



Clinical outcomes in peritoneal dialysis with refractory peritonitis: significance of the day 5 cell count

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Abstract

Background Peritoneal dialysis-associated peritonitis is a common and severe complication of peritoneal dialysis, associated with high morbidity and mortality. However, there's a lack of research on refractory peritonitis, which is difficult to manage and has a poor prognosis. Our study aimed to investigate factors affecting clinical outcomes in peritoneal dialysis patients with refractory peritonitis over a 12-year period at a medical faculty hospital in Turkey.

Methods We conducted a retrospective study at a single center from January 2009 to December 2020, involving 135 patients with 236 episodes of refractory peritonitis. The average age of the patient cohort was 53.0 ± 15.9 years, and 72 (53.4%) of the patients were male. The leading identified causes of end-stage kidney disease were glomerulonephritis, hypertensive glomerulosclerosis, and diabetic nephropathy. Data on microbiological etiology, dialysate white blood cell counts, and patient demographics were analyzed to identify catheter removal risk factors. Statistical significance was set at $p \leq 0.05$.

Results Comparative analysis between patients with and without catheter loss revealed no significant differences in gender, age, presence of diabetes, prior hemodialysis, or duration of peritoneal dialysis. However, multivariate logistic regression analysis showed that a dialysate white blood cell count exceeding $1000/\text{mm}^3$ on day 5 and hospitalization had a positive association with catheter loss, while the presence of gram-positive bacterial growth had an inverse correlation.

Conclusion Our study shows that fifth-day dialysate white blood cell count predicts refractory peritonitis outcomes. Future research should focus on developing tools to manage catheter removal proactively and enhance patient prognosis.

Keywords Peritoneal dialysis · Refractory peritonitis · End-stage kidney disease

Introduction

Peritoneal dialysis-associated peritonitis is a common and serious infectious complication linked to increased morbidity and mortality among peritoneal dialysis (PD) patients. It accounts for over 15% of PD patient deaths and is the leading cause of transitioning to hemodialysis, thereby escalating treatment costs and hospitalizations. [1, 2]. Peritonitis episode with persistently cloudy bags or persistent dialysate white blood cell count $> 100 \times 10^9/\text{L}$ after 5 days of appropriate antibiotic therapy was defined as refractory peritonitis [3]. Severe, refractory, and prolonged peritonitis can cause alterations in the peritoneal membrane, resulting in dialysis inefficiency and increasing the risk

of encapsulating peritoneal sclerosis. Early diagnosis and prompt antibiotic therapy are crucial for effective treatment. However, even with timely and appropriate antibiotic treatment, approximately 20% of peritonitis cases may become refractory [3]. Catheter removal is typically recommended for refractory peritonitis, although some centers may opt for continued antibiotic therapy in certain cases, even if the desired dialysate white blood cell count is not achieved by the fifth day [3].

Despite some identified factors associated with refractory PD-related peritonitis, the literature lacks comprehensive insights into the prognostic determinants of this condition. This study aims to examine the factors influencing clinical outcomes among PD patients with refractory peritonitis within a 12-year cohort at a medical faculty hospital in Turkey [4].

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Methods

We conducted a single-center retrospective study focusing on PD patients diagnosed with refractory peritonitis from January 2009 to December 2020. This study analyzed a total of 236 episodes of refractory peritonitis in 135 patients, with approval from the institutional ethics committee (protocol number: 09.2021.35) and in compliance with the Declaration of Helsinki. All participants provided written informed consent. The definition of refractory peritonitis adhered to the 2016 recommendations provided by the International Society for Peritoneal Dialysis (ISPD), which were the latest available guidelines at the time of the research[5].

The study enrolled patients aged 18 or older who had been undergoing peritoneal dialysis (both continuous ambulatory peritoneal dialysis and automated peritoneal dialysis) for more than 3 months and had experienced an episode of refractory peritonitis. Patients with incomplete medical records were excluded. Data on each patients' medical history, demographics, clinical presentation, and the characteristics and outcomes of their refractory peritonitis episodes were collected from medical records.

Institutional policy for treatment of peritonitis and catheter removal

At our institution, patients are initially treated with intraperitoneal cefuroxime axetil and oral ciprofloxacin upon presentation to address both gram-positive and gram-negative organisms. This treatment is continued for 72 hours. If the patient does not respond, second-line antibiotics such as vancomycin and meropenem are administered. These antibiotics are continued until the results of cultures are reported, and the treatment is then modified accordingly. For cases of culture-negative peritonitis, empirical therapy is maintained to cover both gram-positive and gram-negative organisms. Second-line antibiotics and IV therapy are initiated for patients exhibiting severe symptoms or experiencing sepsis. Additionally, all patients with a prolonged course of antibiotics are prescribed prophylactic oral fluconazole.

Statistical analysis

The study presented categorical variables as percentages and frequencies, and continuous variables as means \pm standard deviations or ranges. Patient characteristics at baseline were assessed using Fisher's exact test and the Pearson chi-square test. Possible

risk factors for catheter removal were analyzed using univariate and multivariate logistic regression analyses. A p value of ≤ 0.05 was considered statistically significant. Statistical analyses were conducted using IBM Statistical Package for Social Sciences (SPSS) Version 25.

Results

The study analyzed 236 cases of refractory peritonitis in 135 patients undergoing peritoneal dialysis. The patients had an average dialysis duration of 38.2 ± 41.2 months, ranging from three to 180 months. The mean age of the patient cohort was 53 ± 15.9 years, with a slight male predominance (53.4%). In descending order, the most prevalent identified causes of end-stage kidney disease were glomerulonephritis (20%), hypertensive glomerulosclerosis (19.3%), and diabetic nephropathy (17.8%) (Table 1).

On the fifth day, dialysate white blood cell counts were equal to or greater than $1000/\text{mm}^3$ in 44.5% of the episodes, between 300 and $1000/\text{mm}^3$ in 19.9% of the episodes, and between 101 and $300/\text{mm}^3$ in 35.6% of the episodes. Of all refractory peritonitis episodes, 25% required hospitalization. Gram-positive, gram-negative, and culture-negative infections accounted for 44.1%, 20.4%, and 30.8% of all peritonitis episodes, respectively. Peritoneal fluid culture data was unavailable for 25 episodes.

In our study, 47 (34.8%) patients required catheter removal, and 2 (1.5%) patients died due to peritonitis-related complications. Upon analysis of patients with and without catheter loss, no statistically significant differences were observed in terms of gender, age, presence of diabetes, prior hemodialysis, or duration of peritoneal dialysis, as shown in Table 1. However, when comparing peritonitis episodes with and without catheter loss, those necessitating catheter removal exhibited higher mean 5th day dialysate white blood cell count (3621.3 ± 3144.1 vs 1589.4 ± 2316.6 cells/ mm^3 ; $p < 0.001$), a higher prevalence of episodes with a white cell count exceeding 1000 cells/ mm^3 (72.3% vs 37.6%, $p < 0.001$) on the 5th day, gram-negative bacterial-associated peritonitis (31.9% vs 14.8%, $p = 0.012$), *Pseudomonas* peritonitis (14.9 vs 1.6%, $p = 0.001$), fungal peritonitis (10.6% vs 0%, $p < 0.001$), and increased rates of hospitalization (53.2% vs 18.0%, $p < 0.001$). Additionally, peritonitis episodes not necessitating catheter removal were characterized by dialysate white blood cell count below 300 cells/ mm^3 (8.5% vs 42.3%, $p < 0.001$) on the 5th day and gram-positive bacterial presence (21.3% vs 43.9%, $p = 0.002$) (Table 2).

We have made a ROC curve analysis to describe a cut-off of white blood cell count in the dialysate on the 5th day. The ROC curve analysis showed the 5th day dialysate white blood cell count $\geq 1000/\text{mm}^3$ predicted catheter removal

Table 1 Demographic characteristics of the patients according to catheter loss

	Patients (n = 135)(%)	Catheter loss (+) (N=47)	Catheter loss (-) (N=88)	p value
Mean age, years	53.0±15.9	53.4±16.2	52.8±15.8	0.853
Female, n(%)	63 (46.6%)	21 (44.6%)	42(47.7%)	0.735
Diabetes mellitus, n (%)	27 (20.0%)	6 (12.7%)	21 (23.8%)	0.117
Prior hemodialysis, n (%)	54 (40.0%)	20 (42.5%)	34 (38.6%)	0.735
Mean duration of PD, months	38.2±41.2	39.5±35.8	37.4±44.0	0.772
Primary kidney disease, n (%)				
Glomerulonephritis	27 (20%)	7 (14.9%)	20 (22.7%)	
Hypertension	26 (19.3%)	9 (19.1%)	17 (19.3%)	
Diabetic kidney disease	24 (17.8%)	6 (12.8%)	18 (20.5%)	
Polycystic kidney disease	10 (7.4%)	5 (10.6%)	5 (5.7%)	
Vesicoureteral reflux	6 (4.4%)	3 (6.4%)	3 (3.4%)	
Nephrolithiasis	5 (3.7%)	3 (6.4%)	2 (2.3%)	
Other	4 (3.0%)	1 (2.1%)	3 (3.4%)	
Unknown	33 (24.4%)	13 (27.7%)	20 (22.7%)	
Number of refractory episodes, n (%)				0.501
1	83 (61.5%)	24 (51.1%)	59 (67.1%)	
2	30 (22.2%)	14 (29.8%)	16 (18.2%)	
3	9 (6.7%)	3 (6.4%)	6 (6.8%)	
4	6 (4.4%)	2 (4.3%)	4 (4.5%)	
5	2 (1.5%)	1 (2.1%)	1 (1.1%)	
6	3 (2.2%)	2 (4.3%)	1 (1.1%)	
7	2 (1.5%)	1 (2.1%)	1 (1.1%)	
Mortality	2 (1.5%)	1 (2.1%)	1 (1.1%)	0.657

Table 2 Episode characteristics according to catheter loss

	Loss (+) (n=47)	Loss (-) (n=189)	p value
Mean 1st day cell count, /mm ³	4759.6 ± 3097.8	4769.3 ± 3106.5	0.985
Mean 5th day cell count, /mm ³	3621.3 ± 3144.1	1589.4 ± 2316.6	<0.001
5th day cell count range			
101–300 /mm ³	4 (8.5%)	80 (42.3%)	<0.001
≥300–1000 /mm ³	9 (19.1%)	38 (20.1%)	1.000
≥1000 /mm ³	34 (72.3%)	71 (37.6%)	<0.001
Culture			
Bacteria			
Gram (+) bacteria	28 (59.6%)	113 (59.8%)	0.856
Gram (-) bacteria	10 (21.3%)	83 (43.9%)	0.002
Microorganism	15 (31.9%)	28 (14.8%)	0.012
Pseudomonas spp	7 (14.9%)	3 (1.6%)	0.001
Fungi (Candida)	5 (10.6%)	0 (0%)	<0.001
Hospitalization, n (%)	25 (53.2%)	34 (18.0%)	<0.001

Bold was used to highlight the statistically significant p values

with 72.3% sensitivity and 65.6% specificity (Area under the curve: 0.739, CI:0.662–0.816, *p* < 0.001) (Fig. 1).

We further evaluated the percentage of the decline of the dialysate white blood cell count from day 1 to day 5 and analysed the associations between the outcomes. Patients

with hospitalization (40.28 ± 37.91 vs 65.68 ± 34.63%, *p* < 0.001), catheter loss (35.18 ± 39.12 vs 65.34 ± 34.08%, *p* < 0.001) as well as the combined outcome (34.13 ± 39.09 vs 65.60 ± 33.85%, *p* < 0.001) had lower rates of decline in dialysate white blood cell count (Table 3). The mortality

5th day white cell count in PD patients with catheter removal

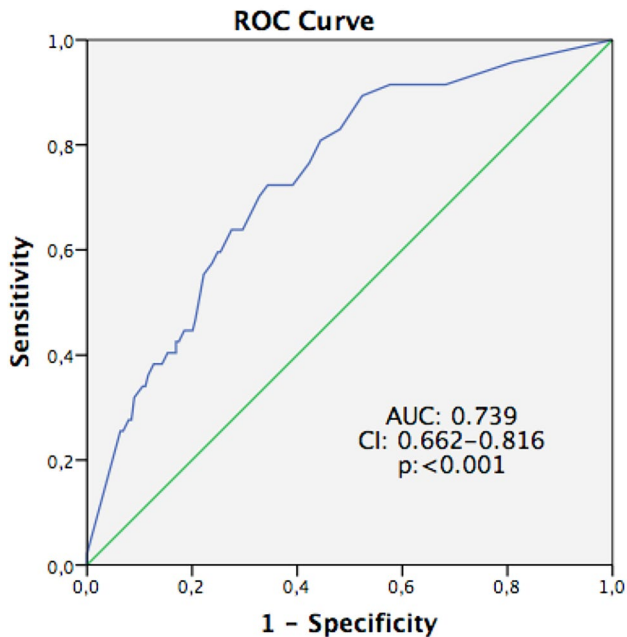


Fig. 1 5th day dialysate white cell count in PD patients with catheter removal

Table 3 Correlations between outcomes and the percentage rate of decline in dialysate white blood cell count from day 1 to day 5

	Percentage decline rate (%)	<i>p</i> value
Hospitalization		< 0.001
Yes (<i>n</i> = 59)	40.28 ± 37.91	
No (<i>n</i> = 177)	65.68 ± 34.63	
Catheter loss		< 0.001
Yes (<i>n</i> = 47)	35.18 ± 39.12	
No (<i>n</i> = 189)	65.34 ± 34.08	
Mortality		0.161
Yes (<i>n</i> = 2)	95.96 ± 3.13	
No (<i>n</i> = 234)	59.02 ± 37.07	
Combined outcome		< 0.001
Yes (<i>n</i> = 47)	34.13 ± 39.09	
No (<i>n</i> = 189)	65.60 ± 33.85	

Bold was used to highlight the statistically significant *p* values

rate did not reach statistical significance since there were only two deaths.

We conducted a comparison between peritonitis episodes with dialysate white blood cell count exceeding and those below 1000 cells/mm³ on the 5th day. Episodes with dialysate white blood cell count surpassing 1000 cells/mm³ exhibited a higher prevalence of gram-negative bacterial

Table 4 Episode characteristics according to 5th day cell count

	> 1000	< 1000	<i>p</i> value
Age	52.4 ± 15.5	53.2 ± 16.0	0.685
Culture	75 (78.9%)	71 (61.2%)	
Bacteria	70 (74.4%)	71 (61.2%)	0.055
Gram (+) bacteria	37 (39.3%)	56 (48.2%)	0.211
Gram (-) bacteria	28 (29.7%)	15 (12.9%)	0.003
Pseudomonas spp	8 (7.6%)	2 (1.5%)	0.068
Fungi (Candida)	4 (4.2%)	1 (0.8%)	0.175
Hospitalization, <i>n</i> (%)	44 (41.9%)	15 (11.4%)	< 0.001
Catheter Removal, <i>n</i> (%)	33 (31.4%)	14 (10.6%)	< 0.001
Recurrent peritonitis, <i>n</i> (%)	2 (1.9%)	4 (3.1%)	0.695
Relapsing peritonitis, <i>n</i> (%)	2 (1.9%)	6 (4.6%)	0.305

Bold was used to highlight the statistically significant *p* values

presence (29.7% vs 12.9%; *p* = 0.003), hospitalization (41.9% vs 11.4%; *p* < 0.001), and catheter loss (31.4% vs 10.6%; *p* < 0.001) (Table 4). Furthermore, a white blood cell count exceeding 1000 on the 5th day and hospitalization demonstrated positive associations with catheter loss, while the presence of gram-positive bacterial growth exhibited an inverse correlation. Multivariate logistic regression analysis adjusting for bacterial organisms, age, sex, presence of DM and PD duration further confirmed that the dialysate white blood cell count and gram (+) bacteria were still associated with catheter loss. The results are presented in Table 5.

Discussion

This study examined 12 years of patient data from a single center to elucidate the association between different features of refractory peritonitis and technical survival and mortality. Our study demonstrated a statistically significant association between catheter loss and the dialysate white blood cell count on the 5th day. Furthermore, cases of refractory peritonitis with gram-positive bacterial growth had a lower risk for technical loss.

Thamishetti et al.[6] retrospectively analyzed data from patients with refractory CAPD peritonitis. In their study, focusing exclusively on patients with refractory peritonitis, a notably high rate of technical loss (85 out of 90 patients) and 5 patient fatalities preceding catheter removal were reported. In contrast, our study, comprising 135 patients, observed a substantially lower technical loss rate (47 patients) with only 2 patient deaths attributed to peritonitis. The heightened incidence of technical loss and mortality in the aforementioned study may be attributed to the identification of fungal growth in 34 out of 93 cases, alongside predominantly gram-negative bacteria as the causative microorganisms in other instances. Additionally,

Table 5 Multivariate Logistic Regression Analysis

A. Non-adjusted correlating factors for catheter loss		
	Exp(B) 95% CI	<i>p</i> value
≥ 1000 /mm ³ 5th day cell count	2.275 (1.022–5.062)	0.044
Hospitalization	3.809 (1.727–8.401)	0.001
Gram (+) bacteria	0.421 (0.185–0.957)	0.039
B. Adjusted correlating factors for catheter loss		
	Exp(B) 95% CI	<i>p</i> value
Age	1.012 (0.987–1.039)	0.343
Male gender	1.080 (0.851–3.806)	0.124
Duration of peritoneal dialysis	1.003 (0.994–1.012)	0.563
Presence of diabetes mellitus	0.347 (0.110–1.097)	0.072
≥ 1000 /mm ³ 5 th day cell count	3.480 (1.622–7.464)	0.001
Gram (+) bacteria	0.298 (0.131–0.677)	0.004

Bold was used to highlight the statistically significant *p* values

the potentially increased dialysate white blood cell count on the fifth day might have contributed to the adverse prognosis, although data regarding fifth-day white blood cell counts were unavailable. Our findings also suggest an association between the presence of gram-negative bacteria and fungal growth, and technical loss, aligning with prior research on peritonitis related to peritoneal dialysis[7–9]. On the contrary, the presence of gram-positive bacteria was associated with lower rates of technical loss, irrespective of other variables in our study.

Multiple studies have analyzed the impact of dialysate white blood cell count on prognosis in PD-related peritonitis. Nochaiwong et al. [10] showed that dialysate white blood cell counts of > 1000/mm³ and > 100 mm³ on days 3–4 and 5, respectively, were predictors of treatment failure in patients with peritonitis. Notably, and in line with our findings, the most significant predictor was the dialysate white blood cell count on day 5. Similarly, Chow et al.'s [11] study of 595 peritonitis cases, a peritoneal dialysate white blood cell count cut-off of > 1090/mm³ on day 3 carried a nine-fold increase in the risk of treatment failure, irrespective of conventional host and bacterial risk factors. Tantiyavarong et al. [12] examined response patterns by tracking changes in dialysate white blood cell counts during the first five days of initial antibiotic treatment. Early response was defined by clinical improvement with dialysate white blood cell count below 100 cells/mm³ within five days of treatment. Delayed response was determined if the white blood cell count in the dialysate gradually decreased, but still remained above 100 cells/mm³ after five days of successful antibiotic treatment. The study suggests that if the rate of white blood cell reduction in the dialysate is approximately 34% (95% CI, 30.7–37), clinicians can adopt a wait-and-see approach instead of immediately removing the peritoneal

dialysis catheter. Conversely, in the same article, if the rate of white blood cell count decline in the dialysate is less than 14.2%, it indicates antibiotic treatment failure. In our study, a ROC curve analysis to determine a cut-off for the percentage decrease in dialysate white blood cell count from day 1 to day 5 showed low sensitivity and specificity. In contrast, the absolute dialysate white blood cell count on day 5 exhibited a stronger association with the endpoints compared to the decrease rate. While our study results align with previous research, it is unique in that it exclusively included PD patients with a persistent dialysate white blood cell count on day 5. Close monitoring of dialysate white blood cell count and culture growths can help identify risk factors in refractory peritonitis cases, which have higher mortality and hospitalization rates. Thus, withdrawing the peritoneal catheter earlier could potentially reduce adverse peritonitis outcomes.

The influence of variables like age and gender on peritonitis prognosis remains disputable. Some studies have linked comorbidities such as DM with a negative prognosis of peritonitis[13–15]. Nevertheless, this research on refractory peritonitis patients demonstrated no significant impact of these factors on prognosis. The exclusion of blood glucose monitoring and markers reflecting diabetes regulation like HbA1c from our study possibly hindered the significance of our result.

There are several limitations to this study. Primarily, despite its extensive sample size, it remains a retrospective and observational analysis. Key laboratory parameters that could potentially forecast peritonitis severity, such as serum white blood cell count and levels of inflammatory markers, were not included. Nevertheless, it stands as the most comprehensive investigation of refractory peritonitis documented in current literature.

In conclusion, our results highlight the significance of the fifth-day dialysate white blood cell count as a valuable prognostic tool for predicting outcomes in refractory peritonitis cases. Future research should focus on devising prediction models to guide catheter removal decisions and enhance prognostic accuracy for peritonitis patients. This subset poses a significant challenge in management and exhibits a grim prognosis. We anticipate that our single-center study, conducted among a substantial cohort of patients experiencing refractory peritonitis episodes, will make a significant contribution to the literature by pinpointing risk factors linked to technical loss.

Declarations

Conflict of interest All the authors have declared no competing interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number: 09.2021.35) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent “Informed consent was obtained from all individual participants included in the study.”

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