declaration of Helsinki.

Statistical analysis

Results of continuous variables were expressed as mean ± standard deviation (SD) for normal distribution. For categorical variables, the results were expressed as frequencies and percentages. Comparisons of continuous variables and categorical data between the two study groups were tested by the *t*-test and Chi-square test.

To increase the power of the statistical analysis, we constructed a propensity score-matching model. The model included age, comorbid diabetes at baseline, and dialysis vintage. Propensity score matching was conducted using a 2:1 matching procedure, whereby each non-survived anuric patient on PD was matched with two survived anuric patients on PD. The predictors for survival were analyzed using a multivariate Cox's proportional-hazard model in which all the significant variables from the univariate analysis were included. Proportional hazard assumptions were tested using Schoenfeld residuals. Survival curves were generated by the Kaplan-Meier method. For the comparison of two scales as predictors for hypoalbuminemia, a receiver operating characteristic (ROC) curves analysis was performed.

We performed subgroup analyses in patients categorized by age ($<$50 years, $\geq$50 years), gender, diabetes, dialysis vintage ($<$5 years, $\geq$5 years), UF volume ($<$1000 mL/day, $\geq$1000 mL/day), hemoglobin ($<$10 g/dL, $\geq$10 g/dL), serum creatinine ($<$10 mg/dL, $\geq$10 mg/dL), total cholesterol ($<$177.5 mg/dL, $\geq$177.5 mg/dL), ferritin ($<$100 mg/dL, $\geq$100 mg/dL), hs-CRP ($<$0.1 mg/dL, $\geq$0.1 mg/dL). All statistical analyses were performed using SAS system for Windows, version 9.2 (SAS Institute Inc., Cary, NC). Differences were regarded as statistically significant when $p < 0.05$.

Results

Demographic data of the study population are shown in Table 1. Among the 505 patients on CAPD in the study, the mean age was 50.29±12.94 years, and the duration of PD was 71.50± 50.34 months. Diabetes was the most common cause of ESRD (39.56%), followed by hypertension (28.40%), glomerulonephritis (25.24%), and others (6.80%). By the end of follow-up, 61 (12.07%) patients had died, and 444 (87.93%) patients were alive. Compared to non-survived patients, survived patients had a lower number of risk factors including older age (49.04±12.66 vs. 59.44±11.23, p$<$0.0001), diabetes as the cause of renal failure (35.65% vs. 66.04%, p$<$ 0.0001), and cardiovascular diseases such as atrial fibrillation and coronary artery disease (p$<$ 0.05, Table 1). In addition, survived patients had significantly higher serum creatinine (11.40± 7.23 vs. 9.90±3.17, p = 0.0053) and serum albumin (3.75±1.62 vs. 3.44±0.45, p = 0.0016) levels than non-survived patients (Table 2).

Univariate Cox regression analysis showed an increasing hazard ratio (HR) for patient survival with increasing patient age, decreasing duration of dialysis, and the presence of accompanying coronary artery disease or diabetes. Additionally, as UF volume, serum creatinine, and serum albumin increased, the HR decreased. Multivariate analysis conducted for these data showed increased HR with significant differences according to patient age (HR = 1.049, p = 0.0034) and diabetes (HR = 2.144, p = 0.0421), and with a decreased HR according to dialysis vintage (HR = 0.976, p = 0.0393) and serum albumin (HR = 0.471, p = 0.0480) (Table 3).

Propensity score analysis was conducted with ratio of 2:1 of survived patients to non-survived patients. Dialysis vintage, age at entry, and diabetes were used as variables for adjustment in the propensity score matching. The analysis was performed in 61 non-survived patients and

Table 1. Demographics of anuric patients on PD.

	Total (N = 505)	Survived (N = 444)	Non-survived (N = 61)	P-value
Dialysis vintage (months)	71.50±50.34	71.17±50.96	73.85±46.02	0.6975
Age at entry (years)	50.29±12.94	49.04±12.66	59.44±11.23	<0.0001
Gender (% male)	289 (57.23)	255 (57.43)	34 (55.74)	0.8019
Primary renal disease (%)				<0.0001
Diabetes	163 (39.56)	128 (35.65)	35 (66.04)	
Hypertension	117 (28.40)	103 (28.69)	14 (26.42)	
Glomerulonephritis	104 (25.24)	101 (28.13)	3 (5.6)	
Others	28 (6.80)	27 (7.52)	1 (1.89)	
Co-morbidity				
Chronic lung disease	20 (5.78)	15 (4.97)	5 (11.36)	0.1550
Coronary artery disease	21 (6.07)	15 (4.97)	6 (13.64)	0.0371
Peripheral vascular disease	7 (2.03)	6 (1.99)	1 (2.33)	1.0000
Cerebrovascular disease	29 (8.38)	23 (7.62)	6 (13.64)	0.2371
Diabetes	189 (46.32)	151 (42.90)	38 (67.86)	0.0005
Congestive heart failure	28 (8.09)	21 (6.95)	7 (15.91)	0.0678
Arrhythmia	6 (1.73)	3 (0.99)	3 (6.82)	0.0292
Connective tissue disease	24 (6.94)	22 (7.28)	2 (4.55)	0.7522
Peptic ulcer disease	13 (3.76)	11 (3.64)	2 (4.55)	0.6746
Mild liver disease	18 (5.22)	13 (4.32)	5 (11.36)	0.0642
Moderate or severe liver disease	10 (2.89)	10 (3.31)	0 (0.00)	0.6220

https://doi.org/10.1371/journal.pone.0196294.t001

122 propensity score-matched survived patients (Table 4). After propensity score matching, survived patients showed higher serum albumin (3.63±0.46 vs. 3.44±0.45, p = 0.0111) and total cholesterol (184.79±45.83 vs. 169.90±41.81, p = 0.0390) levels with significant differences. However, other variables did not show any significant differences between the two groups (Table 5).

In addition, the univariate Cox regression analysis for patient survival showed a decreasing risk with increasing dialysis vintage (HR = 0.982, p = 0.0477), serum albumin (HR = 0.444, p = 0.0083) and total cholesterol (HR = 0.993, p = 0.0371), while no significant differences were observed for the other variables. Multivariate analysis showed a decreasing risk with increasing dialysis vintage (HR = 0.906, p<0.0001) and serum albumin (HR = 0.347, p = 0.0094), though total cholesterol level showed no significant difference between the two groups (HR = 0.992, p = 0.0600) (Table 6).

Analysis using the ROC curve for predicting death according to serum albumin level showed that death could be predicted with a sensitivity of 59.4% and a specificity of 63.2% using a cutoff serum albumin value of 3.6 g/dL. The areas under the curves of serum albumin for predicting survival was 0.658, demonstrating that serum albumin level could be considered as a fair predictor of survival. (Fig 1). When the serum albumin level of 3.6 g/dL was set as the standard, significant differences in the survival rate were observed in unmatched and matched groups (p = 0.0005 and p = 00297) (Fig 2).

The positive association between high albumin level and survival was significantly greater for patients with older age (≥50 years), no diabetes, low UF volume (<1000 mL/day), and low levels of serum creatinine (<10 mg/dL), total cholesterol (<177.5 mg/dL), ferritin (<100 ng/mL), and hs-CRP (<0.1 mg/dL). In the context of albumin levels greater than 3.6 g/dL, a significantly increased survival rate was observed regardless of the sex, duration of dialysis, or hemoglobin level of the patients (Fig 3).

Table 2. Biochemical variables of anuric patients on PD.

	Total (N = 505)	Survived (N = 444)	Non-survived (N = 61)	P-value
Membrane transport status				0.1235
High	41 (25.15)	30 (22.06)	11 (40.74)	
High average/low average	115 (70.55)	100 (73.53)	15 (55.56)	
Low	7 (4.29)	6 (4.41)	1 (3.70)	
UF volume (ml/day)	1112.07±699.24	1130.80±705.34	992.30±652.49	0.1803
Dialysate only weekly Kt/V	1.69±0.56	1.68±0.57	1.75±0.51	0.5425
BMI (kg/M^2)	23.40±3.27	23.38±3.22	23.59±3.66	0.6514
Systolic BP (mmHg)	134.69±23.94	134.53±23.52	135.85±26.99	0.7006
Diastolic BP (mmHg)	82.13±35.12	82.73±37.06	77.82±14.22	0.0673
Hemoglobin (g/dL)	10.48±5.00	10.51±5.32	10.27±1.28	0.4325
BUN (mg/dL)	60.11±26.92	60.63±27.50	56.37±22.12	0.1758
Serum creatinine (mg/dL)	11.22±6.89	11.40±7.23	9.90±3.17	0.0053
Serum albumin (g/dL)	3.71±1.53	3.75±1.62	3.44±0.45	0.0016
Total cholesterol (mg/dL)	176.92±42.65	177.88±42.72	169.90±41.81	0.1815
Triglyceride (mg/dL)	155.49±107.76	157.38±111.48	142.63±77.64	0.2625
LVH on EKG				0.9497
Yes	70 (27.34)	60 (27.27)	10 (27.78)	
No	186 (72.66)	160 (72.73)	26 (72.22)	
Cardiomegaly on CXR				0.7837
Yes	80 (32.26)	69 (31.94)	11 (34.38)	
No	168 (67.74)	147 (68.06)	21 (65.63)	
Ejection fraction (%)	56.74±11.12	57.49±10.42	47.79±35.00	0.1436
Ferritin (ng/mL)	256.55±298.54	263.87±312.34	211.68±191.26	0.2096
ESA dose (U/week)	5352.3±2669.6	5439.9±2740.9	4809.7±2134.2	0.2234
hs-CRP (mg/dL)	0.89±2.22	0.89±2.31	0.88±1.49	0.9810

Abbreviations: UF, ultrafiltration; BMI, body mass index; BUN, blood urea nitrogen; LVH, left ventricular hypertrophy; CXR, chest X-ray; ESA, erythropoiesis-stimulating agent.

Discussion

In this study, based on the results of multicenter prospective observation studies on dialysis patients in Korea, we implemented analyses of the factors that might influence prognosis in anuric patients on PD. Using propensity score matching, analyses with a ratio of 2:1 of survived patients to non-survived patients were conducted according to the differences in patient age, duration of dialysis, and the presence of diabetes. Serum albumin level was found to be an independent predictor for survival in anuric patients on PD. This is the largest prospective study ever published which investigated survival predictors in anuric PD patients.

The increasing dialysis vintage is associated with declining body weight and deterioration of nutritional status, which may affect survival of patients on PD [10]. Because the present study included only the anuric PD patients at the recruitment, the exact duration of dialysis until anuria could not be evaluated. It is difficult to draw a definite conclusion from the univariate and multivariate analysis with duration of dialysis. Nevertheless, the duration of dialysis could be correlated with duration on dialysis of patients when they became anuric, especially when the duration is short. Therefore, relationship between dialysis duration and survival shown in our study might suggest that faster the patient becomes anuric, more likely the patient would not survive long. This has been reported in many studies suggesting preserving residual renal function is an important factor for longer survival in PD patients [11–13].

Table 3. Univariate and multivariate Cox regression analyses of patient survival in anuric patients on PD.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Age at entry (years)	1.101 (1.076–1.128)	<0.0001	1.049 (1.016–1.083)	0.0034
Dialysis vintage (months)	0.948 (0.936–0.959)	<0.0001	0.976 (0.954–0.999)	0.0393
Gender (female vs. male)	0.829 (0.499–1.378)	0.4693		
Coronary artery disease	4.282 (1.791–10.241)	0.0011	1.245 (0.436–3.558)	0.6819
Diabetes	4.758 (2.627–8.618)	<0.0001	2.144 (1.027–4.472)	0.0421
BMI (kg/M^2)	1.076 (0.997–1.162)	0.0602		
Systolic BP (mmHg)	1.009 (0.997–1.021)	0.1558		
Diastolic BP (mmHg)	0.992 (0.972–1.013)	0.4459		
Hemoglobin (g/dL)	0.974 (0.882–1.074)	0.5960		
BUN (mg/dL)	0.996 (0.984–1.008)	0.5312		
Serum creatinine (mg/dL)	0.845 (0.779–0.917)	<0.0001	0.97 (0.869–1.082)	0.5801
UF volume (L/day)	0.557 (0.358–0.865)	0.0093	0.793 (0.487–1.29)	0.3500
Serum albumin (g/dL)	0.387 (0.261–0.573)	<0.0001	0.473 (0.224–1.002)	0.0505
Total cholesterol (mg/dL)	0.990 (0.989–1.002)	0.1496		
Ferritin (ng/mL)	1.000 (0.999–1.001)	0.9341		
hs-CRP (mg/dL)	1.015 (0.845–1.219)	0.8712		
Membrane transport status				
Slow average / Slow	Reference			
Fast / Fast average	2.270(0.854–6.033)	0.1002		

https://doi.org/10.1371/journal.pone.0196294.t003

Nutritional markers are known to be as an important factor for survival in patients on PD [14–16], and among them, serum albumin concentration is often used as a surrogate measure of malnutrition. However, the utility of albumin as a marker of malnutrition in PD has

Table 4. Demographics of anuric patients on PD (matched cohort).

Variables	Total (N = 183)	Survived (N = 122)	Non-survived (N = 61)	P-value
Dialysis vintage (months)	67.06±43.66	63.67±42.21	73.85±46.02	0.1375
Age at entry (years)	57.66±13.28	56.78±14.16	59.44±11.23	0.1692
Gender (% male)	106 (57.92)	72 (59.02)	34 (55.74)	0.6719
Primary renal disease (%)				0.1117
Diabetes	95 (62.50)	60 (60.61)	35 (66.04)	
Hypertension	31 (20.39)	17 (17.17)	14 (26.42)	
Glomerulonephritis	18 (11.84)	15 (15.15)	3 (5.66)	
Others	8 (5.26)	7 (7.07)	1 (1.89)	
Co-morbidity				
Chronic lung disease	13 (9.56)	8 (8.70)	5 (11.36)	0.7562
Coronary artery disease	14 (10.29)	8 (8.70)	6 (13.64)	0.3802
Peripheral vascular disease	3 (2.22)	2 (2.17)	1 (2.33)	1.0000
Cerebro-vascular disease	15 (11.03)	9 (9.78)	6 (13.64)	0.5624
Diabetes	115 (67.25)	77 (66.96)	38 (67.86)	0.9062
Congestive heart failure	16 (11.76)	9 (9.78)	7 (15.91)	0.2995
Arrhythmia	4 (2.94)	3 (6.82)	1 (1.09)	0.0993
Connective tissue disease	6 (4.41)	4 (4.35)	2 (4.55)	1.0000
Peptic ulcer disease	6 (4.41)	4 (4.35)	2 (4.55)	1.0000
Mild liver disease	10 (7.35)	5 (5.46)	5 (11.36)	0.2922
Moderate or severe liver disease	3(2.21)	3 (3.26)	0 (0.00)	0.5508

https://doi.org/10.1371/journal.pone.0196294.t004

Table 5. Biochemical variables of anuric patients on PD (matched cohort).

Variables	Total (N = 183)	Survived (N = 122)	Non-survived (N = 61)	P-value
Membrane transport status				0.3847
High	19 (31.67)	8 (24.24)	11 (40.74)	
High average/low average	38 (63.33)	23 (69.70)	15 (55.56)	
Low	3 (5.00)	2 (6.06)	1 (3.70)	
UF volume (ml/day)	1022.06 ±708.89	1039.98 ±743.87	992.30 ±652.49	0.7004
Dialysate only weekly Kt/V	1.66±0.52	1.58±0.53	1.75±0.51	0.1891
BMI (kg/M^2)	23.73±3.42	23.80±3.30	23.59±3.66	0.6984
Systolic BP (mmHg)	134.38±25.47	133.63±24.74	135.85±26.99	0.5995
Diastolic BP (mmHg)	83.21±56.28	85.98±68.44	77.82±14.22	0.2383
Hemoglobin (g/dL)	10.17±1.47	10.13±1.57	10.27±1.28	0.5309
BUN (mg/dL)	56.12±19.68	56.00±18.43	56.37±22.12	0.9056
Serum creatinine (mg/dL)	9.77±3.39	9.70±3.51	9.90±3.17	0.7145
Serum albumin (g/dL)	3.56±0.46	3.63±0.46	3.44±0.45	0.0111
Total cholesterol (mg/dL)	179.83±44.96	184.79±45.83	169.90±41.81	0.0390
Triglyceride (mg/dL)	159.26±102.25	168.37±112.88	142.63±77.64	0.1285
LVH on EKG				0.9502
Yes	29 (28.16)	19 (28.36)	10 (27.78)	
No	74 (71.84)	48 (71.64)	26 (72.22)	
Cardiomegaly on CXR				0.4165
Yes	29 (29.00)	18 (26.47)	11 (34.38)	
No	71 (71.00)	50 (73.53)	21 (65.63)	
Ejection fraction (%)	52.94±11.09	54.15±9.62	47.67±17.79	0.3793
Ferritin (ng/mL)	271.12±360.31	304.62±425.27	211.68±191.26	0.1682
ESA dose (U/week)	5583.1±2582.8	5718.5±2776.6	4809.7±2134.2	0.1203
hs-CRP (mg/dL)	1.16±2.68	1.28±3.06	0.88±1.49	0.4384

https://doi.org/10.1371/journal.pone.0196294.t005

Table 6. Relative risk of death in anuric patients on PD (matched cohort).

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at entry (years)	1.022 (0.998–1.047)	0.0724	1.000 (0.975–1.026)	0.986
Dialysis vintage (months)	0.982 (0.964–1.000)	0.0477	0.906 (0.877–0.936)	<0.0001
Gender (female vs. male)	0.888 (0.524–1.505)	0.6593		
Coronary artery disease	1.909 (0.771–4.728)	0.1623		
Diabetes	1.335 (0.722–2.470)	0.3574		
BMI (kg/M^2)	1.028 (0.946–1.116)	0.5169		
Systolic BP (mmHg)	1.007 (0.996–1.018)	0.2231		
Diastolic BP (mmHg)	0.997 (0.987–1.007)	0.5142		
Hemoglobin (g/dL)	1.050 (0.863–1.277)	0.6249		
BUN (mg/dL)	1.006 (0.993–1.020)	0.3633		
Serum creatinine (mg/dL)	1.004 (0.924–1.090)	0.9315		
UF volume (L/day)	0.898 (0.605–1.334)	0.5942		
Serum albumin (g/dL)	0.444 (0.243–0.811)	0.0083	0.347 (0.156–0.771)	0.0094
Total cholesterol (mg/dL)	0.993 (0.986–1.000)	0.0371	0.992 (0.984–1.000)	0.0600
Ferritin (ng/mL)	1.000 (0.998–1.001)	0.4613		
hs-CRP (mg/dL)	0.45 (0.755–1.181)	0.6175		
Membrane transport status				
High	Reference			
High average / low average	1.020 (0.446–2.332)	0.9630		
Low				

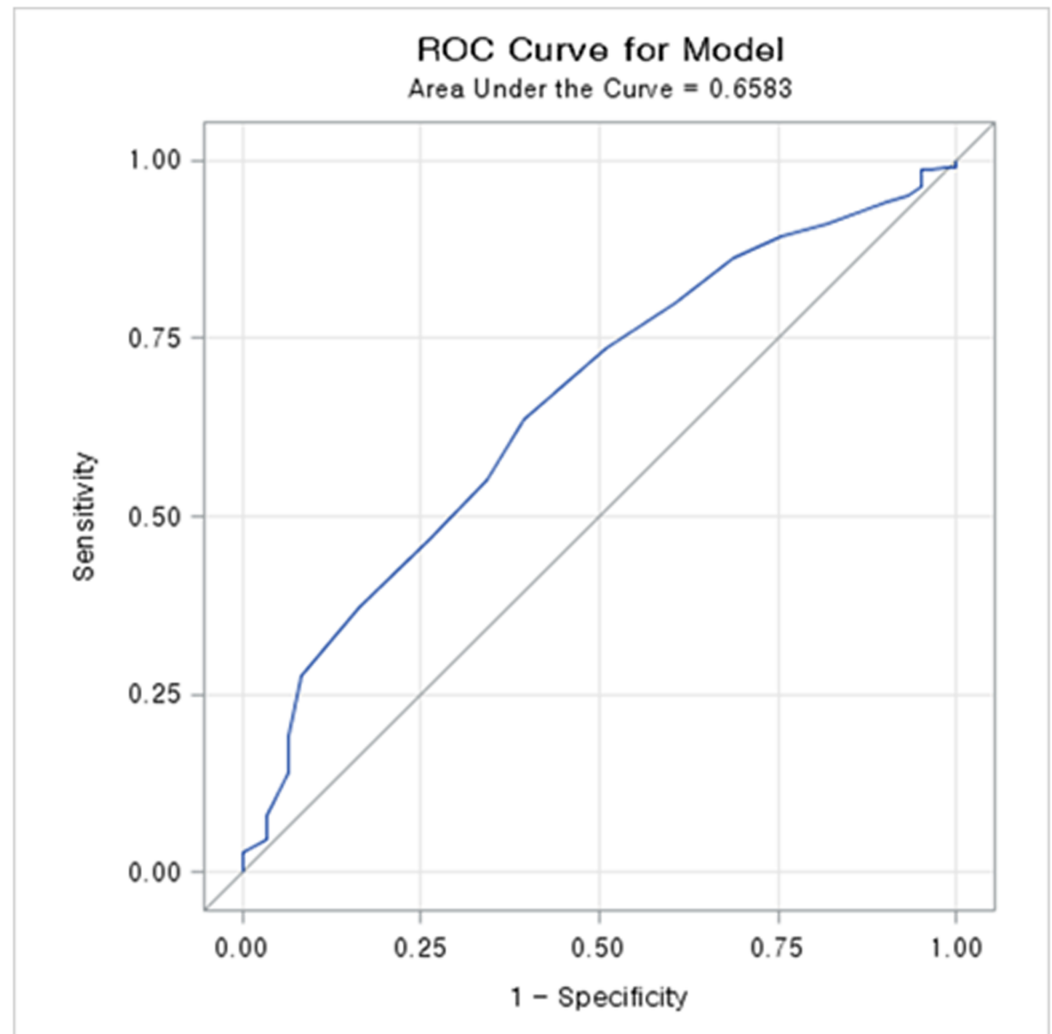https://doi.org/10.1371/journal.pone.0196294.t006

Fig 1. The receiver operating characteristic (ROC) curve for the prediction of death according to serum albumin level.
Serum albumin levels below 3.6 g/dL predicted adverse renal outcome with a 59.4% sensitivity and a 63.2% specificity.

remained controversial. The association between other measures of nutrition and albumin concentration is inconsistent, which may be due to multiple factors. Albumin is a negative acute-phase reactant and its production is suppressed in inflammatory states [17]. In addition to inflammation, peritoneal albumin loss and volume overloading can lead to hypoalbuminemia in patients on PD [18]. Although serum albumin concentration is not an effective isolated marker of nutritional status because of its multiple confounding factors, our study showed that serum albumin level may be considered an important and meaningful factor to facilitate the prediction of prognosis in anuric patients on PD. Jansen et al. also reported that several risk factors such as low serum albumin as well as old age, comorbidity, and dialysis vintage, were significantly associated with worse patient survival [19]. However, they studied with relatively small number of anuric patients, to which comparison with propensity matching could not be applied. Moreover, we found that serum albumin concentration may differently affect patient survival according to age, status of diabetes, UF volume, serum creatinine level, total cholesterol level, ferritin level, and hs-CRP level. To ascertain the cause of the varying effects of
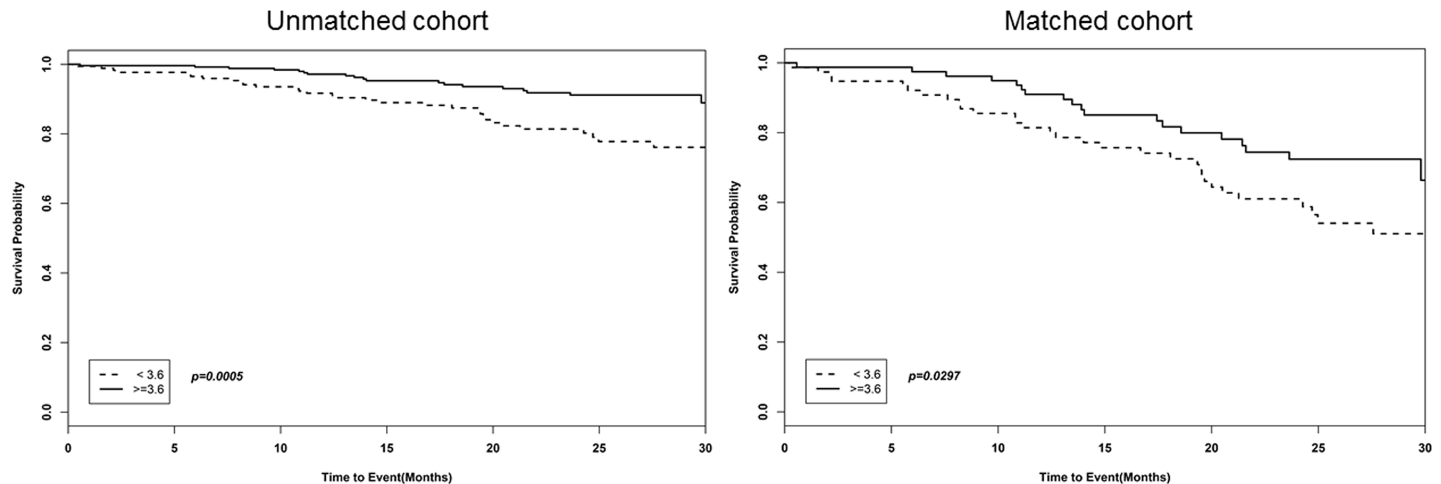
Fig 2. Kaplan-Meier survival curve according to serum albumin level in the unmatched and matched cohorts.

https://doi.org/10.1371/journal.pone.0196294.g002

hypoalbuminemia, further studies that elucidate the relationship between albumin and these factors are warranted.

Increased serum creatinine level has been associated with good survival, whereas lower serum creatinine level has been associated with increased mortality in hemodialysis patients [20, 21]. These findings suggest that serum creatinine level reflects muscle mass and that low muscle mass resulting from malnutrition is associated with poor outcomes. In a previous study, the association between serum creatinine level and survival was observed in a retrospective PD cohort [22]. However, that previous study has a limitation in that residual renal function, which can directly affect serum creatinine level, was unable to be examined. Residual renal function may be better preserved and may contribute more significantly to total creatinine clearance, particularly in patients with a shorter PD duration [23, 24]. Given that residual GFR is an important predictor of survival, the association between serum creatinine and survival may be modified by residual GFR. Since our present study targeted anuric patients with PD, it was possible to exclude the influence of residual renal function on serum creatinine. In the unmatched cohort analysis, survived patients showed increased serum creatinine and a statistically significant difference in the survival rate, which increased with increasing serum creatinine levels and was confirmed in the Kaplan-Meier survival curves. These findings are in accordance with the results of previous studies. However, no significant difference in serum creatinine level was observed between the two groups in the propensity score analysis. This implies that serum creatinine may be used as a marker of nutritional status in patients with ESRD, but that it is not appropriate for predicting survival, especially anuric PD patients. Further studies are needed to verify the association between survival rate and serum creatinine level in anuric patients on PD.

The optimal UF volume of anuric patients on PD remains unknown [25]. The European Best Practice Guideline Working Group on PD recommends the minimum net UF of 1 L/day in anuric patients on PD [26]. However, the International Society for Peritoneal Dialysis states that no definite target for UF can be suggested from the previous studies [27]. In the same context, our study revealed no significant difference in survival rate according to the UF volume was observed in the propensity score analysis. While current guidelines do not adequately address the optimal UF target for anuric patients on PD, optimizing therapy to meet UF goals remains an important clinical target.
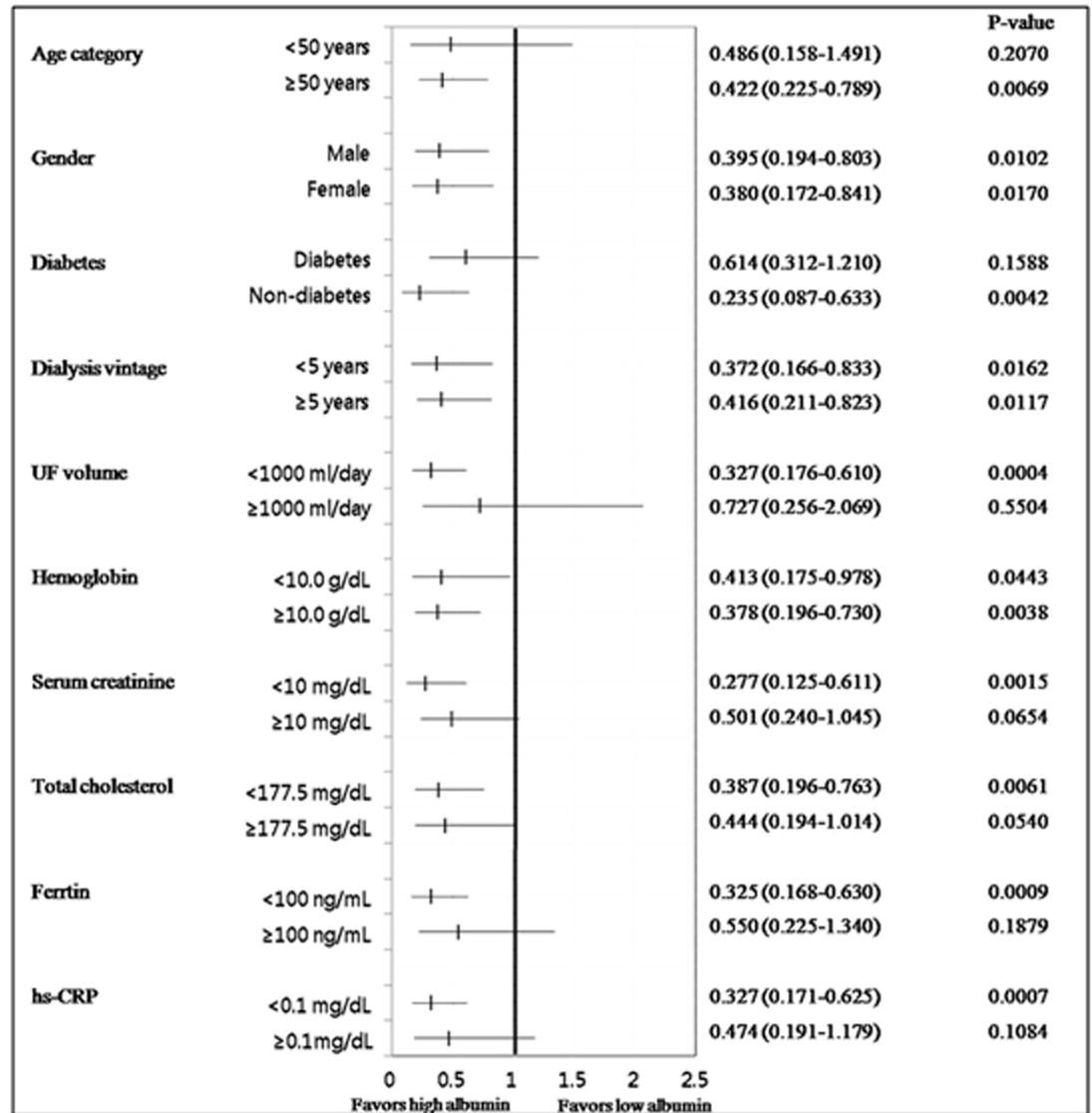
			P-value
Age category	<50 years	0.486 (0.158-1.491)	0.2070
	≥50 years	0.422 (0.225-0.789)	0.0069
Gender	Male	0.395 (0.194-0.803)	0.0102
	Female	0.380 (0.172-0.841)	0.0170
Diabetes	Diabetes	0.614 (0.312-1.210)	0.1588
	Non-diabetes	0.235 (0.087-0.633)	0.0042
Dialysis vintage	<5 years	0.372 (0.166-0.833)	0.0162
	≥5 years	0.416 (0.211-0.823)	0.0117
UF volume	<1000 ml/day	0.327 (0.176-0.610)	0.0004
	≥1000 ml/day	0.727 (0.256-2.069)	0.5504
Hemoglobin	<10.0 g/dL	0.413 (0.175-0.978)	0.0443
	≥10.0 g/dL	0.378 (0.196-0.730)	0.0038
Serum creatinine	<10 mg/dL	0.277 (0.125-0.611)	0.0015
	≥10 mg/dL	0.501 (0.240-1.045)	0.0654
Total cholesterol	<177.5 mg/dL	0.387 (0.196-0.763)	0.0061
	≥177.5 mg/dL	0.444 (0.194-1.014)	0.0540
Ferritin	<100 ng/mL	0.325 (0.168-0.630)	0.0009
	≥100 ng/mL	0.550 (0.225-1.340)	0.1879
hs-CRP	<0.1 mg/dL	0.327 (0.171-0.625)	0.0007
	≥0.1mg/dL	0.474 (0.191-1.179)	0.1084

0   0.5   1   1.5   2   2.5
Favors high albumin   Favors low albumin

Fig 3. Forest plot showing the adjusted hazard ratios for death in the unmatched cohort.

https://doi.org/10.1371/journal.pone.0196294.g003

Bhaskaran et al. performed a retrospective analysis of anuric peritoneal dialysis patients in Canada and were unable to find a significant effect of Kt/Vurea on the relative risk of death [28]. However, multivariate analysis of a prospective cohort study of anuric patients in Hong Kong showed a significant effect of Kt/Vurea on survival advantage [29]. Maarten et al. showed that peritoneal UF rate, Kt/Vurea <1.5/week, and creatinine clearance <40 L/week/1.73 m^2 were associated with an increase in the relative risk of death. Furthermore, they suggested that a Kt/Vurea of 1.7/week and a creatinine clearance of at least 45 L/week were reasonable targets, which is in line with the results of the ADEMEX study in which a further increase in these solute transport levels was not found to lead to better patient survival. The Kidney Disease Outcomes Quality Initiative (KDOQI) provides specific guidelines for PD adequacy since higher small solute clearance is associated with improved survival on PD. According to our results, variations in peritoneal small solute clearances did not correspond to improved survival.

Further studies that assess factors other than small-solute clearances are necessary to determine their effects on survival.

Numerous investigations have recently monitored certain biomarkers such as cardiac troponins and hs-CRP in addition to clinical data such as diabetes and hypertension in order to more clearly identify patients with coronary artery disease and enable the risk stratification of patients with ESRD [30, 31]. Several studies have shown that the elevated hs-CRP is related with cardiovascular disease and patient's death [32–34], whereas other studies have reported no association between hs-CRP and survival [35, 36]. In the present study, significant differences in the prognosis of patients between the two groups according to blood pressure, presence of cardiomegaly in LV hypertrophy on EKG, and CXR were not observed, and similar results were shown in the propensity score analysis. In addition, in terms of hs-CRP level, there was no significant difference between the two groups, and a similar pattern was shown in the propensity score analysis. Previous study demonstrated the relationship between diminished residual renal function and increased level of CRP. However, there are several studies which failed to prove the correlation [37]. Therefore, the question of whether hs-CRP is predictive of clinical outcomes in patients on PD irrespective of peritoneal clearance and residual renal function remains controversial. Further research is necessary to confirm the relevance of hs-CRP level in the prognosis of anuric patients on PD. However, this study showed that low hs-CRP levels decreased the hazard ratio for survival in anuric patients on PD, with higher serum albumin levels.

In conclusion, our study showed that in the absence of residual renal function, serum albumin level is an independent factor that influences the survival of patients on PD. Additionally, patients with relatively older age, no diabetes, peritoneal UF of less than 1000 mL/day, and low serum creatinine, total cholesterol, serum ferritin, and hs-CRP levels, survival rate was found to increase along with increasing serum albumin level. The statistical significance of the results was fortified through propensity score matching that was conducted using prognosis factors gleaned from previous studies of patients on PD. However, further large-scale research is necessary to confirm the relevance of cardiovascular factors, nutritional prognostic factors, and peritoneal clearance in predicting the prognosis of anuric patients on PD.

Author Contributions

Conceptualization: Jang-Hee Cho, Yong-Lim Kim.

Data curation: Hye Min Jang, Yon Su Kim, Shin-Wook Kang, Chul Woo Yang, Nam-Ho Kim.

Formal analysis: Hye Min Jang.

Investigation: Ji-Young Choi, Sun-Hee Park.

Methodology: Jang-Hee Cho, Hye Min Jang.

Supervision: Chan-Duck Kim, Yong-Lim Kim.

Writing – original draft: Ja-Yong Park, Jang-Hee Cho.

Writing – review & editing: Jang-Hee Cho, Chan-Duck Kim, Yong-Lim Kim.

References

1. Valderrabano F, Jones EH, Mallick NP. Report on management of renal failure in Europe, XXIV, 1993. Nephrol Dial Transplant. 1995; 10 Suppl 5: 1–25.

2. Avram MM, Goldwasser P, Erroa M, Fein PA. Predictors of survival in continuous ambulatory peritoneal dialysis patients: the importance of prealbumin and other nutritional and metabolic markers. Am J Kidney Dis. 1994; 23: 91–98. PMID: 8285203

3. Blake PG, Flowerdew G, Blake RM, Oreopoulos DG. Serum albumin in patients on continuous ambulatory peritoneal dialysis—predictors and correlations with outcomes. J Am Soc Nephrol. 1993; 3: 1501–1507. PMID: 8490120

4. Genestier S, Hedelin G, Schaffer P, Faller B. Prognostic factors in CAPD patients: a retrospective study of a 10-year period. Nephrol Dial Transplant. 1995; 10: 1905–1911. PMID: 8592602

5. Davies SJ, Phillips L, Russell GI. Peritoneal solute transport predicts survival on CAPD independently of residual renal function. Nephrol Dial Transplant. 1998; 13: 962–968. PMID: 9568858

6. Kendrick J, Teitelbaum I. Strategies for improving long-term survival in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2010; 5: 1123–1131. https://doi.org/10.2215/CJN.04300709 PMID: 20430945

7. Silberberg JS, Barre PE, Prichard SS, Sniderman AD. Impact of left ventricular hypertrophy on survival in end-stage renal disease. Kidney Int. 1989; 36: 286–290. PMID: 2528654

8. Jones CH, Smye SW, Newstead CG, Will EJ, Davison AM. Extracellular fluid volume determined by bio-electric impedance and serum albumin in CAPD patients. Nephrol Dial Transplant. 1998; 13: 393–397. PMID: 9509452

9. Chung SH, Heimburger O, Stenvinkel P, Bergstrom J, Lindholm B. Association between inflammation and changes in residual renal function and peritoneal transport rate during the first year of dialysis. Nephrol Dial Transplant. 2001; 16: 2240–2245. PMID: 11682675

10. Avram MM, Mittman N, Fein PA, Agahiu S, Hartman W, Chattopadhyay N, et al. Dialysis vintage, body composition, and survival in peritoneal dialysis patients. Adv Perit Dial. 2012; 28: 144–147. PMID: 23311232

11. Diaz-Buxo JA, Lowrie EG, Lew NL, Zhang SM, Zhu X, Lazarus JM. Associates of mortality among peritoneal dialysis patients with special reference to peritoneal transport rates and solute clearance. Am J Kidney Dis. 1999; 33: 523–534. PMID: 10070917

12. Wang AY, Woo J, Wang M, Sea MM, Sanderson JE, Lui SF, et al. Important differentiation of factors that predict outcome in peritoneal dialysis patients with different degrees of residual renal function. Nephrol Dial Transplant. 2005; 20: 396–403. https://doi.org/10.1093/ndt/gfh331 PMID: 15187196

13. Kim HW, Kim SH, Kim YO, Jin DC, Song HC, Choi EJ, et al. The Impact of Timing of Dialysis Initiation on Mortality in Patients with Peritoneal Dialysis. Perit Dial Int. 2015; 35: 703–711. https://doi.org/10.3747/pdi.2013.00328 PMID: 25292405

14. Ramkumar N, Pappas LM, Beddhu S. Effect of body size and body composition on survival in peritoneal dialysis patients. Perit Dial Int. 2005; 25: 461–469. PMID: 16178479

15. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. Am J Clin Nutr. 2004; 80: 324–332. https://doi.org/10.1093/ajcn/80.2.324 PMID: 15277152

16. Dong J, Li YJ, Lu XH, Gan HP, Zuo L, Wang HY. Correlations of lean body mass with nutritional indicators and mortality in patients on peritoneal dialysis. Kidney Int. 2008; 73: 334–340. https://doi.org/10.1038/sj.ki.5002644 PMID: 18033246

17. Sezer S, Ozdemir FN, Akman B, Arat Z, Anaforoglu I, Haberal M. Predictors of serum albumin level in patients receiving continuous ambulatory peritoneal dialysis. Adv Perit Dial. 2001; 17: 210–214. PMID: 11510278

18. Jones CH, Smye SW, Newstead CG, Will EJ, Davison AM. Extracellular fluid volume determined by bio-electric impedance and serum albumin in CAPD patients. Nephrol Dial Transplant. 1998; 13: 393–397. PMID: 9509452

19. Jansen MA, Termorshuizen F, Korevaar JC, Dekker FW, Boeschoten E, Krediet RT. Predictors of survival in anuric peritoneal dialysis patients. Kidney Int. 2005; 68: 1199–1205. https://doi.org/10.1111/j.1523-1755.2005.00512.x PMID: 16105051

20. Walther CP, Carter CW, Low CL, Williams P, Rifkin DE, Steiner RW, et al. Interdialytic creatinine change versus predialysis creatinine as indicators of nutritional status in maintenance hemodialysis. Nephrol Dial Transplant. 2012; 27: 771–776. https://doi.org/10.1093/ndt/gfr389 PMID: 21775764

21. Noori N, Kovesdy CP, Dukkipati R, Feroze U, Molnar MZ, Bross R, et al. Racial and ethnic differences in mortality of hemodialysis patients: role of dietary and nutritional status and inflammation. Am J Nephrol. 2011; 33: 157–167. https://doi.org/10.1159/000323972 PMID: 21293117

22. Park J, Mehrotra R, Rhee CM, Molnar MZ, Lukowsky LR, Patel SS, et al. Serum creatinine level, a surrogate of muscle mass, predicts mortality in peritoneal dialysis patients. Nephrol Dial Transplant. 2013; 28: 2146–2155. https://doi.org/10.1093/ndt/gft213 PMID: 23743018

23. Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA, et al. Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol. 2000; 11: 556–564. PMID: 10703680

24. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int. 2002; 62: 1046–1053. https://doi.org/10.1046/j.1523-1755.2002.00505.x PMID: 12164889

25. Lin X, Lin A, Ni Z, Yao Q, Zhang W, Yan Y, et al. Daily peritoneal ultrafiltration predicts patient and technique survival in anuric peritoneal dialysis patients. Nephrol Dial Transplant. 2010; 25: 2322–2327. https://doi.org/10.1093/ndt/gfq001 PMID: 20118483

26. The European Best Practice Guideline Working Group on Peritoneal Dialysis. Nephrol Dial Transplant. 2005; 20:

27. Lo WK, Bargman JM, Burkart J, Krediet RT, Pollock C, Kawanishi H, et al. Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis. Perit Dial Int. 2006; 26: 520–522. PMID: 16973505

28. Bhaskaran S, Schaubel DE, Jassal SV, Thodis E, Singhal MK, Bargman JM, et al. The effect of small solute clearances on survival of anuric peritoneal dialysis patients. Perit Dial Int. 2000; 20: 181–187. PMID: 10809241

29. Szeto CC, Wong TY, Chow KM, Leung CB, Law MC, Wang AY, et al. Impact of dialysis adequacy on the mortality and morbidity of anuric Chinese patients receiving continuous ambulatory peritoneal dialysis. J Am Soc Nephrol. 2001; 12: 355–360. PMID: 11158226

30. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation. 2002; 106: 2941–2945. PMID: 12460876

31. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003; 107: 363–369. PMID: 12551853

32. Wang AY, Woo J, Lam CW, Wang M, Sea MM, Lui SF, et al. Is a single time point C-reactive protein predictive of outcome in peritoneal dialysis patients? J Am Soc Nephrol. 2003; 14: 1871–1879. PMID: 12819248

33. Ducloux D, Bresson-Vautrin C, Kribs M, Abdelfatah A, Chalopin JM. C-reactive protein and cardiovascular disease in peritoneal dialysis patients. Kidney Int. 2002; 62: 1417–1422. https://doi.org/10.1111/j.1523-1755.2002.kid562.x PMID: 12234314

34. Avram MM, Fein PA, Paluch MM, Schloth T, Chattopadhyay J. Association between C-reactive protein and clinical outcomes in peritoneal dialysis patients. Advances in peritoneal dialysis Conference on Peritoneal Dialysis. 2005; 21: 154–158. PMID: 16686309

35. Herzig KA, Purdie DM, Chang W, Brown AM, Hawley CM, Campbell SB, et al. Is C-reactive protein a useful predictor of outcome in peritoneal dialysis patients? J Am Soc Nephrol. 2001; 12: 814–821. PMID: 11274243

36. Oh KH, Moon JY, Oh J, Kim SG, Hwang YH, Kim S, et al. Baseline peritoneal solute transport rate is not associated with markers of systemic inflammation or comorbidity in incident Korean peritoneal dialysis patients. Nephrol Dial Transplant. 2008; 23: 2356–2364. https://doi.org/10.1093/ndt/gfm921 PMID: 18178604

37. Herzig KA, Purdie DM, Chang W, Brown AM, Hawley CM, Campbell SB, et al. Is C-reactive protein a useful predictor of outcome in peritoneal dialysis patients? J Am Soc Nephrol. 2001; 12: 814–821. PMID: 11274243