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# Peritoneal dialysis-related peritonitis: an analysis of risk factors in Northeast Anatolia*

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**Aim:** Peritonitis is almost the most frequent complication of peritoneal dialysis (PD). Besides being the most frequent reason of hospitalization, peritonitis is also the most important determining factor of mortality-morbidity and technique survival among PD patients. In this study, it was aimed to identify the risk factors for peritonitis in these patients.

**Materials and methods:** In this clinical cohort, records of 218 patients were collected between January 1998 and December 2007. The patients' demographic, clinical, and laboratory parameters were recorded. Results were analyzed to compare patients who never had peritonitis and patients with at least one episode of peritonitis. Independent predictors of peritonitis were assessed using Cox regression, and the hazard ratio (HR) was determined using 95% confidence interval (95% CI).

**Results:** Of over 6304 patient-months, 337 episodes of peritonitis were observed. The overall peritonitis rate was 0.64 attack/year. The risk of peritonitis was lower for PD patients with each 1 g/dL increase in mean albumin levels (HR, 0.39; 95% CI, 0.24-0.65; $P < 0.001$). Variables identified to be associated with an increased likelihood of peritonitis were: the placement of catheter via surgery (HR, 3.97; 95% CI, 2.16-7.29; $P < 0.001$), constipation (HR, 2.22; 95% CI, 1.26-3.92; $P < 0.01$), and amyloidosis (HR, 1.81; 95% CI, 0.93-3.50; $P = 0.078$).

**Conclusion:** Hypoalbuminemia, constipation, the placement of catheter via surgery, and amyloidosis were found to increase the risk of peritonitis in the present study. Such risk factors should be kept in mind during follow-up of patients under PD.

**Key words:** Peritoneal dialysis, peritonitis, risk factors

## Periton diyalizi ile ilişkili peritonit: Kuzeydoğu Anadolu'da risk faktörlerinin analizi

**Amaç:** Periton Diyalizi (PD), son dönem böbrek yetmezlikli hastaların tedavisinde kullanılan renal replasman tedavi seçeneklerinden biridir. Peritonit, PD'nin en sık görülen komplikasyonlarındandır. PD tedavisinde ve teknolojisinde sağlanan gelişmeler nedeni ile peritonit sıklığında azalma olmasına rağmen peritonit hâlâ sorun olmaya devam etmektedir. Bu çalışmada peritonit gelişmesinde etkili olan risk faktörlerinin araştırılması amaçlanmıştır.

**Yöntem ve gereç:** Bu klinik kohortta, Atatürk Üniversitesi Tıp Fakültesi Nefroloji Bilim Dalı'nda Ocak 1998-Aralık 2007 tarihleri arasında Periton Diyalizi Ünitesi'nde takip edilen toplam 218 hastanın dosyaları retrospektif olarak incelendi. Hastaların demografik, klinik ve laboratuar sonuçları kaydedildi. Hastalar, hiç peritonit geçirmeyenler peritonitsiz grup ve en az bir veya daha fazla peritonit geçirenler peritonitli grup olmak üzere 2 gruba ayrıldı. Peritonitle ilgili risk faktörlerini saptamak için Cox regresyon analizi yapıldı, % 95 güven aralığında (GA) "hazard ratio" (HR: Zararlanma oranı) hesaplandı.

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**Bulgular:** Toplam 6304 periton diyaliz ayında 337 peritonit atağı gözlendi. Ortalama peritonit sıklığı 0.64 atak/yıl olarak bulundu. PD hastalarında ortalama albümin düzeyi artıkça peritonit riski 0.39 kat (% 95 GA 0,24 – 0,65; P < 0,001) azalmaktaydı. PD kataterinin cerrahi yöntemle takılması peritonit riskini 3,97 kat (% 95 GA 2,16 - 7,29; P < 0.001), hastalarda konstipasyon olması 2,22 kat (% 95 GA 1,26 - 3,92; P < 0.01), amiloidozun olması 1,81 kat (% 95 GA 0,93 - 3,50; P = 0,078) artırmaktaydı.

**Sonuç:** Sonuç olarak, bu çalışmada hipoalbüminemi, konstipasyon, PD kateterinin cerrahi yöntemle takılması ve amiloidoz peritonit gelişimi için bir risk faktörü olarak tespit edilmiştir. Bu risk faktörleri hastaların takip edilmesinde göz önünde bulundurulmalıdır.

**Anahtar sözcükler:** Periton diyalizi, peritonit, risk faktörleri.

## Introduction

Peritoneal dialysis (PD) is an established treatment modality in end-stage renal disease (ESRD) patients and 150,000 patients are being maintained on PD worldwide (1). Peritonitis is one of the most common complications of PD. Peritonitis, once the most feared complication of PD treatment, remains an issue although there has been a reduction in the incidence rate with recent advances in PD treatment and technologies (2). Besides being the most frequent cause of hospitalization in patients receiving PD, peritonitis is also among the major factors leading to catheter loss and initiating hemodialysis therapy. In addition, peritonitis induces dysfunction in the peritoneal membrane, adversely affecting PD survival and leading to rapid loss of residual renal functions in the long term. Thus, peritonitis seems to be the most important determinant of mortality, morbidity, and technique survival in PD patients (3–5). Rates of peritonitis vary significantly, both among countries and among centers in the same country. This variability may be due to patients' age, gender, race, genetics, educational status, and geographical factors, and may also be associated with peritoneal dialysis materials and the level of training provided by centers to both patients and their staff (6). Therefore, each center should establish its own risk profile and develop strategies accordingly.

In this study, we aimed to investigate the risk profile of patients with peritonitis in Eastern Anatolia and to identify relevant measures in its prevention. As our PD center serves to a wide area and the study includes patients from this wide geographical region, we are of the opinion that the results obtained in the present study will provide significant guidance in determining strategies related with the risk factors of peritonitis.

## Patients and methods

Our PD center is located in the Eastern Anatolia and serves as a reference center in this area. Consecutive patients initiating PD from January 1998 to December 2007 were analyzed in this clinical cohort study. All procedures followed the tenets of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of Atatürk University.

All patients followed by the PD unit of the Atatürk University Nephrology Department were included in the study. Patients below 18 years of age at the time when PD was started and those with inadequate compliance to the follow up schedule (maximum follow up interval requested was 3 months) were all excluded from the study. As a result, a total of 218 patients were included.

The patients were divided into 2 groups. The peritonitis-free group included those who did not experience a peritonitis attack, and the peritonitis group included patients with at least one episode of peritonitis during the treatment period. The diagnosis of peritonitis-complicated PD was based on at least 2 of the following criteria: abdominal pain or cloudy PD effluent, leukocytosis in peritoneal fluid effluent (leukocyte count at least 100/mm$^3$), positive Gram stain or culture of effluent (7). Treatment of peritonitis in all patients was based on the ISPD guidelines (7–9). Analyses of cultures collected from all peritonitis cases and other microbiologic tests were carried out at the Microbiology Laboratory of Atatürk University Faculty of Medicine.

The twin-bag system was employed in all patients and different kinds of PD fluid (Baxter Healthcare and Fresenius Medical Care) were used. Whether the

patient had undergone HD, whether the patient could perform PD alone or with assistance, as well as the use of PD solutions (standard glucose solutions, solutions containing icodextrin, and low-calcium solutions), and the type of PD [continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD)] were documented before initiating PD. It was also determined whether the PD catheter was inserted via open surgical technique or percutaneous Seldinger technique. All patients had undergone cefazolin prophylaxis before attaching the catheters.

ESRD and accompanying diseases were documented. Patients' hepatitis indicators (HBsAg and Anti-HCV) were recorded from their files. Patients were evaluated for constipation at each follow up visit and those with less than 3 bowel movements per week as well as those using laxatives for constipation were considered to have constipation (10).

Patients were categorized according to their educational status as follows: those with high school or university degrees were classified as "high school and above" while others were referred to as "pre-high school". Patients living in an area with a population less than 20,000 were categorized as rural residents and those living in areas with a population 20,000 and above were classified as urban residents (11). Patients' age, sex, body surface area (BSA), and body mass index (BMI) were obtained from their files.

Findings of blood-urea nitrogen (BUN), serum creatinine (Cr), albumin, ferritin, and blood hemoglobin (Hb) were recorded taking the average of all recordings. All laboratory and other data were recorded at the entry visit and then at each follow up visit with an interval of 2-3 months. Values during periods with peritonitis were excluded from the analyses.

Adequacy of dialysis was estimated by measurement of weekly Kt/V for urea and normalized protein nitrogen appearance (nPNA), using standard methods. The transport property of the peritoneal membrane was determined by the standard peritoneal equilibration test.

**Statistical analyses**

Data are presented as frequencies, percentages, means, and standard deviations (SD). Statistical analyses were carried out using SPSS 11.5 for Windows. Student's t test for numeric variables and the Chi-square test for categorical variables were used to compare the 2 groups. Parameters yielding significance at the level of $P < 0.2$ in the univariate analysis were subjected to the Cox regression analysis model to identify risk factors for peritonitis. The backward elimination method was used for Cox regression analysis and the hazard ratio was estimated based on a 95% confidence interval. The level of significance was set to $P < 0.05$.

## Results

The mean age of the subjects was 47.9 ± 17.0 years. One hundred and ten (50.5%) of the patients were females and 108 (49.5%) were males. Of them, 50.5% were living in rural areas and only 17.4% had an educational level of high school and above. Table 1 details the baseline characteristics of 218 patients. The causes of ESRD included diabetes mellitus (24.8%), chronic interstitial nephritis (22.5%), glomerulonephritis (13.3%), hypertension (12.4%), amyloidosis (11.0%), polycystic kidney disease (5.5%), unknown (7.8%), and other (2.8%).

The patients were followed-up with a mean duration of 28.0 ± 17.9 months. In 218 patients enrolled, 337 peritonitis attacks were observed during a total of 6304 patient-months. The mean frequency of peritonitis was 0.64 attacks/year. Staphylococcus coagulase-negative (39.2%) was the most common causative organism (Table 2).

Patients were classified as peritonitis-free (n = 61) and peritonitis group (n = 157). Table 1 presents the differences between these 2 groups and provides a univariate comparison of the patients' demographic, clinical, and laboratory findings. Peritonitis was significantly more frequent in patients with pre-high school educational levels ($P = 0.011$), amyloidosis (borderline significance, $P = 0.07$), constipation ($P = 0.002$), undergoing HD before PD ($P = 0.007$), and requiring assistance to perform PD ($P = 0.05$). Kt/V urea and albumin values were significantly lower in the group of patients with peritonitis ($P = 0.04$ and $P < 0.001$, respectively). Albumin levels of patients with amyloidosis (2.94 ± 0.59 g/dL) were significantly lower than those without amyloidosis (3.18 ± 0.56 g/dL) ($P = 0.047$).

Table 1. Comparison between peritonitis-free and peritonitis group.

| | **Peritonitis-free (n=61)** | **Peritonitis (n=157)** | **P** |
|---|---|---|---|
| Age (years) | 46.5 ± 15.2 | 48.5 ± 17.7 | 0.5 |
| Follow-up duration (months) | 28.0 ± 17.9 | 29.3 ± 19.0 | 0.7 |
| Peritonitis-free time (months) | 28.0 ± 17.9 | 12.24 ± 13.05 | **0.000** |
| Gender (male/female) | 31(50.8%)/30(49.2%) | 77(49%)/80(51%) | 0.8 |
| BMI (kg/m$^2$) | 24.01 ± 5.16 | 23.47 ± 4.81 | 0.5 |
| BSA (m$^2$) | 1.67 ± 0.20 | 1.66 ± 0.24 | 0.6 |
| Living in (rural:urban) areas | | | |
| rural | 24 (39.3%) | 84 (53.5%) | 0.06 |
| urban | 37 (60.7%) | 73 (46.5%) | |
| Educational status | | | |
| Pre-high school | 44 (72.1%) | 136 (86.6%) | **0.011** |
| High school and above | 17 (27.9%) | 21 (13.4%) | |
| Comorbidities | | | |
| Diabetes mellitus | 16 (26.2%) | 38 (24.2%) | 0.7 |
| Hypertension | 50 (82%) | 121 (77.1%) | 0.4 |
| HBsAg (positivity) | 3 (4.9%) | 9 (5.7%) | 0.8 |
| Anti-HCV (positivity) | 4 (6.6%) | 11 (7%) | 0.9 |
| Amyloidosis | 3 (4.9%) | 21 (13.4%) | 0.07 |
| Constipation | 2 (3.3%) | 31 (19.7%) | **0.002** |
| Dialysis type | | | |
| APD | 6 (9.8%) | 23 (14.6%) | 0.4 |
| CAPD | 55 (90.2%) | 134 (85.4%) | |
| PD with assistance | 15 (24.6%) | 60 (38.2%) | 0.05 |
| HD before PD | 30 (49.2%) | 108 (68.8%) | **0.007** |
| PD catheter placement | | | |
| Percutaneous | 25 (41%) | 48 (30.6%) | 0.1 |
| Surgical | 36 (59%) | 109 (69.4%) | |
| PD solutions | | | |
| Standard | 45 (73.8%) | 121 (77.1%) | 0.4 |
| Icodextrin | 12 (19.7%) | 32 (20.4%) | |
| Low-calcium | 4 (6.6%) | 4 (2.5%) | |
| Hemoglobin (g/dL) | 10.65 ± 2.00 | 10.30 ± 1.96 | 0.2 |
| Ferritin (ng/mL) | 397.70 ± 346.81 | 461.39 ± 398.46 | 0.3 |
| BUN (mg/dL) | 49.06 ± 14.19 | 49.98 ± 16.22 | 0.7 |
| Serum Cr (mg/dL) | 7.79 ± 2.71 | 7.49 ± 2.53 | 0.4 |
| Serum Albumin (g/dL) | 3.42 ± 0.40 | 3.05 ± 0.60 | **0.000** |
| Weekly total Kt/V urea | 2.67 ± 1.11 | 2.30 ± 0.78 | **0.04** |
| CrCl (L/week/1.73 m$^2$) | 95.46 ± 55.69 | 83.49 ± 56.27 | 0.2 |
| GFR (L/week/1.73 m$^2$) | 32.52 ± 18.95 | 25.74 ± 23.61 | 0.2 |
| nPNA (g/kg/day) | 1.37 ± 1.04 | 1.11 ± 0.64 | 0.1 |
| Mean D/P creatinine | 0.69 ± 0.10 | 0.71 ± 0.13 | 0.5 |

APD: Automated peritoneal dialysis, BMI: Body mass index, BSA: Body surface areas, BUN: Blood-urea nitrogen, CAPD: Continuous ambulatory peritoneal dialysis, Cr: Creatinine, CrCl: Creatinine clearance, D/P: Dialysate-to- plamsa ratio, GFR: Glomerular filtration rate, nPNA: Normalized protein nitrogen appearance.

Table 2. Micro-organisms in patients with peritonitis.

| **Causative organisms** | **n (%)** |
|---|---|
| Gram-positive organisms | |
| Coagulase-negative staphylococcus | 132 (39.2%) |
| *Staphylococcus aureus* | 21 (6.2%) |
| Alpha-hemolytic streptococci | 17 (5.0%) |
| Non-hemolytic streptococci | 7 (2.1%) |
| *Streptococcus pneumoniae* | 6 (1.8%) |
| *Enterococcus* sp. | 3 (0.9%) |
| Other | 4 (1.2%) |
| Gram-negative organisms | |
| *Escherichia coli* | 20 (5.9%) |
| *Enterobacter* sp. | 14 (4.2%) |
| *Pseudomonas aeruginosa* | 7 (2.1%) |
| Other | 7 (2.1%) |
| *Candida* sp. | 7 (2.1%) |
| *Mycobacterium tuberculosis* | 6 (1.8%) |
| Culture negative | 86 (25.5%) |
| Total | 337 (100.0%) |

### Multivariate analysis

Results with P values less than 0.2 in univariate analysis related to peritonitis development (serum albumin level, constipation, HD prior to PD, educational level, Kt/V urea, person performing PD, place of residence, amyloidosis, and nPNA) were evaluated using Cox regression analysis as a multivariate analysis. Mean serum albumin level, chronic constipation, surgical insertion of the PD catheter, and presence of amyloidosis were identified as the risk factors with multivariate analysis.

Table 3 demonstrates the results of the multivariate analysis (Cox regression analysis). The risk of peritonitis was lower for PD patients with each 1 g/dL increase in mean albumin levels (HR, 0.39; 95% CI, 0.24-0.65; P < 0.001). The risk of peritonitis increased 3.97-fold (95% CI 2.16–7.29; P < 0.001) with surgical insertion of the PD catheter, while presence of constipation increased the risk 2.22 fold (95% CI 1.26–3.92; P < 0.01) and amyloidosis 1.81-fold (95% CI 0.93–3.50; P = 0.078).

## Discussion

The results of the present study demonstrate the increased risk of developing peritonitis with hypoalbuminemia, constipation, surgical insertion of dialysis catheter, and presence of amyloidosis.

Several studies have associated decreased albumin levels with increased mortality and morbidity (12,13). A study by Young et al. (14) reported an increased frequency of peritonitis and longer hospitalization periods in CAPD patients with lower levels of serum albumin. The authors associated this with impairments in the humoral mechanisms. A similar study by Spiegel et al**.** (15) demonstrated increases in the frequency of hospitalization in patients with low serum albumin levels. Prasad et al. (16) identified a significant relationship between serum albumin levels and peritonitis attacks, and described serum albumin level as an important indicator of peritonitis development. A multi-center prospective study by the CANUSA Peritoneal Dialysis Study Group (17) demonstrated a negative relationship between serum albumin concentrations and mortality, technique survival, and hospitalization. In studies categorizing PD patients into peritonitis-free and peritonitis

Table 3. Multivariate Cox regression analysis showing factors associated with dialysis-related peritonitis.

| | HR (95% CI) of developing peritonitis | *P* |
|---|---|---|
| Serum albumin (per 1 g/dL increase) | 0.39 (0.24-0.65) | 0.000 |
| PD catheter placement (via surgery) | 3.97 (2.16-7.29) | 0.000 |
| Constipation | 2.22 (1.26-3.92) | 0.006 |
| Amyloidosis | 1.81 (0.93-3.50) | 0.078 |

CI: confidence interval, HR: Hazard ratio.

groups (16,18,19), albumin levels of patients in the peritonitis group were lower, similar to the results of our study. The multivariate analysis of the present study demonstrated a significant reduction in the risk of developing peritonitis with increased levels of serum albumin. Increased risk of developing peritonitis with hypoalbuminemia may be associated with a compromised immune response as a result of hypoalbuminemia and malnutrition (14,16).

The efficiency of PD catheters depends on their insertion technique rather than their design (20). In a retrospective study evaluating outcomes of PD patients, Ozener et al. (21) observed significantly decreased frequency of peritonitis in patients who were catheterized using the percutaneous technique compared to those who underwent surgical catheterization. However, Roueff et al. (22) noted no significant differences between these 2 techniques in terms of peritonitis. A meta-analysis by Ash (20) of 70 trials evaluated complications associated with catheterization and reported a frequency of 24% for catheter-related infections with the percutaneous method, while the frequency was 35% with surgical catheterization. In our study, the multivariate analysis showed a 3.97-fold increase in the risk of developing peritonitis with the surgical method. The lower risk of peritonitis with the percutaneous method may be associated with the smaller incision area and less muscular and peritoneal trauma as mentioned by Ash (20). Long term controlled studies are needed in order to make stronger deductions in this issue.

Constipation develops in PD patients due to decreased fiber content in consumed foods, reduced liquid intake, electrolyte imbalance, phosphate binders containing aluminum, and calcium and iron preparations. Decreased activity and underlying diseases in these patients also contribute to constipation (23). In our study, the multivariate analysis demonstrated a 2.22-fold increase in the risk of developing peritonitis in the presence of constipation. Singharetnam et al. (24) evaluated PD patients hospitalized for non-peritonitis reasons and reported the occurrence of peritonitis within 48 h in 5 patients with a history of chronic constipation who had received laxatives after admission. They associated this with irritation and infection of the peritoneal membrane due to transmural migration of enteric microorganisms caused by rapid treatment of constipation. Suh et al. (25) reported endogenous peritonitis in 15 of 192 PD patients, and identified that 11 had severe constipation prior to peritonitis. All our subjects received oral treatment for constipation. Occurrence of peritonitis in patients with constipation may be due to transmural migration of enteric microorganisms during constipation treatment, whereas it may also be associated with increased penetration of enteric microorganisms resulting from decreased intestinal flow. We thought that more comprehensive prospective studies are required to elucidate this issue.

In a study comparing outcomes of PD patients with and without amyloidosis, Altiparmak et al. (26) noted no significant differences between these 2 patient groups in terms of peritonitis. A further study by Sahin et al. (27) comparing PD patients and HD patients with amyloidosis reported more frequent infections in PD patients, most of which were peritonitis. In our study, the multivariate analysis of patients with amyloidosis regarding occurrence of peritonitis demonstrated a 1.81-fold increase in the risk of developing peritonitis (borderline significance). However, other systemic effects and hypoalbuminemia in patients with amyloidosis may be considered as significant factors regarding infection susceptibility.

Diabetes mellitus is one of primary causes of renal failure in patients undergoing renal replacement therapy due to ESRD worldwide (28). Conflicting data have been reported regarding differences between diabetic and non-diabetic patients in terms of incidence of peritonitis. Some studies with PD patients have reported diabetes mellitus as a risk factor for peritonitis (18,19,29), and this has been associated with compromised immune response in the defense system of the peritoneum in PD patients with diabetes mellitus (18). In some large studies, on the other hand, diabetes mellitus was not described as a risk factor for developing peritonitis (30,31). In accordance with the above findings, diabetes mellitus was not found to be a risk factor for peritonitis in our study.

In conclusion, our study demonstrated that hypoalbuminemia, constipation, surgical insertion of the dialysis catheter, and presence of amyloidosis were risk factors for developing peritonitis in PD patients.

Prevention and treatment of hypoalbuminemia in PD patients is important in minimizing the potential risk of peritonitis. Percutaneous placement of the PD catheter seems to be a safe and advantageous method. Associated with less trauma and lower incidence of peritonitis, the percutaneous technique should be used for patients wherever applicable. Preventing constipation, maintaining a balanced diet, and ensuring liquid-electrolyte balance are important in preventing the risk of peritonitis in PD patients. Monitoring the patients closely against possible occurrence of peritonitis, particularly in those with amyloidosis, should be considered. Further prospective studies are needed to support our findings. We suggest each PD center study their own risk factors and develop appropriate strategies.

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