

## Original Article

# Analysis of risk factors for refractory peritonitis in patients undergoing peritoneal dialysis

Dan Yuan<sup>1\*</sup>, Zhenxing Sun<sup>2\*</sup>, Yanan Shi<sup>1</sup>, Jingjing Zhou<sup>1</sup>, Chunxia Shi<sup>1</sup>, Zhongxin Li<sup>1</sup>

<sup>1</sup>Department of Nephrology, Beijing Luhe Hospital, Capital Medical University, Beijing 101100, China;

<sup>2</sup>Department of Neurosurgery, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 102218, China. \*Equal contributors and co-first authors.

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**Abstract:** Objective: To explore the risk factors for refractory peritonitis in patients undergoing peritoneal dialysis. Methods: We retrospectively collected data from 130 patients who underwent peritoneal dialysis (PD) and received peritonitis treatment at the Renal Disease Center of Beijing Luhe Hospital affiliated with Capital Medical University from January 1, 2016 to January 30, 2023. According to clinical treatment results, patients with refractory peritonitis were classified as the refractory group (n=52 cases), and those with non-refractory peritonitis were classified as the non-refractory group (n=78 cases). Baseline information and laboratory indicators of patients in each group were collected, and Logistic regression model was used to identify the risk factors for the poor prognosis of peritonitis patients. Results: There were statistically significant differences in dialysis time, dialysate sugar concentration and inducement type between the refractory group and the non-refractory group ( $P<0.05$ ). The values of peripheral white blood cells (pWBC), T helper 2 cell (Th2), T regulatory cell (Treg), Treg/Th17 and C-reactive protein (CRP) in the refractory group were significantly higher than those in the non-refractory group, while the values of T helper 17 cell (Th17) and albumin (ALB) were significantly lower (all  $P<0.05$ ). There were no significant differences in serum creatinine, blood urea, Th1, hemoglobin (Hb) and blood calcium levels between the two groups (all  $P>0.05$ ). Gram-positive bacteria were the main pathogenic bacteria of peritonitis in all groups. The proportion of enterococcus/streptococcal peritonitis in the refractory group was higher than that in the non-refractory group ( $P<0.05$ ). Logistic regression identified elevated pWBC, higher dialysate sugar concentration, exit-site infection and gram-negative bacteria infection as independent risk factors for refractory peritonitis in patients undergoing PD (all  $P<0.05$ ). Conclusion: Elevated pWBC, high glucose dialysate concentration, exit-site infection, and gram-negative bacteria infection are risk factors for refractory peritonitis in patients undergoing PD.

**Keywords:** Peritoneal dialysis, early-onset peritonitis, risk factors, prognosis

## Introduction

Peritoneal dialysis (PD) and hemodialysis are important alternative therapies for kidney diseases such as acute kidney injury and chronic renal failure [1]. Compared with hemodialysis, peritoneal dialysis offers several advantages: simpler operation, more stable hemodynamics, and better protection of residual renal function. It utilizes the semi-permeability characteristic of the peritoneum and injects dialysate into the peritoneal cavity through a catheter under the action of gravity to form a concentration difference and complete a substance exchange process [2]. This process primarily aids in protecting the residual renal function of patients,

removing metabolites and toxic substances, and maintaining the balance of water and electrolyte. Study [3] has shown that the 5-year survival rate of PD patients is significantly higher than that of hemodialysis patients, making PD a widely used clinical practice. With the continuous improvement of medical technology, PD has achieved good results in the relief and treatment of some kidney diseases. However, factors such as non-strict aseptic operation, low immunity of patients, advanced age, and dialysate pollution are still likely to cause various complications [4]. Peritonitis, in particular, poses significant clinical risks, causing peritoneal transport dysfunction, triggering ultrafiltration failure, and potentially leading to

dialysis failure, which is one of the main risk factors for hospitalization, extubation, withdrawal from treatment and even death of dialysis patients [5].

Early recognition and intervention of high-risk patients are crucial due to the severe consequences of peritonitis. Reports [6] indicate that the risk of peritonitis is significantly higher between the third and sixth months after starting peritoneal dialysis, leading many patients to switch to hemodialysis within the first six months. Current research on early-onset peritonitis primarily focuses on the risk factors for its initial occurrence [7], with relatively little attention given to its early detection, clinical characteristics and treatment outcomes. Therefore, this study retrospectively analyzed the clinical data of PD patients with peritonitis during regular follow-up in our hospital, to explore its clinical characteristics and treatment prognosis, so as to guide the clinical management measures, reduce the incidence of early peritonitis, and improve the clinical outcome of peritoneal dialysis.

### General material and methods

#### *General material*

A total of 130 patients who underwent PD and received peritonitis treatment (they had their first peritonitis onset during regular follow-up) in the Nephropathy Center of Beijing Luhe Hospital Affiliated with Capital Medical University from January 1, 2016 to January 30, 2023 were retrospectively included as the research subjects. According to the clinical treatment results, patients with refractory peritonitis were classified as the refractory group (n=52 cases), and patients without refractory peritonitis were classified as the non-refractory group (n=78 cases). This study was approved by the Ethics Committee of Beijing Luhe Hospital, Capital Medical University.

#### *Diagnosis standard*

Diagnostic criteria for peritonitis [8]: (1) Clinical manifestations such as abdominal pain, turbid effluent, and peritonitis-related symptoms with or without fever; (2) White cells count in the dialysate (retention time  $\geq 2$  h)  $>100/\mu\text{L}$ , with multinucleated white cells is  $>50\%$ ; (3) Positive bacterial culture in exudate. A diagnosis of peri-

tonitis required at least two of the above three criteria.

Early-onset PD-related peritonitis was defined as peritonitis that occurs within 6 months of peritoneal dialysis initiation.

Refractory peritonitis was defined as no improvement in symptoms and persistently cloudy peritoneal dialysis effluent after five days of standard antibiotic therapy.

#### *Criteria of inclusion and exclusion*

Inclusion criteria: (1) Age  $\geq 18$  years old; (2) Confirmed diagnosis of chronic renal failure [9] by medical history, laboratory tests and imaging examinations, and first-time peritoneal dialysis catheterization at our hospital; (3) Regular follow-up and regular treatment; (4) Duration of peritoneal dialysis at our hospital exceeding 3 months; (5) Complete clinical data.

Exclusion criteria: (1) Pre-existing inflammatory disease within 1 month before the commencement of peritoneal dialysis; (2) Peritonitis caused by chemical factors or other non-infectious factors; (3) Exogenous infection caused by dialysis fluid pollution; (4) Complicated with systemic infection; (5) Undergoing hemodialysis or kidney transplantation; (6) Long-term treatment with immunosuppressive agents or hormones; (7) Presence of active cerebral hemorrhage or severe organ dysfunction.

#### *Methods*

##### *Diagnosis and treatment process of peritonitis:*

For patients diagnosed with peritonitis, the peritoneal effluent was collected for routine analysis, smear, and culture using blood culture flask for both aerobic and anaerobic bacteria. If the patient also exhibited exit-site infection, a bacterial culture of the secretion at the exit site was performed simultaneously. Empirical anti-infective therapy, covering both Gram-positive and Gram-negative bacteria, was initiated immediately upon diagnosis of peritonitis. Routine examinations of the peritoneal effluent were conducted on the third and fifth days after the initiation of medication to assess the treatment's effectiveness. Antibiotics were adjusted based on the drug sensitivity results obtained from the bacterial culture report. The treatment was considered effective if the symptoms of peritonitis were

completely relieved, the peritoneal dialysis effluent became clear, and the white cell count in the dialysis solution returned to normal levels. However, if refractory peritonitis occurred, or if fungal culture results were positive in the peritoneal dialysis solution, the dialysis tube was removed. In cases of serious complications, patients were transitioned to hemodialysis. Additionally, the protocol covered cases where patients died within 30 days of the onset of peritonitis or as a result of hospitalization due to peritonitis.

*Data collection and relevant definition:* General information, including age, gender, primary disease, combined disease, dialysis duration, mode of peritoneal dialysis, body mass index (BMI), and timing and types of antibacterial drugs used, was collected and compared between the refractory and non-refractory groups.

Clinical data, including the onset time of peritonitis, precipitating factors, clinical symptoms, time from the first symptom to medical consultation, occurrence of exit-site infection [10] within six months from the start of peritoneal dialysis (exit-site infection refers to an infection occurring at the site where the peritoneal dialysis catheter exits the body), total white blood cells (pWBC) in the exudate at the time of diagnosis and 3 days after medication, biochemical indicators, and bacterial culture and drug sensitivity results, were collected and compared between the two groups.

*Detecting machine and method:* Venous blood (5 ml) was collected from patients in the morning on an empty stomach and centrifuged at a speed of 3000 r/min for 10 minutes to collect the upper layer of serum, which was stored in a freezer at -80°C.

The routine blood test was detected with a blood analyzer. The hemoglobin (Hb) level was detected by automatic blood cell analyzer. The levels of blood calcium, albumin (ALB) and C-reactive protein (CRP) were detected by an automatic biochemical analyzer. The levels of regulatory T cells (Treg) and helper cells (Th)1, Th2 and Th17 in the peripheral blood were detected by flow cytometry. The peritoneal dialysis solution with the abdominal retention time of  $\geq 2$  h was retained, and the WBCs in the peritoneal dialysis solution were counted manually using a microscope. The peritoneal dialy-

sis effluent was cultured using a fully automated rapid microbial culture system. The effluent was incubated at 37°C in an automatic incubator. If positive specimens were identified, the specimens were stained and transferred to petri dishes for culture at 37°C in a 5% CO<sub>2</sub> incubator for 1-7 days. Biochemical and drug sensitivity tests were further conducted for those with positive cultures of the main pathogenic bacteria.

### *Statistical analysis*

SPSS 25.0 software was utilized for statistical analysis. The measurement data conforming to a normal distribution were expressed as the mean  $\pm$  standard deviation, and compared using an independent sample t test; while those with a skewed distribution were expressed as M(P25, P75), and a nonparametric test for two independent samples was chosen. Enumeration data were expressed as frequency and percentage, and inter-group comparison was examined by Chi-square or Fisher's exact probability method. For indicators with statistical difference between groups, a binary Logistic regression model was used for single factor analysis, and the differential indicators were then included in the multi-factor regression model, and the forward stepwise regression method was used to identify the risk factors for refractory peritonitis. A P-value of less than 0.05 was considered statistically significant. The research process is shown in **Figure 1**.

## **Results**

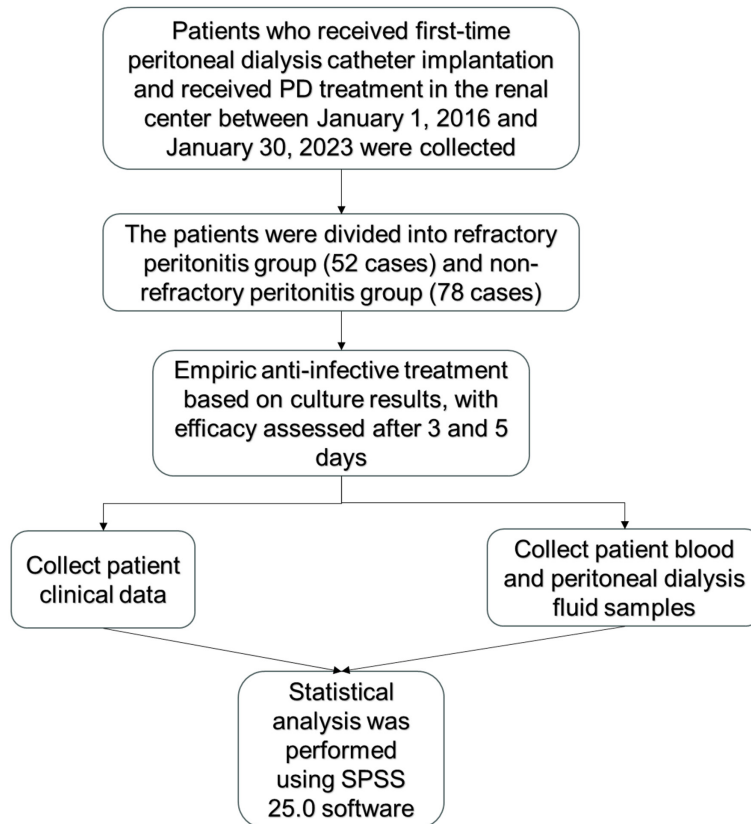
### *Comparison of baseline data of two groups of patients*

There were no statistically significant differences between the two groups in terms of gender, age, BMI and disease type (all  $P > 0.05$ ). However, significant differences were found in dialysis time, dialysate glucose concentration, and precipitating factor type between the refractory group and the non-refractory group (all  $P < 0.05$ ), as shown in **Table 1**.

### *Comparison of serum biochemical indicators between the two groups of patients*

The levels of pWBC, Th2, Treg, Treg/Th17 and CRP in the refractory group were significantly higher than those in the non-refractory group,

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**Figure 1.** The research process.

while those of Th17 and ALB were significantly lower (all  $P < 0.05$ ). There were no significant differences in blood creatinine, blood urea, Th1, Hb and blood calcium levels between the two groups (all  $P > 0.05$ ), as shown in **Table 2** and **Figure 2**.

The levels of hemoglobin, fasting blood glucose, TC, LDL-C in the refractory group were significantly higher than those in the non-refractory group (all  $P < 0.05$ ). However, there were no statistically significant differences in serum potassium, serum phosphorus, TG, HDL-C, serum albumin levels between the two groups ( $P > 0.05$ ), as shown in **Table 3**.

### *Comparison of pathogenic bacteria examination results between the two groups*

Gram-positive bacteria were the predominant pathogens causing peritonitis in both groups. The proportion of Enterococcus/Streptococcus infection in the refractory group was significantly higher than that in the non-refractory group (21.15% VS 6.41%) ( $P < 0.05$ ), as shown in **Table 4**.

### *Risk factors for refractory peritonitis in PD patients by Logistic regression analysis*

Significant variables in Univariate analysis and clinically relevant data were further included in the Logistic regression model. The results showed that pWBC [3.916 (1.267-6.754)], dialysate glucose concentration [2.540 (1.189-5.413)], exit site infection [3.086 (1.360-7.035)] and Gram-negative bacterial infection [3.501 (1.145-7.680)] were independent risk factors for refractory peritonitis in patients undergoing peritoneal dialysis (all  $P < 0.05$ ), as shown in **Table 5**.

### **Discussion**

Peritoneal dialysis is an effective treatment for end-stage renal disease. Despite continuous advancements in technology, the mortality of peritoneal dialysis (PD) patients remains high. Peritonitis, a common complication of PD, significantly impacts the therapeutic efficacy and life expectancy of these patients [11]. There are various reports on the risk factors for peritonitis in China and abroad [12-14]. Some studies suggest that the wide application of antibiotics is related to the occurrence of peritonitis, while other factors such as hyponatremia and concomitant intestinal obstruction have also been identified as risk factors. With the gradual improvement of prevention and control strategies for peritonitis in recent years, the incidence and influencing factors have evolved. This study retrospectively analyzed the clinical data of PD patients with peritonitis in our hospital to explore the risk factors affecting its occurrence and prognosis.

This study observed significant differences in dialysis duration, dialysate glucose concentration, and precipitating factor type between the refractory group and the non-refractory group. Similar results were reported by Liu et al. [15], who investigated the risk factors and countermeasures for early-onset PD-related peritonitis

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**Table 1.** Comparison of baseline data between the two groups ( $\bar{x} \pm s$ , %)

Group		Non-refractory group (n=78)	Refractory group (n=52)	T value	P value
Gender	Male	41	24	0.162	0.421
	Female	37	28		
Age (years)		57.54 $\pm$ 5.52	61.10 $\pm$ 5.08	2.948	0.120
Dialysis duration (years)		2.76 $\pm$ 0.15	4.21 $\pm$ 0.39	4.821	0.037
BMI (kg/m <sup>2</sup> )		22.18 $\pm$ 0.42	22.37 $\pm$ 0.51	0.755	0.434
Underlying disease	Hypertension	29 (33.33)	33 (37.93)	3.176	0.058
	Diabetes	21 (10.48)	19 (21.84)		
	Coronary heart disease	8 (24.14)	11 (12.64)		
Dialysate glucose concentration	Low	36 (46.15)	12 (23.08)	5.768	0.022
	High	28 (35.89)	23 (44.23)		
Precipitating factor	Exit site infection	19 (24.35)	21 (40.38)	5.267	0.022
	Enterogenous infection	25 (32.05)	14 (19.23)		
	Dystrophy	28 (35.89)	10 (12.64)		
	Unclear	6 (7.69)	7 (13.46)		

**Table 2.** Comparison of inflammation-related indicators ( $\bar{x} \pm s$ )

Group	Non-refractory group (n=78)	Refractory group (n=52)	t value	P value
pWBC (/ $\mu$ L)	28.58 $\pm$ 3.05	180.75 $\pm$ 20.12	11.807	<0.001
Blood creatinine ( $\mu$ mol/L)	864.32 $\pm$ 211.56	891.84 $\pm$ 214.29	1.623	0.101
Blood urea (mmol/L)	17.33 $\pm$ 1.48	18.40 $\pm$ 1.73	0.721	0.425
Th1 (%)	34.2 $\pm$ 5.41	34.3 $\pm$ 5.82	0.188	0.734
Th2 (%)	1.98 $\pm$ 0.84	3.46 $\pm$ 0.46	6.622	<0.001
Th17 (%)	2.21 $\pm$ 0.31	1.95 $\pm$ 0.22	10.179	<0.001
Treg (%)	4.33 $\pm$ 1.02	7.41 $\pm$ 1.15	11.057	<0.001
Treg/Th17	1.96 $\pm$ 0.18	3.80 $\pm$ 0.13	10.841	<0.001
Blood calcium (g/L)	1.92 $\pm$ 0.23	1.86 $\pm$ 0.21	0.990	0.576
Hb (g/L)	77.43 $\pm$ 4.85	76.93 $\pm$ 5.27	0.492	0.316
ALB (g/L)	39.15 $\pm$ 2.63	33.42 $\pm$ 2.49	10.345	<0.001
CRP (g/L)	5.96 $\pm$ 0.97	13.48 $\pm$ 2.12	10.685	<0.001

through clinical studies. A previous study [16] showed that the long-term peritoneal exposure to sugar-containing dialysate in patients can lead to changes in peritoneal mesothelial cells and impaired immune function, resulting in decreased dialysis efficiency and severe consequences such as peritoneal sclerosis and ultra-filtration failure. The analysis suggests that the occurrence of peritonitis might be related to the morphological and functional changes of the peritoneum in patient.

In addition, if the exit site infections are not promptly controlled, pathogenic bacteria can migrate along the catheter into the abdominal cavity, causing peritonitis [17]. Therefore, medi-

cal staff should immediately administer local anti-infective treatments when symptoms of tunnel mouth infection are observed to prevent peritonitis caused by bacterial migration. Studies [18, 19] have shown that inflammatory state and malnutrition are prominent features of PD patients. When the peritoneal immune defense function is compromised, the interaction between inflammation and malnutrition can lead to cytokine dysfunction. Albumin (ALB) and Treg/Th17-related cytokines, key indicators of immune function, provide valuable guidance and predictive insights into the decline in immune function and the extent of damage in patients [20]. The results of this study showed that the levels of pWBC, Th2,

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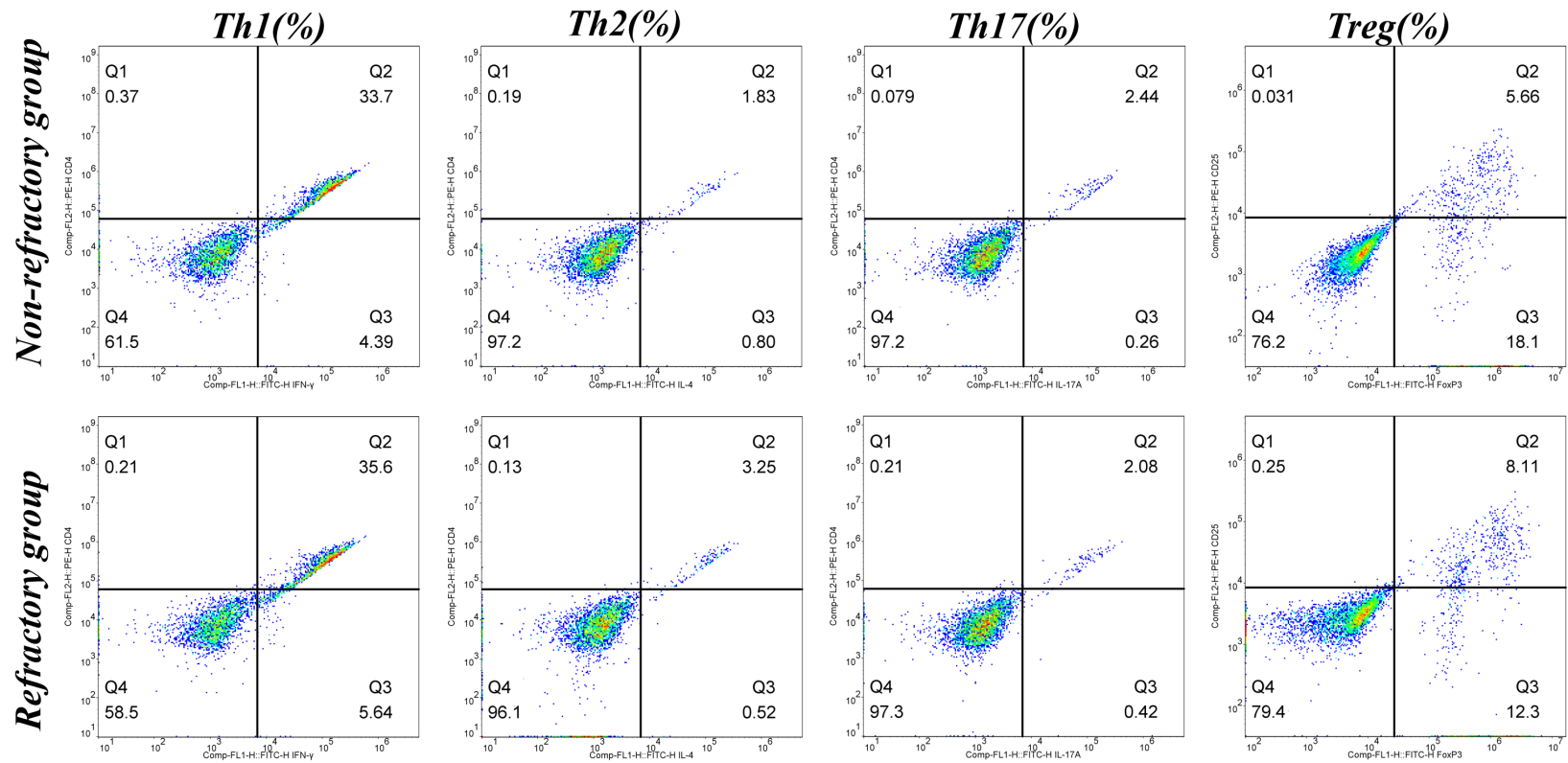


Figure 2. Typical figures of flow cytometry.

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**Table 3.** Comparison of the serum biochemical results ( $\bar{x} \pm s$ )

Group	Non-refractory group (n=78)	Refractory group (n=52)	t value	P value
Haemoglobin (g/L)	82.58±2.78	95.26±3.12	7.259	0.001
Fasting blood glucose (mmol/L)	5.83±1.56	6.35±1.69	5.623	0.007
Serum potassium (mmol/L)	4.37±0.89	4.40±0.73	0.354	0.779
Serum phosphorus (mmol/L)	1.79±0.32	1.93±0.38	0.988	0.234
TC (mmol/L)	3.99±0.36	4.46±0.35	4.622	0.023
TG (mmol/L)	1.29±0.21	1.35±0.22	0.179	0.669
HDL-C (mmol/L)	1.13±0.18	1.26±0.15	1.007	0.249
LDL-C (mmol/L)	2.36±0.69	2.80±0.81	3.841	0.039
Serum albumin (g/L)	33.69±5.32	34.19±6.21	0.779	0.594

**Table 4.** Comparison of pathogenic bacteria between the two groups (%)

Group		Non-refractory group (n=78)	Refractory group (n=52)	T value	P value
Gram-negative bacteria	Enterobacter cloacae	0 (0.00)	0 (0.00)	1.075	0.327
	Escherichia coli	7 (8.97)	4 (7.69)		
Gram-positive bacteria	Staphylococcus aureus	9 (11.53)	7 (13.46)	6.200	0.015
	Coagulase negative staphylococci	1 (1.28)	2 (3.85)		
	Enterococcus/streptococcus	5 (6.41)	11 (21.15)		
Fungus	Candida albicans	1 (1.28)	1 (1.92)	0.392	0.784
	Candida parapsilosis	1 (1.28)	1 (1.92)		
	Candida glabrata	1 (1.28)	2 (3.85)		

**Table 5.** Risk factors for refractory peritonitis identified by Logistic regression analysis

Variable	$\beta$	SE	Wald value	P value	OR value (95% CI)
pWBC	1.361	0.588	1.387	0.015	3.916 (1.267-6.754)
Dialysate glucose concentration	0.938	0.391	5.681	0.030	2.540 (1.189-5.413)
Tunnel mouth infection	1.123	0.424	4.065	0.032	3.086 (1.360-7.035)
Gram-negative bacterial infection	1.259	0.569	1.843	0.025	3.501 (1.145-7.680)
Constant	-7.912	2.485	8.191	0.003	-

Treg, Treg/Th17 and CRP in the refractory group were significantly higher than those in the non-refractory group, while the levels of Th17 and ALB were significantly lower. This indicates that the inflammatory response changes and immune function decline were more pronounced in the PD patients complicated with refractory peritonitis, which aligns with the previous research conclusions [21]. Treg and Th17-related cytokines are important regulatory cell subsets in human body [22]. With disease progression, PD patients often experience reduced nutrient intake and reserves. This, combined with inadequate adherence to aseptic techniques and non-standardized operations, leads to decreased liver synthetic func-

tion and lower ALB levels [23]. Consequently, the patient's homeostasis is disrupted, resulting in an immunosuppressive state that necessitates the synthesis and secretion of large amounts of Treg to maintain immune balance. Unlike Th1, which secretes cytokines directly to kill pathogens, Th17 recruits neutrophils to induce Th1 and Th2 differentiation and activate inflammatory responses, thereby achieving immune defense [24]. However, increased CRP levels can lead to metabolic disorders. Research [25] has shown that individualized dietary guidance is conducive to improving the levels of various nutritional indicators in PD patients. Therefore, clinical medical care should focus on strengthening the nutritional

assessment of patients, and timely detect malnutrition events such as hypoproteinemia to reduce the risk of peritonitis.

It has been pointed out [26] that *Staphylococcus aureus* often co-occurs with exit-site and tunnel infections; it is highly toxic and easily forms a biofilm, leading to refractory infection. The results of this study showed that Gram-positive bacteria were the predominant pathogens of peritonitis in all groups. The proportion of *Enterococcus*/*Streptococcus* peritonitis was significantly higher in the refractory group than that in the non-refractory group. Previous studies have reported that the prognosis of Gram-negative bacterial peritonitis was poor, likely due to the higher virulent and biofilm production of Gram-negative bacteria [27].

In this study, the significant factors in univariate analysis and deemed clinically relevant were further included in the Logistic regression model. The results showed that pWBC, high dialysate glucose concentration, exit-site infection and Gram-negative bacteria infection were the independent risk factors for refractory peritonitis in patients undergoing peritoneal dialysis. It is believed that the self-resistance and immunity of peritoneal dialysis patients were lower than those of the normal population. The use of high-glucose dialysate to reduce hypoglycemia incidence also creates a conducive environment for bacterial growth, thereby affecting dialysis efficacy. It has been reported [28] that long-term use of non-bio-compatible traditional sugar-containing dialysate can gradually increase the thickness of the subcutaneous compact zone, change the structure and function of the peritoneum, and cause peritoneal fibrosis. The use of new bio-compatible dialysis solutions may reduce peritoneal interstitial fibrosis and transparent angiogenesis, thereby protecting peritoneal function and prolonging the technical survival time [29].

### Conclusion

In summary, elevated pWBC, high glucose dialysate concentration, exit-site infection, and Gram-negative bacterial infection are risk factors for refractory peritonitis in patients undergoing peritoneal dialysis. To mitigate these factors, timely and appropriate measures should be implemented to reduce the incidence of

early-onset peritoneal dialysis-related peritonitis. Utilizing biocompatible dialysate can help protect peritoneal function. Additionally, attention should be given to identifying the pathogens responsible for peritonitis and analyzing drug sensitivity results to avoid adverse outcomes. There are some limitations to this study. Being a retrospective study, the baseline information included is based on laboratory data at the time of peritonitis, which may introduce bias. Furthermore, this study only analyzes the short-term prognosis of peritonitis, without addressing long-term outcomes. Therefore, prospective multi-center studies are needed to further confirm these results. Future research should also focus on investigating the mechanisms underlying the prognosis of early-onset peritonitis.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Zhongxin Li, Department of Nephrology, Beijing Luhe Hospital, Capital Medical University, No. 82, Xinhua South Road, Tongzhou District, Beijing 101100, China. Tel: +86-13621211613; E-mail: lhy6806@ccmu.edu.cn

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