

Effect of Initial Peritoneal Equilibration Test Results on Mortality in Peritoneal Dialysis Patients

Periton Diyalizi Hastalarında Başlangıç Peritoneal Eşitleme Testi Sonuçlarının Mortaliteye Etkisi

ABSTRACT

OBJECTIVE: We studied the effect of initial peritoneal equilibration test (PET) results on mortality in peritoneal dialysis (PD) patients besides classical mortality markers.

MATERIAL and METHODS: Seventy-eight patients were enrolled. Initial PET and biochemical and clinical findings were recorded after the beginning of PD. Survival analysis model included comorbidities, PD modality, peritoneal modality change during follow-up, history of peritonitis, calcium X phosphorus, dialysate volume, presence of anuria, ultrafiltration volume, albumin, Kt/V, normalized protein equivalent of nitrogen appearance (nPNA), and peritoneal permeability.

RESULTS: The mean age was 55.2±13.8 (52.6%, female) years and PD duration was 49.7±26.1 months. When current conditions of the patients were evaluated, 42.3% of the 78 patients received PD treatment, 24.4% switched to hemodialysis, 6.4% had kidney transplantation and 26.9% died. The most significant factors determining patient survival were age, albumin and weekly total Kt/V according to the Cox regression analysis using the backward elimination method. When Cox regression analysis was repeated by the forward selection method, albumin was detected as the most significant factor determining patient survival.

CONCLUSION: Albumin was found to be the most important factor predicting patient survival among peritoneal permeability, nPNA, PD modality, weekly total Kt/V, dialysate volume, ultrafiltration volume on the initial PET.

KEY WORDS: Mortality, Peritoneal dialysis, Peritoneal equilibration test

ÖZ

AMAÇ: Periton diyalizi (PD) hastalarında klasik mortalite belirteçlerinin yanı sıra bazal peritoneal eşitleme testi (PET) verilerinin de mortaliteye etkisini araştırdık.

GEREÇ ve YÖNTEMLER: Çalışmaya 78 hasta dahil edildi. Periton diyalizine başladıktan sonraki ilk PET sonuçları ve eş zamanlı biyokimyasal ve klinik bulguları kaydedildi. Hastaların demografik özellikleri yanında komorbidite varlığı, periton diyalizi modalitesi ve takiplerinde periton modalite değişimi varlığı, peritonit öyküsü, kalsiyum X fosfor, diyalizat volümü, anüri varlığı, ultrafiltrasyon volümü, albümin, normalize protein katabolizma hızı (nPKH), peritoneal geçirgenlik, total Kt/V'yi içeren sağkalım analizi modeli oluşturuldu.

BULGULAR: Yaş ortalaması 55,2±13,8 (%52,6 kadın) yıl ve PD süreleri ise 49,7±26,1 ay idi. Hastaların güncel durumları kontrol edildiğinde 78 hastadan %42,3'ü PD'ye devam etmekte idi, %24,4'ü hemodiyalize geçiş yapmıştı, %6,4'ü böbrek nakli olmuş ve %26,9'u ise ölmüştü. Backward metodu ile uygulanan Cox regresyon analizine göre hasta sağ kalımını belirleyen en önemli faktörler yaş, albümin ve haftalık total Kt/V olarak saptandı. Cox regresyon analizi 'forward' metodu ile tekrarlandığında hasta sağ kalımını belirleyen en önemli faktör olarak albümin saptandı.

SONUÇ: Klasik mortalite belirteçleri ile beraber başlangıç PET testi verilerinden periton zarı geçirgenlik tipi, nPKH, PD modalitesi, haftalık total Kt/V, diyalizat volümü, ultrafiltrasyon volümü değerlendirildiğinde hasta sağ kalımını belirleyen en önemli faktör olarak albümin saptandı.

ANAHTAR SÖZCÜKLER: Mortalite, Periton diyalizi, Peritoneal eşitleme testi

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Received : 31.10.2017

Accepted : 23.01.2018

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INTRODUCTION

End-stage renal disease (ESRD) has a high mortality rate and the cardiovascular and non-cardiovascular mortality in dialysis patients has been reported to be approximately eight times higher than in the general population (1). Age, diabetes and hypoalbuminemia in peritoneal dialysis (PD) patients are considered risk factors that predict mortality (2,3). The peritoneal equilibration test (PET) is a standard test used to evaluate the peritoneal permeability characteristics of PD patients and is one of the most important practical applications in deciding treatment and follow-up of patients (4). Patients with PD are proven to have different peritoneal membrane permeability properties that can be identified and classified by using PET which helps to define the relationship of dialysis duration with solute permeability, glucose absorption, solute clearance, and ultrafiltration volume. The multicenter CANUSA study found that higher permeability was associated with worse patient survival and technical failure, independent of other significant risk factors such as residual renal function, comorbidity and age (5). However, these findings have not been confirmed by many other studies, including the ADEMEX study, which showed that these findings were not affected by survival of patients with high permeability PD (6,7). There is not enough study in Turkey about the effect of initial PET on mortality in patients starting PD although there are conflicting results in the literature. We investigated the factors affecting mortality by evaluating the initial PET values in patients in our hospital because of the high mortality rates among PD patients and because the few studies in our country on this group of patients have excluded classical mortality markers and especially initial PET data.

MATERIAL and METHODS

In this study we retrospectively analyzed 133 adult patients treated between October 2007 and April 2014 in our hospital in the PD unit. We included 78 of these patients who were followed up for at least one year in the study. Thirty-seven patients were excluded.

A total of 18 patients were excluded because of incomplete data, and 37 patients were excluded due to a follow-up period less than one year. Clinical and laboratory findings of the 78 patients were analyzed during follow-up at our hospital and the results were recorded.

Age, gender, height, weight, cause of ESRD, chronic kidney disease (CKD) duration, onset date of PD and comorbidities were recorded. The number of episodes of peritonitis during follow-up, if any, and the changes in the PD regimen were recorded.

The first PET was performed one to three months after the onset of the study and biochemical parameters were examined. Serum uric acid, phosphorus, calcium, total cholesterol, low density lipoprotein, high density lipoprotein, triglyceride,

hemoglobin, hematocrit and parathyroid hormone levels were measured after a 12-hour fast on the day PET was performed.

24-hour urine and 24-hour dialysate were collected before the test in all patients who underwent standard PET. Presence of residual renal function was defined as glomerular filtration rate ≥ 1 ml/min/1.73 m² and 24-hour urine >100 ml. Other patients were regarded as anuric.

PET was performed by filling the peritoneal cavity with two liters of dialysis solution containing 2.3% or 2.27% glucose after a routine nocturnal exchange. Urea, creatinine and glucose levels in the dialysate samples obtained at onset, 2nd hour and 4th hour were studied together with the same parameters in the plasma sample obtained at the 2nd hour of PET. The total amount of ultrafiltration at the end of the exchange was recorded. PET results were examined using the 'Renal Soft (TM)-Version 2.0 Baxter Healthcare, Inc.' program. Dialysate to plasma (D/P) ratio for creatinine (Cr) (D/P Cr) was measured at the 4th hour. D/P Cr at the 4th hour was used to classify patients as low (D/P Cr ≤ 0.49), low average (D/P Cr = 0.50 to 0.64), high average (D/P Cr = 0.65 to 0.80) or high (D/P Cr ≥ 0.81) transporters according to the criteria defined by Twardowski et al. (4). Low and low average transporters are called "low transporter" and high average and high transporters are called "high transporter".

Peritoneal, renal and total Kt/V urea were calculated according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines (8). Protein equivalent of nitrogen appearance (PNA) was calculated using the methods described by Randerson et al. and normalized to actual weight (9). PNA (g/day) was calculated as 5.02 x [generation rate of urea (mg/min) + 3.12]. Normalized PNA (nPNA) was obtained by dividing PNA by body weight.

The patients were grouped according to dialysis modalities as the CAPD (continuous ambulatory peritoneal dialysis) group in which the participants had more than two manual twin bag exchanges per day, and the APD (automated peritoneal dialysis) group in which patients were on continuous cyclic PD or nocturnal intermittent PD modality.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. For descriptive statistics, numbers and percentages were used for categorical variables and the mean and standard deviation were used for numerical variables. The independent samples t-test and Mann-Whitney U test were used for comparison of two groups for variables with and without normal distribution. The rate of the categorical variables among the groups was tested by the chi-square test. Backward elimination for the Cox regression model was used for survival analysis including age, gender, duration of chronic kidney disease, primary kidney disease, presence of anuria, serum albumin, hemoglobin, calcium X phosphorus, presence of peritonitis, presence of peritoneal modality change during their follow-up, peritoneal permeability, peritoneal

dialysis modality, dialysate volume, ultrafiltration volume, nPNA, and total Kt/V. Survival analysis was performed using the Kaplan-Meier estimator. Determinant factors were tested by Cox regression analysis. Statistical significance level of alpha was accepted as $p < 0.05$.

RESULTS

Forty-one patients (52.6%) were female and the mean age of the patients was 55.2 ± 13.8 years. The median duration of predialysis CKD was 24 (Interquartile range 3-48) months and the mean PD duration was 49.7 ± 26.1 months. Primary kidney diseases, comorbidities and laboratory values of the patients are presented in Table I.

Nine patients (11.5%) underwent hemodialysis (HD) and the other patients preferred PD as the initial renal replacement therapy type. During the analysis, 22 patients (28.2%) were

anuric, 73 patients (93.6%) had CAPD, and 5 patients (6.4%) had APD treatment. During the study, 19 patients (24.4%) switched from CAPD to one of the APD regimens while the others continued with the same regimen from the beginning.

During the follow-up period, at least one episode of peritonitis was detected in 58 patients (74.4%) and the peritonitis rate was recorded as 32.6 episodes per a thousand patient-months. According to the initial PET results, peritoneal permeability was low in 6 patients (7.7%), low average in 19 patients (24.4%), high average in 40 patients (51.3%), and high in 13 patients (16.7%). The PET results of the patients are given in Table II.

A total of 33 patients (42.3%) continued with PD, 19 patients (24.4%) switched to HD after 50.5 ± 24.9 months of PD, 5 patients (6.4%) had renal transplantation after 58.3 ± 29.6 months of PD and 21 patients (26.9%) died after 50.1 ± 31.4 months of PD (Figure 1).

The estimated median survival time was 100 months (range: 85.7-114.3 months). One-year survival rate was 98.7%, three-year survival rate was 84.5% and five-year survival rate was 74.4%. Survival curves are given in Figure 2.

The mean age of the surviving patients was lower and the mean albumin levels was higher ($p=0.022$ and $p=0.006$, respectively) when compared to patients who died. Comparison of factors affecting survival between living patients and those who died is presented in Table III.

Table I: Demographic, clinical, and laboratory features of the patients (n=78).

Parameter	(n, %)
Primary kidney disease	
Diabetic Nephropathy	24, 30.8%
Hypertensive Nephrosclerosis	14, 17.9%
Chronic Glomerulonephritis	4, 5.1%
ADPKD	5, 6.4%
Others	11, 14.1%
Unknown	20, 25.6%
Comorbidities	
Ischemic Heart Disease	12, 15.4%
Cerebrovascular Disease	1, 1.3%
Peripheral Artery Disease	1, 1.3%
Others	5, 6.4%
	Mean±Std
Glucose (mg/dl)	133.1±84.9
Urea (mg/dl)	85.2±33.0
Creatinine (mg/dl)	6.2±2.7
Albumin (g/dl)	3.6±0.4
Hemoglobin (g/dl)	10.7±1.5
Uric acid (mg/dl)	5.9±1.2
Phosphorus (mg/dl)	4.4±1.1
Ca x P (mg ² /dl ²)	39.1±10.5
BMI (kg/m ²)	26.8±5.3
Total cholesterol (mg/dl)	205.1±47.8
Parathormone (pg/ml)	441.8±392.2

Ca: Calcium, **P:** Phosphorus, **BMI:** Body Mass Index, **ADPKD:** Autosomal Dominant Polycystic Kidney Disease.

Table II: Initial peritoneal equilibration test results of the patients (n=78).

Parameter	Mean±Std
Dialysate volume (ml)	8542±1497
Ultrafiltration volume (ml/day)	252±169
Urine amount (ml)	1362±921
Total urea clearance (L/week/1.73 m ²)	102.1±50.2
Dialysate urea clearance (L/week/1.73 m ²)	60.8±42.2
Residual urea clearance (L/week/1.73 m ²)	41.2±34.2
Total creatinine clearance (L/week/1.73 m ²)	107.9±48.3
Dialysate creatinine clearance (L/week/1.73 m ²)	45.5±22.0
Residual creatinine clearance (L/week/1.73 m ²)	62.4±49.0
eGFR (ml/min)	6.4±5.3
nPNA (g/kg/day)	1.5±1.0
Weekly total Kt/V	2.8±1.2
Weekly dialysate Kt/V	1.7±1.1
Weekly residual Kt/V	1.1±0.9

eGFR: Estimated glomerular filtration rate, **nPNA:** Normalized protein equivalent of nitrogen appearance.

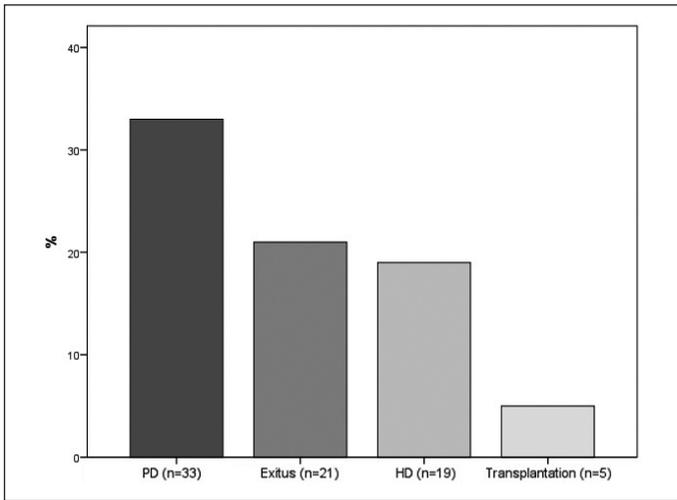


Figure 1: Clinical outcomes of the patients.

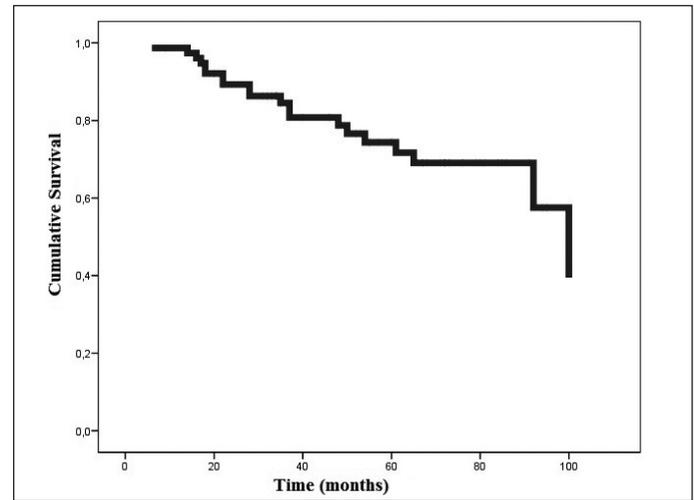


Figure 2: Survival curve of the patients.

Table III: Comparison of the factors that affected survival of living and non living patients.

		Survival		P
		Yes (n=57)	No (n=21)	
Age (years)		53.1±13.9	61.0±11.8	0.022
Duration of CKD (month)		36.7±55.2	43.4±70.7	0.570
Gender (n, %)	Female	32 (56.1)	9 (42.9)	0.297
	Male	25 (43.9)	12 (57.1)	
Primary kidney disease (n,%)	Diabetic Nephropathy	15 (26.3)	9 (42.9)	0.686
	Nephrosclerosis	10 (17.5)	4 (19.0)	
	Glomerulonephritis	3 (5.3)	1 (4.8)	
	ADPKD	4 (7.0)	1 (4.8)	
	Others	10 (17.5)	1 (4.8)	
	Unknown	15 (26.3)	5 (23.8)	
Presence of anurea (n,%)		15 (26.3)	7(33.3)	0.571
Albumin (g/dl)		3.7±0.4	3.4±0.4	0.006
Hemoglobin (g/dl)		10.6±1.4	10.7±1.7	0.791
Peritoneal modality change during follow-up (n,%)		15 (26.3)	4 (19.0)	0.507
Peritoneal permeability (n, %)	Low Transporter	21 (36.9)	4 (19.1)	0.176
	High Transporter	36 (63.1)	17 (80.9)	
CaxP (mg ² /dl ²)		40.3±10.9	36.1±8.6	0.062
PD modality (n,%)	CAPD	52 (91.2)	21 (100)	0.316
	APD	5 (8.8)	0 (0.0)	
nPNA (g/kg/day)		1.6±1.1	1.4±0.5	0.809
Weekly total Kt/V		2.9±1.3	2.7±1.1	0.464
Dialysate volume (ml)		8638±1483	8283±1538	0.467
Ultrafiltration volume (ml/day)		237±149	292±213	0.211
History of peritonitis (n, %)		41 (71.9)	17 (81.0)	0.418

CKD: Chronic kidney disease, ADPKD: Autosomal Dominant Polycystic Kidney Disease, Ca: Calcium, P: Phosphorus, PD: Peritoneal dialysis, CAPD: Continuous ambulatory peritoneal dialysis, APD: Automated peritoneal dialysis, nPNA: Normalized protein equivalent of nitrogen appearance.

Table IV: Factors determining survival of the patients with Cox regression model backward method.

	p	HR	CI %95	
Age (years)	0.049	1.038	1.000	1.078
Albumin (g/dl)	0.002	0.169	0.055	0.524
Weekly total Kt/V	0.041	0.528	0.286	0.974
Dialysate volume (ml)	0.053	1.000	0.999	1.000

HR: Hazard ratio, CI: Confidential interval.

Model 1: Age, gender, duration of chronic kidney disease, primary kidney disease, presence of anuria, serum albumin, hemoglobin, calcium X phosphorus, presence of peritonitis, presence of peritoneal modality change during their follow-up, peritoneal permeability, peritoneal dialysis modality, dialysate volume, ultrafiltration volume, nPNA, and total Kt/V.

According to the Cox regression analysis using the backward elimination method, the most important factors determining patient survival were age, albumin and weekly total Kt/V (Table IV).

When Cox regression analysis was repeated by the forward selection method, albumin was found to be the most important factor determining patient survival ($p=0.001$, Hazard Ratio=0.167, Confidence interval: 95%, 0.060-0.465).

DISCUSSION

End-stage renal disease patients receiving PD are at a higher risk of death compared with the general population (1). In their study including 4249 patients, Neovius et al. demonstrated that the mortality rate was 9.2-fold higher in patients with PD than in the general population (10). According to the 2015 renal registry report from our country, cardiovascular events were the leading cause of death in PD patients (46.4%) followed by cerebrovascular causes (20.6%) and infections (18.6%) (11).

Due to the high mortality rates among patients receiving PD treatment and the low number of studies that specifically examined initial PET data in our country, we retrospectively screened the charts of 78 patients admitted to our hospital and investigated the factors that affected mortality.

We found that 42.3% of the PD patients who were followed up for a mean of 49.7 months continued with PD, 24.4% switched to HD, 6.4% had kidney transplantation, and 26.9% of them died. A study by Unal et al. from our country reported that 41.8% of 392 PD patients died, had been followed up for an average of 44.5 months, 11.7% had kidney transplantation and 33.7% of them received HD (12). In a prospective study from our country which included 171 PD patients who were followed up for seven years, Türkmen et al. reported that 26.3% of subjects died, 10.5% of them continued with PD, 50.9% received HD and 12.3% of them had kidney transplantation (13). Although

Türkmen et al. reported a mortality rate similar to that in our study, the rate of switching to HD was higher. This may be due to the fact that the follow-up period was 84 months. The estimated median survival time in patients studied in our study was 100 months. The 1-, 2-, 3-, 5- and 8-year survival rates were 98.7%, 89.3%, 84.5%, 74.4% and 57.5%, respectively. In a study where mean follow-up and median survival were similar to that in our study, survival rates were 94.7%, 89.9%, 81.9%, 65.8% and 45.6% at 1, 2, 3, 5 and 8 years, respectively (12). The study of Sipahioğlu et al. which has the highest number of relevant patients in our country evaluated 12-year follow up-data of 423 PD patients and the mortality rate was found to be 21%. The 1-, 3-, 5-, 8-, and 10-year survival rates were 96.9%, 83.8%, 68.8%, 50.2%, and 40.7%, respectively. Although mortality and survival rate were similar to our study in the study of Sipahioğlu et al., mortality predictors were found to be age, transfer to PD from HD, comorbid cardiovascular disease, serum creatinine level, total Kt/V urea, peritonitis rate, and dialysate-to-plasma creatinine ratio (14). Another similarity of this study with ours is the predictors of mortality among which age and Kt/V are similar. The other mortality predictor of our study was serum albumin level similar to the studies performed by Ünal et al. and Türkmen et al. (13,14).

Peritoneal dialysis patients have different peritoneal membrane permeability properties. These differences can be determined and classified by using PET which helps define the relationship of dialysis duration with solute permeability, glucose absorption, solute clearance, and ultrafiltration volume. In patients with high membrane permeability, small solutes, such as urea and creatinine, have higher clearance. However, these patients are more likely to suffer peritoneal protein loss and are more susceptible to subsequent ultrafiltration insufficiency and hypervolemia and higher systemic effects of glucose, and in addition, hyperpermeability is associated with malnutrition, chronic inflammation and more common comorbidities. The multi-center CANUSA study found that higher peritoneal transport was associated with worse patient survival and technique failure, independent of other significant risk factors such as renal function, comorbidity and age (5). However, these findings have not been confirmed by many other studies, including the ADEMEX study (6,7) which has shown that these findings had no effect on survival of patients with high-permeability PD. In their study, Chang et al. found that APD patients who did not survive had higher peritoneal membrane permeability than living patients ($p<0.05$) whereas peritoneal membrane permeability did not affect mortality (7). Although 93.6% of patients followed at our clinic were CAPD patients, there was no effect of initial peritoneal membrane permeability on mortality ($p=0.456$). In a meta-analysis by Brimble et al., each 0.1 unit increase in D/P Cr in PD patients increased the relative risk for mortality by 1.15 fold (95% confidence interval 1.17-1.23; $p<0.001$) (15). This result corresponds to an increased mortality risk of 21.9%, 45.7% and 77.3% in low-average, high-

average and high permeability, respectively, compared to low permeability.

Cardiovascular events, which may be associated with uremic toxins, volume status, vascular calcification, anemia, hypoalbuminemia, and chronic inflammation, are the most common cause of death in dialysis patients. Hypoalbuminemia is a well-known reason of mortality and morbidity in the dialysis population. Hypoalbuminemia is not just a sign of a decrease in the body's protein pool, but also is an indication of anorexia, inflammation, and volume in dialysis patients. PD patients have more albumin loss than HD patients. It has been demonstrated by several studies that low serum albumin significantly increases all-cause mortality in HD patients, but there are limited data on the PD population. Recently, Mehrotra et al. reported in their study including 130.052 dialysis patients that the 12171 PD patients with basal serum albumin levels <3.0 g/dl had a more than 3-fold higher adjusted risk of all-cause and cardiovascular mortality than HD patients. It was found that the risk of death increased significantly when albumin was <4.0 g/dl in HD patients and <3.8 g/dl in PD patients (16). In the same study, an increase of 0.3 g/dl in albumin also reduced mortality. In another large study, the NECOSAD study, a decrease of 1 g/dl in serum albumin caused an increased mortality risk of 47% in HD patients and 38% in PD patients (17). In our study, similar to the literature, the mean albumin level was higher ($p=0.006$) and albumin was found to be the most important factor determining patient survival according to the Cox regression analysis performed by the forward selection method. The role of albumin (a negative acute phase reactant) in predicting mortality may be related to malnutrition and inflammation. The mean nPNA value was 1.5 and the mean body mass index value was 26.8 and were considered to be adequate indicators of nutritional status and it was thought that the effect of albumin level on mortality could be related with inflammation. However, since the level of C-reactive protein, which is a strong indicator of inflammation, was not available in all charts, it was not possible to make a definite comment on this issue.

Today, diabetic nephropathy is the main etiological factor in dialysis patients with chronic renal failure. Due to hemodynamic instability and vascular access pathway problems, PD has priority in diabetic patients. Fang et al. found that the most important factor affecting mortality in diabetic patients was age (18). Coronel et al. found that age, type 2 diabetes, and cerebrovascular disease were the determinants of mortality in PD patients according to PD outcomes over 25 years in their center in Spain and reported that type 2 diabetes patients had significantly higher mortality rates than type 1 diabetes patients ($p<0.001$) (19). Age, which is one of the classical mortality markers in dialysis patients, was found to be one of the most important factors determining patient survival according to Cox regression analysis applied by the backward elimination method in our study ($p=0.049$). The mean age of the non-survival group

was significantly higher than that of the living group ($p=0.02$). In studies from both our country and other countries, age was associated with high mortality risk (7, 12, 19).

The main limitation of our study was the enrollment of a low number of patients from a single center because of the gradually decreasing number of PD patients in our country. However, the patients were distributed homogeneously (93.6% CAPD) and the patients were followed up for a long period. Another limitation is the lack of data on C reactive protein at the beginning of the study as an important inflammatory biomarker.

In our study, albumin was found to be the most important factor in predicting patient survival among peritoneal permeability, nPNA, PD modality, weekly total Kt/V, dialysate volume, and ultrafiltration volume on the initial PET.

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