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Original Article

ORIGINAL ARTICLE

A predictive model of treatment effectiveness of refractory peritoneal dialysis–related peritonitis in patients with peritoneal dialysis: a single-center observational study in South China

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ABSTRACT

Background. To prevent loss of peritoneal function caused by persistent abdominal inflammation, the guidelines recommend early extubation in patients with refractory peritoneal dialysis (PD)-associated peritonitis (rPDAP). In attempt to pinpoint high-risk patient cohorts that did not respond to treatment for refractory peritonitis, we created a model to predict the effectiveness of peritonitis treatment.

Methods. This observational cohort study included PD patients from 1 January 2011 to 31 December 2020. Multivariate logistic regression analysis was used to explore the factors affecting the occurrence and prognosis of rPDAP, and to construct a predictive model for the success of rPDAP treatment. Receiver operator characteristic curve, calibration and decision curve were drawn to evaluate the predictive performance of the model.

Results. A total of 1397 cases of PDAP occurred in our center during the study period, of which 558 cases were diagnosed as rPDAP. The incidence of refractory peritonitis was 0.047 cases/patient-year. In the study, 440 cases with rPDAP were included. Among them, 304 cases (69.1%) had been successfully cured, while 136 cases (30.9%) were treatment failure, of which 19 cases (13.9%) died, 85 cases (62.5%) transferred to hemodialysis and 32 cases (23.5%) were relapse/recurrent peritonitis. Dialysate culture results showed 132 (30.0%) cases were infected with Gram-positive bacteria and 161 (36.6%) Gram-negative bacteria. Multivariate logistic regression analysis showed that episodes of peritonitis previously $\leq$3 times were correlated with the better prognosis of rPDAP, but white blood cell (WBC) counts in peritoneal dialysate on the third day of peritonitis or WBC counts on the fifth day $\geq 300 \times 10^6$/L, the pathogenic microorganism with Gram-negative bacteria, as well as longer duration of PD were associated with poor outcomes. The C-statistical value of the training data set was 0.870 (95% confidence interval 0.821–0.918). The calibration curve and clinical decision-making curve also proved that this nomogram could accurately predict the success of treatment in patients with refractory peritonitis.

Conclusion. The nomogram model created through internal verification indicated a strong clinical application value and a high prognostic prediction accuracy for rPDAP.

Keywords: ISPD guidelines, nomogram, pathogenic microorganism, peritoneal dialysis associated peritonitis, refractory peritonitis

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KEY LEARNING POINTS

What was known:

- In the actual treatment of refractory peritonitis, doctors and patients often postpone extubation for various reasons, and any patient has an inherent risk of treatment failure.
- However, events that occur within 5 days of the start of conventional antibiotic treatment may also affect it.

This study adds:

- Early identification of high-risk groups of refractory peritonitis with technical failure can improve the prognosis and management of peritoneal dialysis–associated peritonitis (PDAP) patients.
- We hope that drawing a nomogram based on the prediction model will help to intuitively identify the high and low probability of successful cure of refractory peritonitis.

Potential impact:

- If the possibility of cure is low, it is recommended to temporarily switch to hemodialysis and timely removal of the peritoneal dialysis catheter to avoid further complications.
- According to the probability of treatment success, targeted management measures are taken to reduce the extubation rate of refractory PDAP, providing a decision-making basis for the clinical treatment of refractory PDAP.

INTRODUCTION

While the incidence of peritoneal dialysis (PD)-associated peritonitis (PDAP) has improved recently, the frequency of refractory PDAP (rPDAP) has not decreased [1]. About 13.8% of patients with peritonitis had not cleared peritoneal dialysate after 10 days of antibiotic treatment [2]. Furthermore, 14% of patients with severely infected rPDAP experienced complications such as dialysate and prolonged abdominal inflammation, necessitating recurrent drainage [3]. In order to preserve peritoneal function in the event that patients with rPDAP return to PD in the future, the 2016 ISPD guidelines advise that patients with rPDAP be extubated as soon as possible [4]. The updated 2022 guidelines include adjustments to the suggestion of "extubating immediately" patients with unclear peritoneal dialysate on the fifth day of peritonitis, but they do not provide a clear advice for when to extubate [5]. Since only 6.3% of patients with peritonitis resume therapy after being extubated, the decision to remove the catheter is critical [6]. However, during the real course of treating peritonitis, physicians and patients frequently put off extubation for a variety of reasons, and there is some inherent risk of treatment failure for any given patient. Nevertheless, occurrences within 5 days after the start of routine antibiotic therapy may also impact it, so we expect the early model to explain both types of data. The prognosis and management of PDAP patients can therefore be improved by early identification of high-risk groups of refractory peritonitis patients with technical failure.

Establishing prediction models for the prognosis of PDAP has been commonplace in recent years [7–9]. However, few models could accurately forecast how rPDAP treatment will turn out. The research on rPDAP was mainly focused on the spectrum analysis of pathogenic bacteria [10]. By analyzing the clinical data of rPDAP in PD patients in our center, we explored the factors affecting the prognosis of rPDAP patients and predicted the risk of treatment failure in rPDAP patients. According to the probability of successful treatment, targeted management measures should be taken to reduce the extubation rate of rPDAP, so as to provide decision-making basis for clinical treatment of rPDAP.

MATERIALS AND MEDTHODS

Study design and population

Whether rPDAP can be cured is an important issue, and its result determines the technical survival of PD. The purpose of this study was to develop and verify a predictive model for the cure of refractory peritonitis in PD patients.

The subjects were PD patients without renal transplantation or long-term hemodialysis (HD) history (>3 months) who developed rPDAP and were hospitalized or outpatients in The First Affiliated Hospital of Sun Yat-sen University from January 2011 to December 2020. All patients were followed up until death, conversion to HD or cures after stopping antibiotic therapy. The inclusion criteria were (i) age ≥18 years old, (ii) regular follow-up and regular treatment (iii) after 5 days of appropriate antibiotic treatment persistent effluent turbidity or persistent effluent white blood cell (WBC) $>100 \times 10^6$/L. Exclusion criteria were (i) delay of formal treatment for more than 72 h, (ii) absence of important data or (iii) dialysate culture results were fungal. All patients were divided into training group and verification group, and 70% (308 cases) of the patients were randomly assigned to the training cohort, which was used to build a predictive model to predict treatment failure in rPDAP patients. The remaining 30% (132 cases) of the patients were assigned to the test queue to verify the performance of the model. There was no statistical difference in the incidence of treatment failure between the training queue and the test queue (31.8% vs 28.7%, $P = .28$).

The study followed the Helsinki Declaration. The research scheme was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University.

Management protocol

When patients reported symptoms such as turbid dialysate, abdominal pain or fever, peritoneal dialysate was collected and analyzed immediately. If WBC counts were $>100 \times 10^6$/L or polymorphonuclear cells (PMN) accounted for more

than 50% in the dialysate, empirical intraperitoneal antibiotics were given immediately. The choice of empirical antimicrobial agents was determined by the attending physician. First-generation cephalosporins or vancomycin were often used to cover Gram-positive bacteria and third-generation cephalosporins or aminoglycosides are used to cover Gram-negative bacteria. The leukocytes in dialysate were reexamined every day after intraperitoneal injection of antibiotics. After 5 days of appropriate antibiotic treatment, patients with persistent cloudy effluent or persistent effluent WBC $>100 \times 10^6$/L were considered for a diagnosis of rPDAP.

After the patient was diagnosed with refractory peritonitis, the attending doctor comprehensively evaluated the next treatment plan of the patient according to the changing trend of the patient's dialysate leukocyte level and clinical manifestations, dialysis age, dialysis ultrafiltration status, etc. Patients with severe peritonitis who had fever (body temperature exceeds 37.5°C), positive blood culture, pneumonia, septic shock, etc., were treated with combined intravenous antibiotics, whether or not refractory peritonitis developed. For patients with a downward trend in dialysate white blood cell count, if was is a culture result, the corresponding antibiotics were adjusted according to Gram-positive or Gram-negative bacteria for treatment, and the course of treatment was usually 2 weeks. For peritonitis caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Enterococcus*, a 3-week course of treatment was recommended. In view of the high recurrence rate and recurrence rate of peritonitis caused by *Escherichia coli*, a 3-week course of treatment was recommended. According to the specific situation of the patient, third-generation cephalosporins or third- and fourth-generation quinolones and other antibiotics could be used empirically for treatment.

Data collection

Baseline data were collected 1–3 months before the onset of peritonitis, including demographic data (age, sex), end-stage renal disease, diabetes mellitus, body mass index, 24-h urine output, self-care ability, duration of dialysis (months), pathogenic bacteria, laboratory variables [hemoglobin, serum albumin (ALB), serum creatinine, uric acid, carbon dioxide binding rate, measured glomerular filtration rate (mGFR), triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, parathyroid hormone, serum potassium, serum sodium, serum calcium, serum phosphorus, urea clearance normalized to total body water (Kt/V), dialysate-to-plasma ratio of creatinine at 4 h (D/P4)]. The laboratory variables were measured in the central laboratory of the hospital, and the urine volume was the average urine volume 1 month before hospitalization. GFR was the mean of urea and creatinine clearance, calculated from 24-h urine collections and indexed for body surface area. In addition, peritoneal dialysate WBC and the proportion of PMN were tested on the first, third and fifth day after peritonitis. Duration of antibiotic therapy, duration of dialysis and symptoms (abdominal pain, fever, diarrhea, dialysate turbidity, intestinal obstruction) were collected according to the patient's medical records. The initial empirical antibiotic treatment scheme and drug sensitivity test are presented to determine whether the initial treatment is standardized. Initial empirical antibiotic regimens were classified as: first-generation cephalosporins + third generation cephalosporins (cefazolin/cefradine + ceftazidime), first-generation cephalosporins + aminoglycosides (cefazolin/cefradine + amikacin/gentamicin) and other regimens (amikacin/gentamicin/ceftazidime + vancomycin). Record the results of antibiotic susceptibility testing for ceftazidime, gentamicin, vancomycin, ceftriaxone or levofloxacin.

Definitions

The diagnosis of PDAP should have at least following two conditions: (i) the clinical features are consistent with those of peritonitis, that was, abdominal pain and/or turbid dialysate; (ii) the WBC of the dialysate is $>100 \times 10^6$/L (at least 2 h after staying in the abdomen) and the proportion of PMN >50%; and (iii) positive bacterial culture in the dialysate [5]. rPDAP was defined as persistent effluent turbidity or persistent effluent WBC $>100 \times 10^6$/L after 5 days of appropriate antibiotic treatment [5]. Catheter exit-site infection (ESI) was defined as the presence of purulent discharge, with or without erythema of the skin at the catheter–epidermal interface [11]. Cure was defined as complete resolution of peritonitis together with none of the following complications: relapse/recurrent peritonitis, catheter removal, transfer to HD for >30 days or death [5]. Peritonitis-related death was defined as (i) sepsis secondary to peritonitis, (ii) positive dialysate culture or turbid fluid death, (iii) death within 14 days after the onset of peritonitis or (iv) death during hospital visits due to peritonitis [12].

Relapsing peritonitis was defined as the occurs of the same pathogen or culture-negative peritonitis within 4 weeks after the end of the complete treatment of the previous peritonitis (based on the last infusion of antibiotics) (including two times of the same specific pathogen or one of the cultures is negative, such as the previous culture is negative and the second culture is a specific pathogen, or the previous culture was a specific pathogen and the second culture is negative) [5]. Recurrent peritonitis referred to peritonitis that occurs again within 4 weeks after the last peritonitis was cured, but the pathogen is different [5]. Fever was defined as an axillary temperature >37.5°C. Intestinal obstruction was defined as symptoms such as nausea, vomiting, cessation of flatulence and defecation, and intestinal dilatation, fluid accumulation and gas accumulation on supine X-ray films.

Statistical analysis

The classification variable was expressed in frequency and percentage, and the continuous variable was the mean ± standard deviation. Continuous variables that did not conform to normal distribution were described using median and interquartile range. The continuous variables were analyzed by Student's *t*-test or Mann–Whitney U test, and the classified variables were analyzed by chi-square test or Fisher's exact test. The proportion of missing values of all variables was <15%, and the missing data was calculated by MissForest method [13]. Univariate and multivariate logistic regression analysis were performed on the prediction factors of refractory peritonitis treatment success. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate analysis. Then a nomogram was drawn according to the multivariate logistic regression model to evaluate the probability of successful treatment of refractory peritonitis.

Hosmer–Lemeshow test was used to evaluate the goodness of fit of logistic regression model. The effect of the model was evaluated by receiver operating characteristic (ROC) curve [14]. At the same time, calibration curves and decision-making curves were drawn to evaluate the diagnostic accuracy and clinical effectiveness of the model. All the analyses were done in R language, Version4.2.2 (the basis of R statistical calculation),

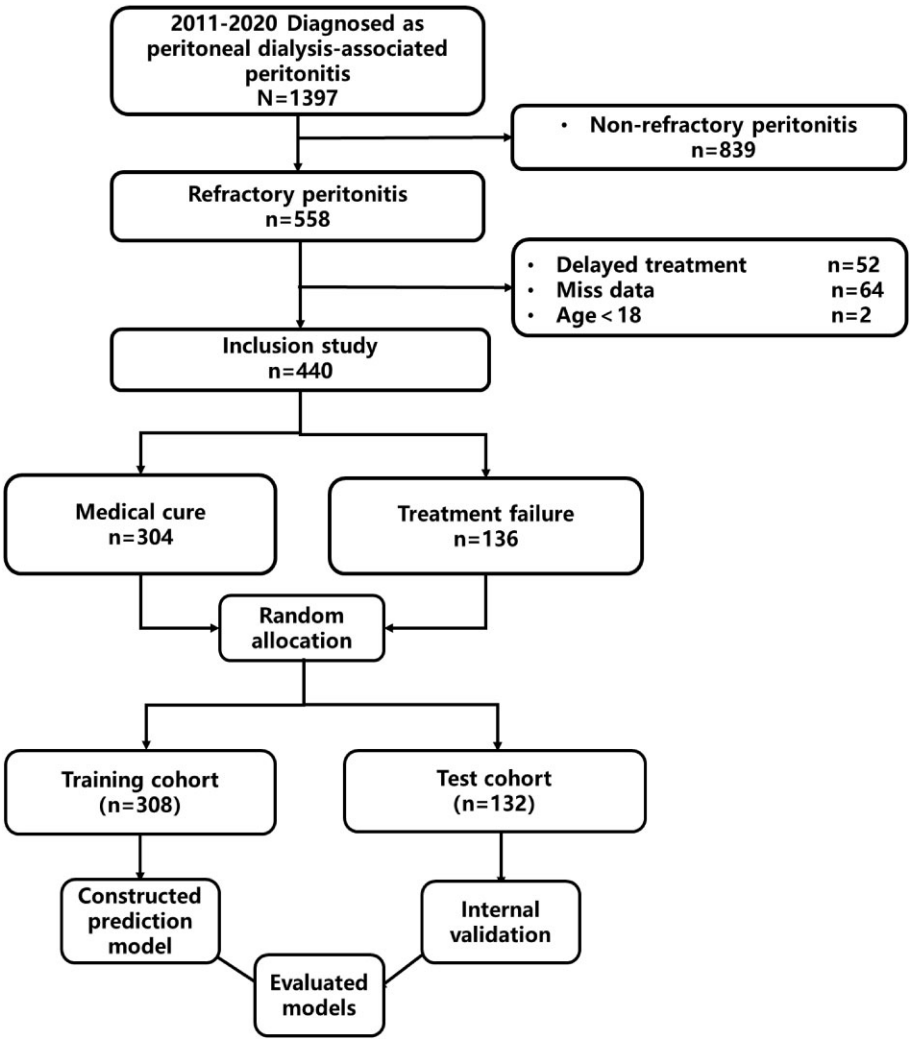

Figure 1: Flow chart for construction of predictive models.

and use "autoReg," "survival," "rmda," "rms" and "ROCR" packages.

RESULTS

During the study period, a total of 1397 cases of PDAP occurred in our center, of which 558 cases were diagnosed as rPDAP—418 of these cases (74.9%) required hospitalization. The incidence of peritonitis was 0.15 cases/patient-year, and the incidence of refractory peritonitis was 0.047 cases/patient-year, including 2 cases under 18 years old, 52 cases of delayed treatment >72 h and 64 cases of data deletion. Finally, 440 cases with rPDAP were included, four patients in the study used automated PD, and the rest used continuous ambulatory PD (CAPD) mode of dialysis. Among them 304 cases (69.1%) had been successfully cured (included 12 patients who were temporarily converted to HD), while 136 cases (30.9%) were treatment failure, of which 19 cases (13.9%) died, 85 cases (62.5%) transferred to HD (7 cases experienced catheter removal and reinsertion) and 32 cases (23.5%) were relapse/recurrent peritonitis. Among the patients transferred to HD, 69 cases had the peritoneal dialysis catheter removed within 1 week after HD transfer. The flow chart of this study is shown in Fig. 1.

Patient characteristics and clinical symptoms

The baseline characteristics of all patients are shown in Table 1. The median age of rPDAP patients was 53.0 (41.0, 64.0) years, the median duration of dialysis was 32.5 (13.7, 65.1) months and the average course of treatment was 17.6 ± 7.4 days. There was male 208 cases (47.3%) and 93 patients with diabetes (21.1%). The most common primary renal disease was glomerulonephritis (n = 245, 55.7%), followed by diabetic nephropathy (n = 81, 18.4%) and previous peritonitis ≤3 times in 353 cases (80.2%). Among the recorded combined symptoms, catheter infection (n = 16 cases, 3.6%), abdominal pain in about 83.0% (365 cases), fever in 35.7% (157 cases), diarrhea in 42.5% (187 cases) and 98% (431 cases) of patients had turbid dialysate. The intestinal obstruction (P = .006) between the cure group and the failure group were statistically significant and were included in the univariate analysis.

Table 1: Baseline demographic and laboratory parameters of rPDAP episodes.

Variable	Total ($n = 440$)	Cure ($n = 304$)	Treatment failure ($n = 136$)	P
Age (years)	53.0 (41.0, 64.0)	52.7 (40.0, 63.0)	54.4 (44.5, 65.5)	.05
Male, *n* (%)	208 (47.3)	146 (48)	62 (45.6)	.71
BMI (kg/m^2)	22.1 ± 3.4	22.0 ± 3.3	22.4 ± 3.3	.39
DM, *n* (%)	93 (21.1)	63 (20.7)	30 (22.1)	.85
Selfcare, *n* (%)	368 (83.6)	262 (86.2)	106 (77.9)	.06
Duration of antibiotic therapy (days)	17.6 ± 7.4	18.1 ± 6.3	16.5 ± 9.3	.09
Duration of dialysis (months)	32.5 (13.7, 65.1)	26.0 (8.9, 52.0)	52.1 (28.1, 80.1)	**<.001**
ESI, *n* (%)	16 (3.6)	6 (2.1)	10 (7.4)	**.012**
Previous peritonitis ≤3 times, *n* (%)	353 (80.2)	260 (85.5)	93 (68.4)	**<.001**
Primary renal disease, *n* (%)				.79
Glomerulonephritis	245 (55.7)	168 (55.3)	77 (56.6)	
Diabetes	81 (18.4)	54 (17.8)	27 (19.9)	
Hypertension	37 (8.4)	28 (9.2)	9 (6.6)	
Other	77 (17.5)	54 (17.8)	23 (16.9)	
Organisms, *n* (%)				**.028**
Gram-negative	132 (30.0)	103 (33.9)	29 (21.3)	
Gram-positive	161 (36.6)	100 (32.9)	61 (44.9)	
No growth	117 (26.6)	82 (27)	35 (25.7)	
Polymicrobial and other	30 (6.8)	19 (6.2)	11 (8.1)	
Laboratory parameter				
Hb (g/L)	105.2 ± 19.6	104.60 ± 19.5	106.42 ± 19.6	.375
ALB (g/dL)	34.7 (31.2, 38.2)	35.1 (31.50, 38.60)	33.9 (30.15, 36.65)	**.005**
Scr (mg/dL)	922.5 ± 293.1	917.6 ± 292.3	948.0 ± 295.7	.75
Total cholesterol (mg/dL)	4.8 (4.00, 5.70)	4.8 (4.05, 5.65)	4.8 (3.90, 5.80)	.62
Triglyceride (mmol/L)	1.4 (0.94, 2.02)	1.4 (0.94, 2.02)	1.4 (0.92, 2.10)	.59
UA (mg/dL)	381.0 (338.0, 448.5)	390.0 (342.5, 453.0)	376.0 (325.0, 428.0)	.10
CO_2 (mmol/L)	27.0 (25.0, 29.0)	26.0 (24.0, 29.0)	27.0 (25.0, 29.0)	.17
K (mmol/L)	3.9 (3.54, 4.34)	3.9 (3.56, 4.37)	3.9 (3.50, 4.20)	.56
Na (mmol/L)	139.0(137.0, 141.0)	139.0 (137.0, 141.00)	138.0 (136.0, 140.0)	**.009**
Ca (mmol/L)	2.2 (2.1, 2.4)	2.2 (2.11, 2.35)	2.3 (2.14, 2.38)	.51
P (mmol/L)	1.6 (1.26, 1.91)	1.5 (1.26, 1.87)	1.6 (1.30, 1.93)	.49
i-PTH (mmol/L)	514.2 ± 562.0	465.21 ± 517.68	625.52 ± 640.12	.12
HDL (mmol/L)	1.1 (0.9, 1.4)	1.2 (0.90, 1.42)	1.1 (0.90, 1.31)	.09
LDL (mmol/L)	2.8 (2.3, 3.5)	2.8 (2.34, 3.50)	2.8 (2.33, 3.50)	.76
mGFR (mL/min/1.73 m^2)	1.09 (0.14, 3.07)	1.48 (0.27, 3.45)	0.33 (0.00, 1.90)	**<.001**
Total Kt/V	2.3 ± 0.6	2.3 ± 0.6	2.3 ± 0.7	.63
Urine output (mL/day)	400.0(50.0, 900.0)	500.0 (100.0, 1000.0)	100.00 (0.0, 500.0)	**<.001**
D/P_4	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	.36
Initial symptoms and signs, *n* (%)				
Abdominal pain	365 (83.0)	250 (82.2)	115 (84.6)	.64
Fever	157 (35.7)	102 (33.6)	55 (40.4)	.19
Diarrhea	187 (42.5)	124 (40.8)	63 (46.3)	.33
Turbid dialysate fluid	431 (98.0)	298 (98)	133 (97.8)	1.00
Intestinal obstruction	15 (3.4)	5 (1.6)	10 (7.4)	**.006**
Day 1 effluent WBC (10^6/L)	1100.0 (420.0,2860.0)	1059.0 (432.0, 2800.0)	1415.0 (393.5, 3260.0)	.27
Day 3 effluent WBC (10^6/L)	426.5 (190.0,1278.8)	334.0 (172.8, 914.3)	1034.2 (219.3, 2045.4)	**<.001**
Day 5 effluent WBC (10^6/L)	352.0 (200.0,1034.0)	259.0 (184.2, 510.5)	965.0 (425.5, 2073.2)	**<.001**
Day 1 effluent PMN proportion	0.9 (0.7, 0.9)	0.85 (0.70, 0.92)	0.85 (0.741, 0.92)	**.006**
Day 3 effluent PMN proportion	0.72 (0.49, 0.85)	0.70 (0.42, 0.85)	0.80 (0.60, 0.90)	.09
Day 5 effluent PMN proportion	0.71 (0.42, 0.86)	0.71 (0.41, 0.86)	0.81 (0.61, 0.91)	.06
Day 1 effluent WBC <300 × 10^6/L, *n* (%)	53 (17.3)	39 (16.8)	14 (18.9)	.58
Day 3 effluent WBC <300 × 10^6/L, *n* (%)	183 (41.6)	147 (48.4)	36 (26.5)	**<.001**
Day 5 effluent WBC <300 × 10^6/L, *n* (%)	196 (44.5)	177 (58.2)	19 (14)	**<.001**
Initial IP antibiotic regimens, *n* (%)				.07
1st-GCEP + 3ird-GCEP	259 (58.9)	188 (61.8)	71 (52.2)	
1st-GCEP + AMIN	130 (29.5)	89 (29.3)	41 (30.1)	
Other	51 (11.6)	27 (8.9)	24 (17.6)	

Data are presented as mean ± standard deviation, median (interquartile range) or *n* (%).

BMI, body mass index; Hb, hemoglobin; DM, diabetes mellitus; Scr, serum creatinine; UA, uric acid; CO_2, carbon dioxide binding rate; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; i-PTH, parathyroid hormone; K, serum potassium; Na, serum sodium; Ca, serum calcium; P, serum phosphorus; 1st-GCEP, first-generation cephalosporin; 3ird-GCEP, third-generation cephalosporin; AMIN, aminoglycosides.

$P < 0.05$ indicates that the test is statistically significant

Table 2: Comparison of microbiology between the two groups.

Organisms	Total ($n = 440$)	Treatment success ($n = 304$)	Treatment failure ($n = 136$)
Gram-positive, *n* (%)	132 (30.0)	103 (33.9)	29 (21.3)
Staphylococcus	47 (10.7)	34 (11.2)	13 (9.6)
Streptococci	53 (12.0)	49 (16.1)	4 (2.9)
Enterococci	26 (5.9)	15 (4.9)	11 (8.1)
Other	6 (1.4)	5 (1.6)	1 (0.7)
Gram-negative, *n* (%)	161 (36.6)	100 (32.9)	61 (44.9)
Escherichia coli	96 (21.8)	61 (20.1)	35 (25.7)
Klebsiella species	14 (3.2)	12 (3.9)	2 (1.5)
Pseudomonas	13 (3.0)	3 (1.0)	10 (7.4)
Other	38 (8.6)	24 (7.9)	14 (10.3)
Culture negative, *n* (%)	117 (26.6)	82 (27)	35 (25.7)
Polymicrobial, *n* (%)	26 (5.9)	19 (6.2)	7 (5.1)
Gram-negative	5 (1.1)	3 (1)	2 (1.5)
Gram-positive	11 (2.5)	10 (3.3)	1 (0.7)
Mixed	10 (2.3)	6 (2)	4 (2.9)
Other, *n* (%)	4 (0.9)	0 (0)	4 (2.9)

Pathogenic microorganisms

For the results of pathogenic microorganisms see Table 2. Gram-positive bacteria accounted for 30.0% of the total samples, of which 33.9% were successfully treated and 21.3% were failed. Among Gram-positive bacteria, *S. aureus* and *Streptococci* were the two most common types. Gram-negative bacteria accounted for 36.6% of the total samples, and the proportion was higher in the treatment failure group, reaching 44.9%. *Escherichia coli* was the most common type of Gram-negative bacteria, accounting for 21.8% of the total samples, of which 20.1% were treated successfully and in 25.7% treatment failed. In addition, some samples were culture negative, accounting for 26.6% of the total samples. Polymicrobial infections accounted for 5.9% of the total samples, with 6.2% in the successful treatment group and 5.1% in the failed treatment group. Among the multi-species infections, mixed infection with Gram-negative bacteria and Gram-positive bacteria accounted for 2.3%.

Antibiotic susceptibility tests

The drug sensitivities for all available pathogens are listed in Table 3. *Staphylococcus aureus* was completely sensitive to vancomycin (29/0/0), and sensitivities to ceftriaxone and levofloxacin were 65.5% (19/1/9) and 86.2% (25/2/2), respectively. *Streptococcus* was completely sensitive to vancomycin (23/0/0) and to levofloxacin (82.6%) (19/0/4). Methicillin-resistant *Staphylococcus aureus* was completely sensitive to vancomycin (3/0/0), and 33.3% (1/0/2) to levofloxacin. Methicillin-resistant coagulase negative *staphylococcus* was completely sensitive to vancomycin (8/0/0) and to levofloxacin (50%) (4/2/2). The sensitivity rate of *Enterococcus* to vancomycin was 80% (4/0/1), and it was completely sensitive to ceftriaxone (5/0/0). High level aminoglycoside-resistant *Enterococcus* (was completely sensitive to vancomycin (2/0/0). The sensitivities of *E. coli* to ceftazidime and levofloxacin were 91.1% (41/0/4) and 95.6% (43/2/0), respectively. The sensitivity of *E. coli* [extended-spectrum β-lactamase-positive (ESBL+)] to gentamicin was 55.5% (10/0/8) and that to ceftriaxone was 69.5% (16/1/6). *Klebsiella* was completely sensitive to vancomycin and ceftazidime (4/0/0) and 50% sensitive to ceftriaxone (2/0/2). *Klebsiella* ESBL+ was completely sensitive to vancomycin, but not to ceftriaxone (0/0/3). *Pseudomonas* was completely sensitive to ceftazidime (8/0/0) and gentamicin (2/0/0), and 87.5% sensitive to levofloxacin (7/0/1).

Construction of clinical prediction model for rPDAP

In addition to ESI and previous peritonitis history, the preliminary analysis of the experimental indexes showed that there were significant statistical differences in ALB, serum sodium, mGFR and urine volume between the cure group and the treatment failure group. The WBC in peritoneal dialysate in the failed group was significantly higher than that in the cure group on the third and fifth day. The difference in peritoneal dialysate PMN on the first day between the two groups was also statistically significant (Table 1).

Based on univariate analysis of training data set, we get the following results. Duration of PD [odds ratio (OR) 0.98, 95% confidence interval (CI) 0.97–0.99, $P < .001$], previous peritonitis ≤3 times (OR 5.89, 95% CI 2.92–11.89, $P < .001$), ALB (OR 1.09, 95% CI 1.03–1.15, $P < .001$), serum sodium (OR 1.14, 95% CI 1.04–1.24, $P = .003$), urine volume (OR 1.21, 95% CI 1.30–1.16, $P < .001$), mGFR (OR 1.33, 95% CI 1.11–1.61, $P = .03$), PMN in peritoneal dialysate on the first day of peritonitis (OR 0.20, 95% CI 0.05–0.84, $P = .03$), WBC in peritoneal dialysate on the fifth day of peritonitis $>300 \times 10^6$/L (OR 0.09, 95% CI 0.04–0.22, $P < .001$), WBC in peritoneal dialysate on the third day of peritonitis (OR 0.97, 95% CI 0.96–0.99, $P < .001$) and the types of pathogens with Gram-negative (OR 0.27, 95% CI 0.12–0.62, $P = .002$) were related to the prognosis of treatment of refractory peritonitis ($P < .05$). These variables were included in the multivariate analysis of logistics regression (Table 4).

Finally, according the results of multivariate analysis of training data set, previous peritonitis ≤3 times (OR 6.57, 95% CI 2.51–17.22, $P < .001$) and were correlated with the better prognosis of rPDAP, while WBC in peritoneal dialysate on the third day of peritonitis (OR 0.98, 95% CI 0.96–1.00, $P < .04$), or on the fifth day of peritonitis $\geq 300 \times 10^6$/L (OR 0.10, 95% CI 0.04–0.29, $P < .001$), the pathogenic microorganism with Gram-negative bacteria (OR 0.29, 95% CI 0.10–0.87, $P = .03$) and the duration of PD (OR 0.98, 95% CI 0.97–0.99, $P = .01$) were associated with poor outcomes of rPDAP. All these variants were included in the final prediction model ($P < .05$) (Table 4).

Application scenario of clinical prediction model

The practical application of the model is shown in Fig. 2. The model is based on the assumption of a PD patient: four previous cases of peritonitis, dialysate culture results of Gram-negative organisms, dialysis duration of 48 months, peritoneal dialysate WBC on Day 3 was 2500×10^6/L and peritoneal dialysate WBC on Day 5 was 250×10^6/L. The scores are 0, 28, 66, 76 and 88, respectively, with a total score of 253. The probability of cure was 0.692 (95% CI 0.416–0.876).

Validation of clinical prediction model

In order to verify the performance of the model, bootstrap self-sampling was used to obtain the logistic regression internal verification area under the curve (AUC) CI and draw the ROC curve. In the internal verification using the training data set, the C-statistical value of nomogram to predict the cure probability of refractory peritonitis was 0.870 (95% CI 0.821–0.918), while

Table 3: Available susceptibility test results for refractory peritonitis-causing bacteria.

Organisms	Ceftazidime S/I/R	Gentamicin S/I/R	Vancomycin S/I/R	Ceftriaxone S/I/R	Levofloxacin S/I/R
Gram-positive (74)					
Staphylococcus (29)	–	–	29/0/0	19/1/9	25/2/2
Streptococci (23)	–	17/0/6	23/0/0	–	19/0/4
MRSE (3)		3/0/0	3/0/0		1/0/2
MRSCON (8)		6/0/2	8/0/0		4/2/2
Enterococci (5)		5/0/0	4/0/1	5/0/0	4/0/1
Enterococci HLAR+ (2)		0/0/2	2/0/0		2/0/0
Other Gram-positive organisms (4)			4/0/0	3/1/0	4/0/0
Culture negative (91)					
Escherichia coli (45)	41/0/4	28/2/9	–	39/0/6	43/2/0
Escherichia coli ESBL+(23)	8/4/11	10/0/8		16/1/6	9/6/8
Klebsiella (4)	4/0/0	–	4/0/0	–	2/0/2
Klebsiella ESBL+ (3)	0/0/3	2/1/0	4/0/0	–	0/0/3
Pseudomonas (8)	8/0/0	2/0/0	–	–	7/0/1
Other Gram-negative bacilli (8)	7/1/0	3/0/1		8/0/0	7/0/1

S, susceptible; R, resistant; I, intermediate; –, not detected; MRSE, methicillin-resistant *Staphylococcus aureus*; MRSCON, methicillin-resistant *Staphylococcus coagulase* negative; HLAR, high level aminoglycoside resistance.

Table 4: Univariate and multivariable logistic regression of rPDAP cure.

Variable	Univariate		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Duration of dialysis (months)	0.98 (0.97–0.99)	<.001	0.98 (0.97–0.99)	**.01**
Previous peritonitis ≤3 times	5.89 (2.92–11.89)	<.001	6.57 (2.51–17.22)	**<.001**
ESI (*n*, %)	3.05 (0.79–11.76)	.11		
Organisms				
Gram-positive	Reference		Reference	
Gram-negative	0.27 (0.12–0.62)	.002	0.29 (0.10–0.87)	**.03**
No growth	0.42 (0.18–1.01)	.053	0.11 (0.03–0.39)	**<.001**
Polymicrobial	0.33 (0.09–1.20)	.09	0.17 (0.03–0.90)	**.04**
ALB (g/dL)	1.09 (1.03–1.15)	.003	1.08 (1.00–1.17)	.06
Na (mmol/L)	1.14 (1.04–1.24)	.003	0.99 (0.88–1.11)	.84
mGFR (mL/min/1.73 m^2)	1.33 (1.11–1.61)	.002	1.28 (0.98–1.68)	.07
Urine output (10 L/day)	1.21 (1.3–1.16)	<.001	1.06 (0.94–1.18)	.36
Intestinal obstruction	0.24 (0.95–17.68)	.06		
Day 1 effluent PMN proportion	0.20 (0.05–0.84)	.03	0.29 (0.04–2.14)	.23
Day 3 effluent WBC (10^8/L)	0.97 (0.96–0.99)	<.001	0.98 (0.96–1.00)	**.04**
Day 5 effluent WBC ≥300 × 10^6/L	0.09 (0.04–0.22)	<.001	0.10 (0.04–0.29)	**<.001**

P < 0.05 indicates that the logistics single or multiple regression test is statistically significant.

in the internal verification of the verification data set, the C-statistical value of successful treatment of refractory peritonitis was 0.785 (95% CI 0.680–0.890) (the corresponding ROC curve is shown in Fig. 3A and B). Hosmer–Lemeshow goodness of fit test was performed on the prediction model, and the result of the training set was *P*-value = .65.

The calibration curves of the training set and the verification set showed that the actual measured values of the cure probability of refractory peritonitis predicted by their nomogram were in good agreement (the corresponding calibration curves are shown in Fig. 4A and B). Finally, we drew the decision-making curve for the two groups of data, compared the clinical outcome of non-intervention based on the variables of the predictive model, and came to the conclusion that the use of this model would improve the clinical outcome of refractory peritonitis and increase the final benefit (the decision-making curve is shown in the chart in Fig. 5A and B).

Sensitivity analysis

We found that the five independent risk factors of logistics regression were all within the top 10 of the importance orders of the random forest model variables, showing a relatively good outcome similarity (Fig. 6A). The top 10 important variables in the importance ranking of the variables in the random forest model include 5 variables in the in the final prediction model (the fifth day of peritonitis less 300 × 106/L, WBC in peritoneal dialysate on the third day, previous peritonitis <3 times, pathogenic microorganism, duration of PD). The ROC curve of the validation set of the

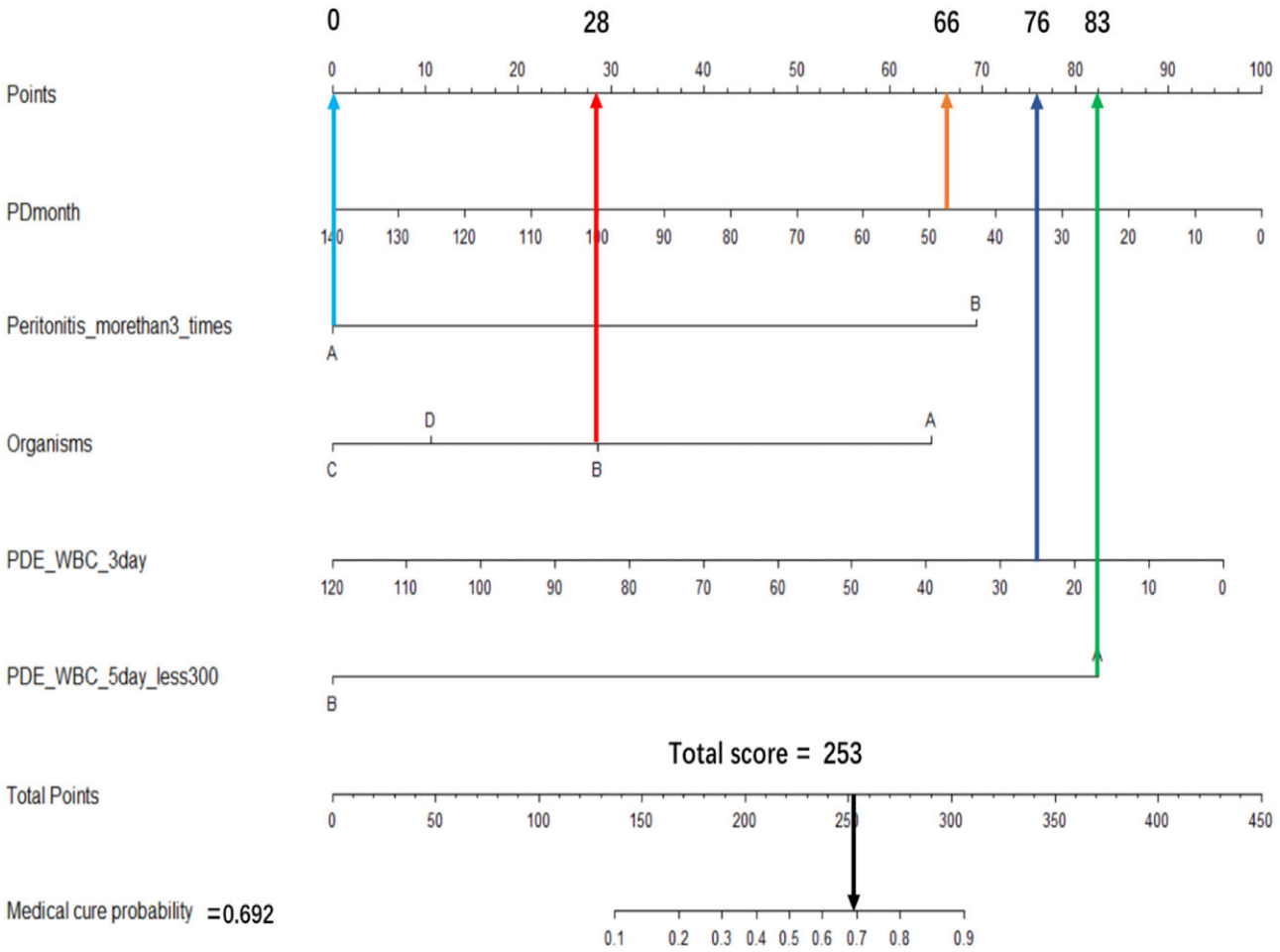

Figure 2: Nomogram for predicting cure of rPDAP. The scores of peritoneal dialysate WBC count on the fifth day $<300 \times 10^6$/L, WBC on the third day ($\times 10^8$/L), pathogen, previous peritonitis >3 times and duration of dialysis (months) were 83, 76, 28, 0 and 66, respectively. The probability of cure is 0.692 (95% CI 0.416–0.876).

prediction model based on the machine learning algorithm is lower than the AUC curve of the training set of the prediction model constructed by logistics regression (Fig. 6B).

DISCUSSION

In our study, the incidence rate of refractory peritonitis was 0.047 cases/patient-year, accounting for 39.9% of the total peritonitis. The results of ascitic fluid culture were mainly Gram-negative bacteria, and 69.1% patients with refractory peritonitis were successfully treated. The multiple linear regression effect significant independent variables were combined and screened into the nomogram model, including: previous peritonitis >3 times, the pathogenic microorganism, WBC in peritoneal dialysate on the fifth day of peritonitis $>300 \times 10^6$/L, WBC in peritoneal dialysate on the third day of peritonitis, and the duration of PD. The internal verification results showed that the model had a good quantitative prediction function for the successful treatment of refractory peritonitis. The AUC calculated by ROC analysis using the training data set and the validation data set were both above 0.75, which could be a relatively accurate prediction of treatment success for refractory peritonitis.

In this study, the average age of patients is relatively young [53 (41–64) years], which is consistent with the prevalence of primary nephropathy (glomerulonephritis 55.7%). This cohort feature has been reported many times in previous studies in our center and was considered to be related to the incidence of low early technique failure [15, 16].

According to a center in Taiwan, the incidence of peritonitis was 0.25 cases/patient-year, the incidence of rPDAP was 0.036 cases/patient-year [10]. In addition, about 34.6% of patients with refractory peritonitis eventually withdrew from treatment. According to a study of 930 PD patients in northern India, the incidence of rPDAP was 0.014 cases/patient-year, and about 42% of the patients failed treatment [17]. It is worth noting that although the incidence of peritonitis in our center was low (0.15 cases/patient-year), the incidence of refractory peritonitis was relatively high (0.047 cases/patient-year). Although there were different incidence rates, the high treatment failure rate of refractory peritonitis seriously affected the technical survival of PD patients.

According to our data, refractory peritonitis accounts for 39.9% of all peritonitis cases. We consider that the higher incidence of refractory peritonitis was related to the facts that patients with long vintage of PD as well as some patients delayed or failed to receive regular antibiotic treatment in time. In a prospective study by our center, the 5-year technique survival rate of PD patients can reach 85% [18], and the characteristics of poor nutrition, reduced immunity, reduced residual

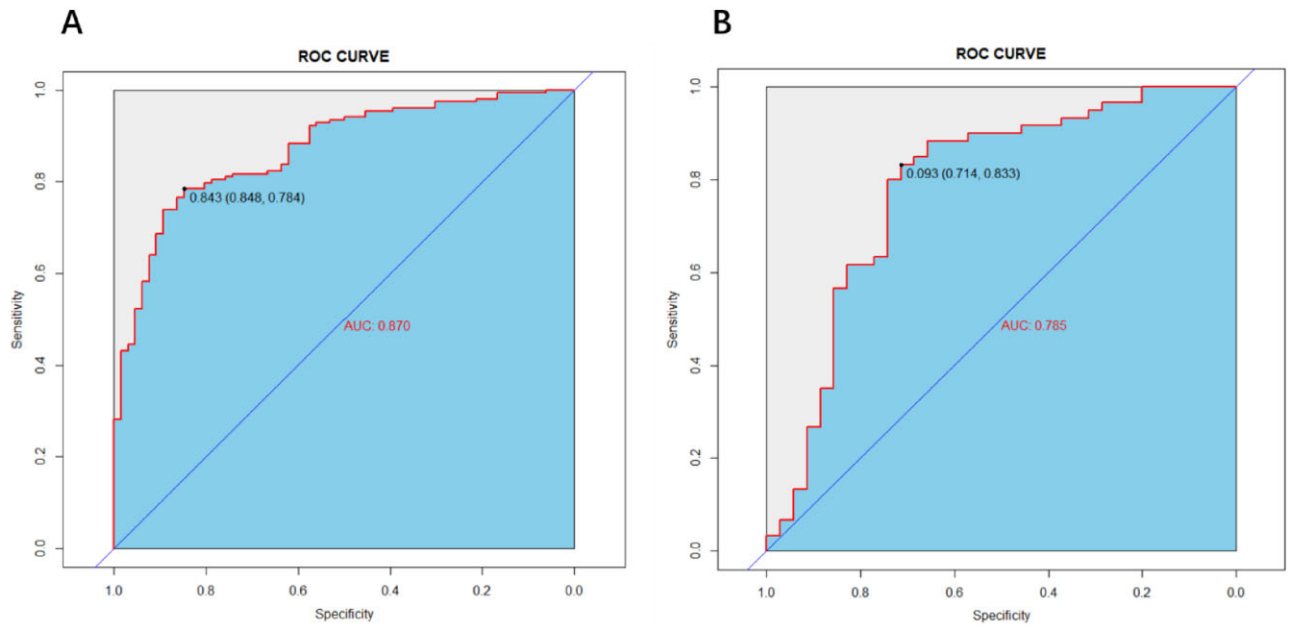

Figure 3: ROC curve of training set (**A**) and verification set (**B**) based on nomogram.

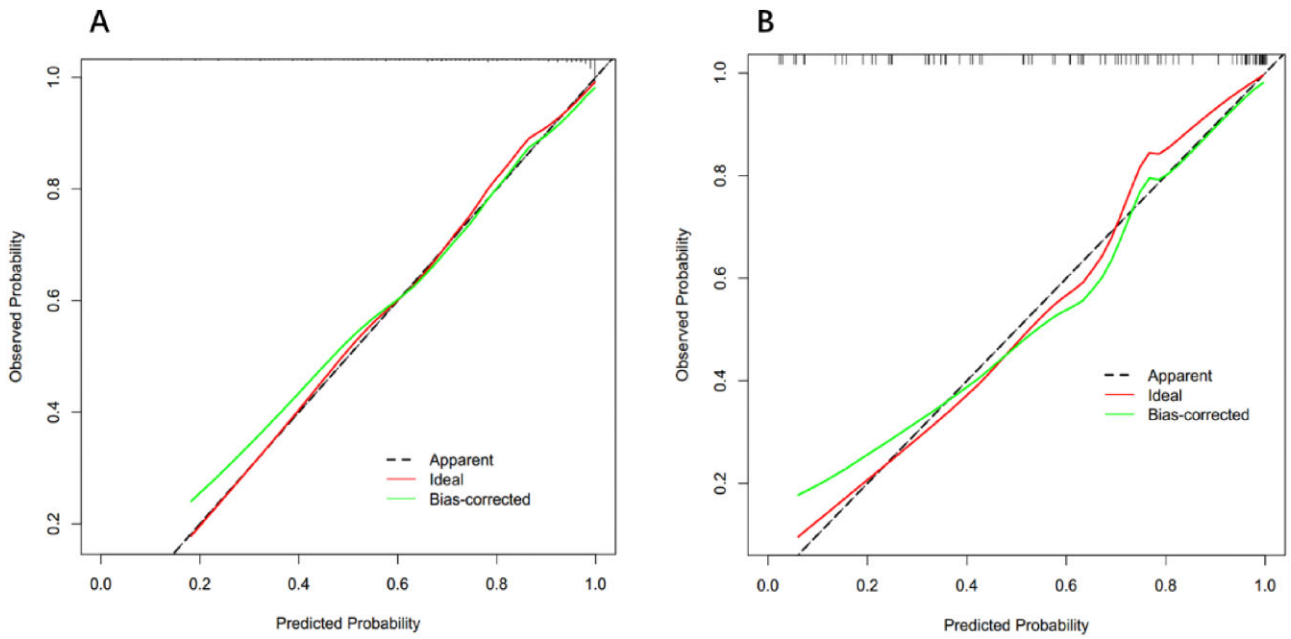

Figure 4: Calibration curve of prediction model (**A**) calibration curve of training set and (**B**) calibration curve of verification set.

kidney function and increased drug-resistant strains in these patients with long vintage of PD may lead to an increased incidence of refractory peritonitis [16, 19, 20]. Due to the long-time span, delayed treatment due to long distance and subjective reasons were also an important cause of refractory peritonitis, about 9.3% (52 cases) of patients with refractory peritonitis received regular antibiotic treatment 72 h after the onset of symptoms. Two recent studies on refractory peritonitis in China also reported relatively high rates of refractory peritonitis of 32% and 34% [21, 22], although they did not provide data on patients with delayed treatment.

The 2022 ISPD guidelines recommend that antibiotics should be adjusted for treatment once the results of culture and drug sensitivity are known [5]. If patients can carry out dialysate culture in time, the results of dialysate culture can usually be obtained before the time of diagnosis of refractory peritonitis, and then the antibiotic regimen can be adjusted according to the routine results of dialysate. Therefore, unlike the treatment of general peritonitis, the treatment of refractory peritonitis is often not empirical but adjusted. In our study, the negative rate of dialysate culture in rPDAP was slightly higher than that in the previous PDAP study (26.6% vs 24.2%) [23]. Thammishetti *et al.*'s

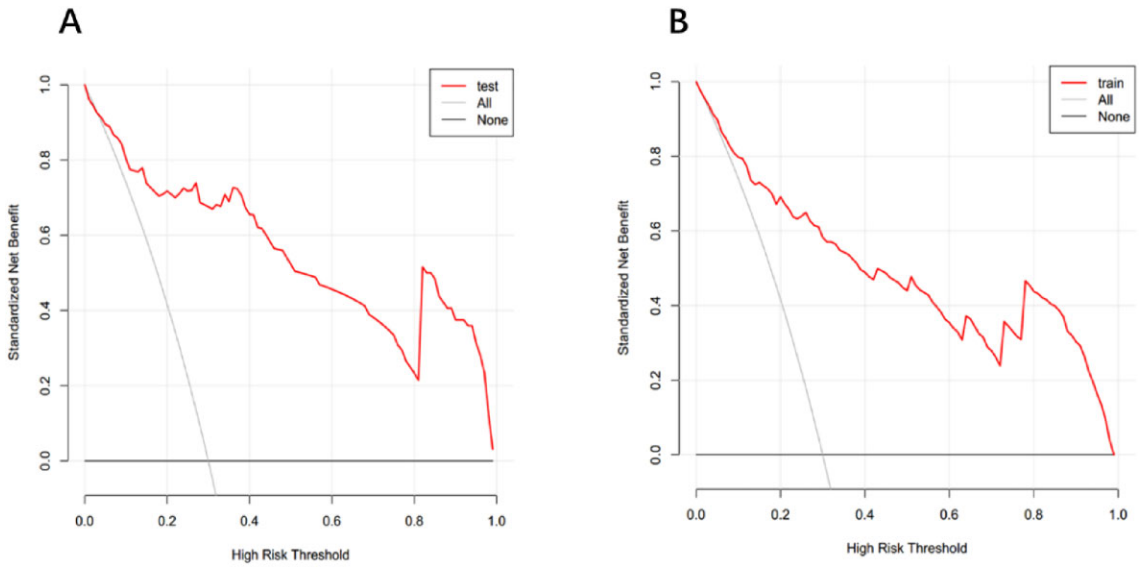

Figure 5: Decision curve analysis for the prediction model. (**A**) Training cohort, (**B**) validation cohort. The black horizontal line "None" represents the zero net benefit rate without treatment strategy adjustment, while the grey curve "All" represents the change of the net benefit rate with probability threshold. The net benefit of the predictive model (red line) is higher than that of the "All" or "None" treatment strategy (blue line or red line), indicating that the use of this model will improve the clinical outcome of refractory peritonitis and increase the final benefit.

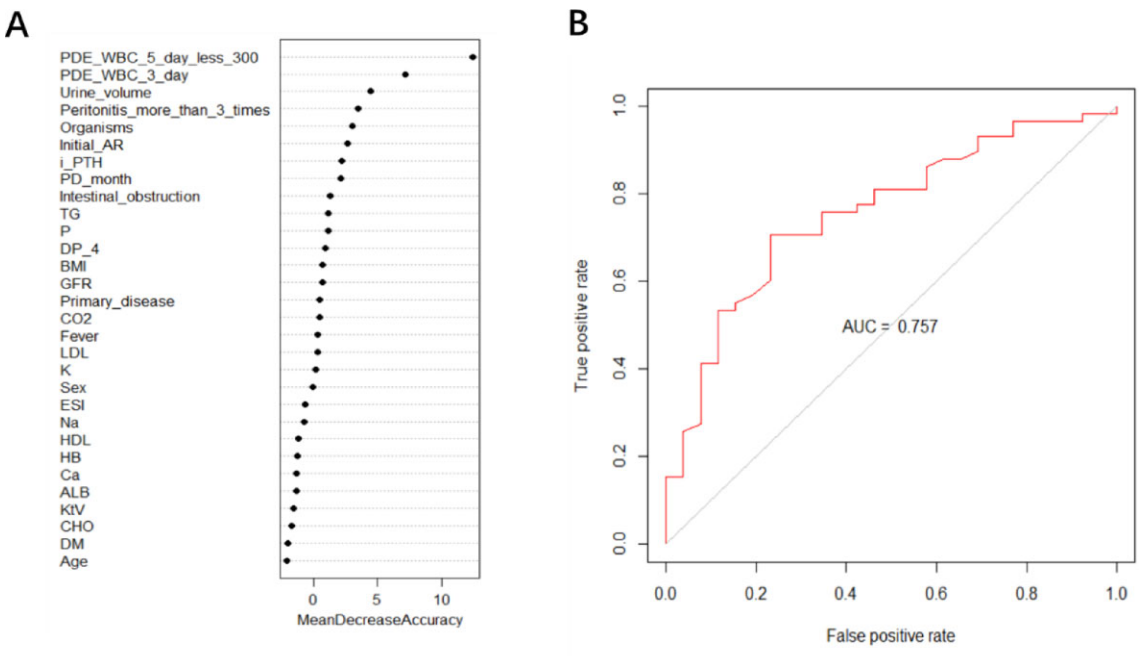

Figure 6: Ranking the importance of clinical covariates based on a random forest model (**A**) and the ROC curve in the validation set of the random forest model predicted the efficacy of refractory peritonitis (**B**). Initial AR, initial IP antibiotic regimens; i-PTH, parathyroid hormone; TG, triglyceride; P, serum phosphorus; BMI, body mass index; CO_2, carbon dioxide binding rate; LDL, low-density lipoprotein; K, serum potassium; NA, serum sodium; HDL, high-density lipoprotein; Hb, hemoglobin; Ca, serum calcium; DM, diabetes mellitus.

study of 93 cases of rPDAP showed that Gram-positive bacteria accounted for 11.8% and Gram-negative bacteria accounted for 17.2% in their cohort of refractory peritonitis [17]. In the study by Wang *et al.*, Gram-positive bacterial infection was dominant (70.4%), mainly *Staphylococcus* (51.9%) [10]. These results are different from our study, which may be related to the different pathogenic bacterial spectrum and drug resistance rate in our dialysis center. Since the prognosis of various Gram-negative bacterial peritonitis is worse than that of Gram-positive bacterial peritonitis [24], this may be the reason why Gram-negative bacteria are more likely to develop into refractory peritonitis. In this study, the proportion of culture-negative peritonitis

was higher than the requirement of the 2022 ISPD guidelines that the culture-negative rate should be <15%. We believe that this may be related to the presence of peritonitis caused by atypical pathogens (mycobacteria, mycoplasma, viruses, etc. [25]) in patients with refractory peritonitis. This type of peritonitis is often difficult to culture, so it is difficult to diagnose and has a poor prognosis, resulting in poor treatment effects and easy development into refractory peritonitis. In addition, some patients used antibiotics before early standardized treatment culture or delayed culture (some patients referred from grassroots hospitals failed to use centrifugation culture for culture), resulting in negative culture results for patients, making it impossible to choose appropriate antibiotics for anti-infection treatment.

In previous models for predicting the outcome of peritonitis treatment, WBC in peritoneal dialysate had always been an important predictor [7, 8]. WBC in peritoneal dialysate on Day 5 was the most important predictor in a study using machine learning to evaluate the outcome of peritonitis treatment [9]. In a study in Hong Kong, WBC >1000/mm^3 in peritoneal dialysate on Day 3 (OR 9.03, 95% CI 4.40–18.6) and Day 5 (OR 7.38, 95% CI 3.38–16.1) were both important predictors of peritonitis leading to technical failure [26]. A prediction model in Thailand that included multicenter data showed that the cell count on Day 5 could better reflect the effect of treatment. The predicted distribution fraction of WBC count >1000/mm^3 on the fifth day was higher than >1000/mm^3 (6.5 vs 1.5) on the third-fourth day of dialysis [8]. In our prediction model includes the WBC of peritoneal dialysate on the peritonitis 3rd day and the WBC of peritoneal dialysate the peritonitis 5th day were less 300 × 10^6/L. When we tried to include the white blood cells of peritoneal dialysate <300 × 10^6/L on the fifth day and <300 × 10^6/L in the third day of peritoneal dialysate into the final model, we found that there was a negative correlation between the third day WBC of dialysate <300 × 10^6/L and the successful outcome of the treatment. We believe that the WBC of peritoneal dialysate on the fifth day affected the final result in multivariate analysis. It should be considered that on the third day, the WBC of peritoneal dialysate <300 × 10^6/L, while on the fifth day, the treatment of patients with WBC level of dialysate is prolonged due to repeated WBC level of dialysate increasing, which leads to treatment failure.

The results of this study also showed that the duration of peritoneal dialysis was an independent risk factor for treatment failure of rPDAP, and the average duration of dialysis in the cure group was significantly shorter than that in the failure group [26.0 (8.9, 52.0) vs 52.1 (28.1, 80.1)]. Many studies have shown that long-term dialysis vintage was an independent risk factor for extubation, death and treatment failure in PDAP patients. A study in the USA showed that patients with long dialysis time have lower albumin level and tend to have a poor prognosis when they encounter peritonitis [27]. In addition, continuous exposure to glucose and glucose degradation products in patients with long-term PD leads to impaired peritoneal function, which leads to withdrawal from PD [28]. Our study also found that previous PDAP >3 times also predicted treatment failure in rPDAP. An earlier study suggested that frequent peritonitis was an independent risk factor for death. For every 0.5 times per year increase in the incidence of peritonitis, the risk of death increased by 4% to 11% [29]. With the increase of dialysis age, the gradual indifference of aseptic concept and non-standard operation of patients can easily lead to repeated occurrence of PDAP. Repeated inflammation can accelerate protein loss and further aggravate malnutrition [30]. Therefore, when patients with long dialysis vintage and recurrent PDAP develop refractory peritonitis, strengthening the management and retraining of this population may help to reduce the incidence of rPDAP and reduce the incidence of technical failure.

Compared with the previous peritonitis prognosis prediction model, our prediction model may be more accurate, which may be related to the cohort we selected. After initial treatment, there are more conditions to predict the diagnosis of refractory peritonitis than newly occurred peritonitis. In addition, our included sample size has a significant advantage over previous studies of refractory peritonitis. Finally, the application of nomogram can obtain the data needed for decision-making more intuitively and conveniently, and provide intuitive reference for clinical decision-making. For the patients with high cure rate, continuous antibiotic treatment should be given and the observation period of extubation should be prolonged appropriately. If the cure rate is low, it is recommended to transfer to HD and pull out the catheter directly to avoid further complications.

However, there are still some defects in this model that need to be improved. First of all, other inflammatory indicators of PDAP, including C-reactive protein, procalcitonin and interleukin-6, may also be related to predicting the treatment outcome of dialysis patients, but they were not included in the final predictive model. Second, retrospective observational methodology is prone to selection biases and confounding factors that may not be fully accounted for. Third, some patients had delayed treatment due to emergency referrals, which may affect the patients. Finally, this is a single-center study, which may limit the generalizability of findings. Relatedly, we need external validation of the nomogram in different geographical and clinical settings.

CONCLUSION

In summary, we established a model to predict the treatment outcome of refractory peritonitis and drew a nomogram to help doctors evaluate the probability of successful treatment of PDAP. This model can be used to evaluate when the patient's dialysate WBC is still >100 × 10^6/L on the fifth day after regular antibiotic treatment. When the risk of treatment failure is high, patients should be transferred to HD treatment and there should be timely removal of the PD catheter to reduce the occurrence of severe peritonitis complications. Improving this nomogram still requires external verification by other peritoneal dialysis centers or larger peritoneal dialysis data sets.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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