A Prediction Model for Cure of Peritoneal Dialysis-Associated Peritonitis: A Multicenter Study

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Research Article

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Abstract

Aim

Peritoneal dialysis (PD)-associated peritonitis (PDAP) is a severe complation of PD. And it is an important issue about whether it can be cured. At present, there is no available prediction model for peritonitis cure. Therefore, the present work aimed to develop and validate a risk prediction model for peritonitis cure in PDAP patients.

Methods

PD patients who developed PDAP from four dialysis centers in Northeast China were followed up. According to the region of PD, data were divided into training and validation datasets. First of all, a nomogram for peritonitis cure was established based on the training dataset. Later, performance of the nomogram model was assessed by discrimination (C-statistic), calibration and decision curves.

Results

In total, 1063 episodes of peritonitis were included in the final analysis, including 806 in the training dataset and 257 in the validation dataset. During the follow-up period, 621 and 199 cases in the training and validation datasets, respectively, reported peritonitis cure. Predictors incorporated in the final nomogram model included PD duration, serum albumin, antibiotics prior to admission, and type of causative organisms. The C-statistic values were 0.76 (95% CI: 0.72–0.80) in the training dataset and 0.77 (95% CI: 0.70–0.84) in the validation dataset. The nomogram exhibited favorable performance in terms of calibration in both the training and validation datasets.

Conclusion

This study develops a practical and convenient nomogram for the prediction of peritonitis cure in PDAP patients, which assists in the clinical decision-making.

Introduction

Aim

End-stage renal disease (ESRD) is a condition characterized by a high mortality rate and reduced quality of life, and for patients receiving dialysis, they experience tremendous burdens[1]. Peritoneal dialysis (PD) is a home-based and cost-effective dialysis modality for ESRD patients, which can be customized depending on the value, expectation, and lifestyle of patients[2]. PD has been increasingly utilized in many countries over the past decade[3], and China is becoming a country with the largest number of PD patients in the world[4]. In light of the rapid spread of coronavirus disease 2019 (COVID-19) throughout the world, PD offers a great advantage over hemodialysis (HD) as an efficient renal replacement therapy with a low risk of coronavirus infection[5].

Peritoneal dialysis-associated peritonitis (PDAP) is a severe complication of PD. The incidence rate and outcome of peritonitis vary greatly across different countries[6]. Despite the application of appropriate antibiotic therapy, PDAP still affects the mortality and technological survival rates of patients, and contributes to the added hospitalization events and treatment costs[7, 8]. On the other hand, severe peritonitis episodes may progress to encapsulating peritoneal sclerosis, which precludes successful PD[9]. It is a crucial clinical issue for clinicians to get a better outcome of this patient population. If individual peritonitis cure can be predicted based on the comprehensive assessment of the patient's condition, a precise therapy and care strategy can be implemented to minimize patient sufferings and save medical resources.

Several prognostic factors for PDAP cure have been reported in studies, including modifiable risk factors and nonmodifiable risk factors[10]. However, to our knowledge, there is few available prediction model for the outcome of peritonitis at present. Therefore, this study aimed to establish and validate a prediction nomogram model to guide clinical decision-making and improve the quality of PDAP treatment.

Materials And Methods

Study participants

All PD patients who developed PDAP during the study period from January 1st, 2013 to December 31st, 2019 were included and followed up in this study. Altogether 1145 PDAP episodes were collected from four dialysis centers in Northeast China (Second Hospital of Jilin University, First Hospital of Jilin University, Jilin FAW General Hospital, and Jilin Central Hospital). The diagnosis of PDAP was made based on the presence of any two of the following features: (1) clinical features consistent with peritonitis, *i.e.*, abdominal pain and/or cloudy dialysis effluent; (2) white cell count (WBC) in dialysis effluent > 100/μL after a dwell time of at least 2 h, with > 50% polymorphonuclear leucocytes; and (3) positive culture of dialysis effluent[7]. Meanwhile, the patient exclusion criteria were as follows, (1) those whose medical records were incomplete, (2) those younger than 18 years old, (3) those whose dialysis effluent was not cultured, (4) those treated with immunosuppressant medications, and (5) those with chronic liver disease at the time of PD diagnosis. According to the different regions of PDAP patients, data were divided into training (First Hospital of Jilin University, Jilin Central Hospital) and validation (Jilin FAW General Hospital, Second Hospital of Jilin University) datasets. In line with the guidelines set forth by the International Society for Peritoneal Dialysis, PDAP was treated with standard antibiotics covering both gram-positive and gram-negative pathogens. Once the culture results and sensitivities were known, antibiotic therapy was adjusted to narrow-spectrum agents. Treatment with effective antibiotics lasted for 2-3 weeks according to the type of organism. PD catheters were removed in accordance with the ISPD peritonitis recommendation. Informed consent was waived due to the retrospective and non-interventional design of this study by the Ethics Committee of Second Hospital of Jilin University (No. 2020026). Members of the Ethics Committee of Second Hospital of Jilin University are as follows: Wei Yang; Xiujuan Fu; Yajuan Zheng; Jincheng Wang; Tiejun Wang; Bin Liu; Pinghui Sun;

Tianmin Xu; Zhonghai Yan; Xuan Zhang; Xuewen Zhang; Yunfeng Zhang; Junling Yang; Yanling Yin; Huiling Ji; Zhenghong Yan. All procedures in this study were performed in line with the Helsinki declaration.

Data collection

Clinical information, including prognostic factors associated with peritonitis cure in PD, was retrieved from the medical records of patients[11-13]. For each episode of peritonitis, we recorded the patient age at the time of PDAP, gender, number of PDAP episodes, PD duration, antibiotics used prior to admission, presence of protopathy and comorbidities [such as hypertension, diabetes mellitus (DM) or cardiovascular disease (CVD)]. Additionally, we also recorded results of various laboratory tests, including WBC count, serum albumin, hemoglobin, blood urea nitrogen (BUN), serum creatinine, blood ions (sodium, potassium, calcium, phosphorus), PD cell count on admission, presence of causative organisms, and exit-site infection. Further, the causative organisms in effluent samples were subcategorized into culture-negative organisms, gram-positive (Staphylococcus aureus, Cocoagulase-negative Staphylococcus, Corynebacterium, Enterococcus, others), gram-negative (pseudomonas aeruginosa, Escherichia coli, Klebsiella Pneumoniae, Enterobacter species, others), polymicrobial, Mycobacterium tuberculosis or fungi. Polymicrobial peritonitis was defined as the presence of two or more cultured pathogens in the PD solution. All biochemical measurements were completed using the standard laboratory techniques.

Outcome

The primary outcome of interest was peritonitis cure, which was defined as the absence of a subsequent peritonitis event (relapse or recurrence), PD catheter removal, or transfer to HD (deemed permanent transfer to HD, or temporary transfer with failure to return to PD within the modality switch date 84 days), or death within 50 days after the onset of a peritonitis episode[14].

Statistical analysis

Logistic regression was utilized to determine the potential outcome predictors in the training dataset. Risk factors associated with peritonitis cure were identified through univariate analysis, then, the significant risk factors were further incorporated into the multivariate logistic regression model. Thereafter, a nomogram was constructed based on the multivariate logistic regression model to calibrate the probability estimates of peritonitis cure individually. In the nomogram model, categorical covariates were considered as dummy variables. All variables incorporated in logistic regression were predictors with <10% of missing values. Continuous variables were interpolated by mean or median according to the type of distribution, whereas categorical variables were interpolated by mode.

Internal validation was accomplished in the entire training dataset. Moreover, the C-statistic was calculated to assess the model discrimination using Stata, and the calibration curve was subsequently plotted.

External validation was performed in the validation dataset based on the prediction model. The predicted value was obtained by employing the prediction function of Stata. Thereafter, the C-statistic was calculated to assess the model discrimination, and the calibration curve was plotted. Moreover, decision curves were also plotted to evaluate the clinical usefulness of the nomogram.

Statistical analysis was carried out using SPSS (version 22.0, IBM, New York, United States) and Stata (version 15.0; StataCorp LP) software. A *P*-value less than 0.05 was considered as statistically significant.

Results

Characteristics of study participants

During the study period, 1145 episodes of peritonitis from all the four centers met the criteria for PDAP. Among these candidate participants, 60 were excluded due to missing data, immunosuppressant medications, or liver disease at the initiation of PD. Additionally, 10 were further eliminated for being younger than 18 years of age, and 12 for no culture of dialysis effluent (Figure 1). Therefore, 1063 episodes of PDAP were finally included for analysis. Among them, 820 episodes were cured, yielding the overall cure rate of 77.1%. According to the region of PDAP, the episodes were divided into training (n = 806) and validation (n = 257) datasets. During the follow-up period, 621 and 199 cases of peritonitis cure were observed in the training and validation datasets, respectively. Patient demographics, clinical manifestations, and laboratory parameters in the training dataset recorded at baseline are shown in Table 1.

Model establishment

In this study, the prediction model was established based on the training dataset. Upon univariate analysis, four variables (including PD duration, serum albumin, antibiotics prior to admission, and type of causative organisms) were significantly associated with peritonitis cure. Therefore, these four predictors were incorporated into the final prediction model for multivariable analysis (Table 2). A nomogram for the practical application of this model is displayed in Figure 2. Its usage was illustrated with a hypothetical patient with PD duration of 1 year, no antibiotics prior to admission, a serum albumin of 40 g/L, and Escherichia coli infection (Figure 2, vertical lines). The points for PD duration, no antibiotics prior to admission, serum albumin and bacterial infection for this patient were 2.5 , 1.5, 3 and 7, respectively, resulting in the total points of 14, which represented approximately 0.84 of cure probability. It assisted in the identification of patients with a high or low probability of cure. If it intended to be cure, continuous maintenance of antibiotic therapy should be given. If it intended not to be cure, early catheter removal and device insertion for temporary HD might be advised.

Model validation

Internal validation of the prediction model

In the training dataset, the C-statistic for the prediction of peritonitis cure by the constructed nomogram was 0.76 (95% CI: 0.72–0.80) (Figure 3a), indicating reasonable model discrimination. Besides, the calibration curve demonstrated that the probability of peritonitis cure predicted by the nomogram was relatively well matched with the actual measurement (Figure 3b).

External validation of the prediction model

In the validation dataset, the C-statistic for the prediction of peritonitis cure by the constructed nomogram was 0.77 (95% CI: 0.70–0.84) (corresponding ROC curve is displayed in Figure 4a). In addition, the calibration curve exhibited good agreement between the nomogram-predicted value and the actual measurement (Figure 4b). A decision curve was also plotted to evaluate the clinical usefulness of the nomogram (Figure 5). Based on the above results, our nomogram accurately predicted patients with or without cure.

Discussion

A novel prediction model for peritonitis cure among PDAP patients was established and validated in this multicenter study. PD duration, serum albumin, antibiotics prior to admission, and type of causative organisms were included in the prediction model. Based on our results, the as-constructed model showed good performances in calibration and discrimination, with the C-statistic of over 0.75. Using the nomogram, it is possible to stratify individual peritonitis episodes and make reasonable treatment decisions. To our knowledge, this is the first prediction nomogram for predicting PDAP cure in patients initializing PD developed in a multicenter study.

There are few reports concerning the prediction model of peritonitis cure in PDAP population. Surapon Nochaiwong *et al.* developed a prediction score for the treatment failure among PD patients, which incorporated DM, systolic blood pressure (SBP), dialysate leukocyte count on day 3–4, and dialysate leukocyte count on day 5[15]. Nevertheless, their model did not incorporate pathogenic bacteria, and no external validation was conducted. Different from this study, their outcome was treatment failure containing catheter removal, transfer to HD, or peritonitis-associated mortality. As a matter of fact, their risk factors for the outcome were inconsistent.
In our study, the prediction nomogram model was more intuitive and applicable to clinical practice. The treatment decision should be made by taking into comprehensive consideration of a PDAP patient.

According to our results, a shorter PD duration was related to the possibility of peritonitis cure, which was supported by several reports. For instance, a study found that PD duration less than 2.4 years was associated with a higher resolution rate than that longer than 2.4 years [16]. Another study indicated that a longer PD duration at the onset of peritonitis was related to a longer duration from PD effluent abnormalities to treatment with appropriate antibiotics, which further led to adverse outcomes[17]. Similar finding was also obtained from other study, which was that patients receiving long-term dialysis were prone to gram-negative bacterial infection and worse

treatment outcomes compared with those undergoing short-term dialysis[18]. There are inconsistent results regarding the impact of PD duration on the outcome of PDAP in literature. For instance, Yang *et al.* did not find the relationship between PD duration and catheter loss[19]. The differences may be ascribed to the different definitions of study outcome. Our data confirmed that the increased PD duration reduced the probability of peritonitis cure in all the episodes of peritonitis. We infer that continuous exposure to glucose and glucose degradation products may lead to tissue toxicity in the peritoneum, resulting in peritoneal dysfunction[20]. This may further make it difficult to eliminate inflammation.

Another novel predictive factor for cure identified in this study was no antibiotics prior to admission. As far as we know, the relationship between antibiotics prior to admission and PDAP outcome remains unclear so far. On the one hand, the application of antibiotics at home may be related to serious patient condition, which results in the low possibility of cure. On the other hand, some patients applying antibiotics by themselves live far away from the PD center, and the remote distance from the hospital is also one of the risk factors for peritonitis and technique failure[21]. Moreover, in our study, the application of antibiotics was not standardized at home by PDAP patients, which delayed the optimal timing of standard treatment[17] and added to the difficulty in cure.

It was observed in this dataset that a higher level of serum albumin predicted a higher probability of peritonitis cure. In contrast to our study, one article considered that serum albumin level did not affect the non-resolution of peritonitis[22]. Another study reported that serum albumin was not the risk factor for the poor outcomes of PDAP patients[23]. Such differences may be attributed to their relatively small sample sizes that are insufficient to find the association between serum albumin and the outcome of PDAP. Hypoalbuminemia is identified as a risk factor for peritonitis in PD patients[24-26]. As reported in one study, hypoalbuminemia, a marker of malnutrition and inflammation, also predicted the all-cause, cardiovascular, and infection-related mortality in patients receiving PD[27]. Moreover, a higher daily protein intake in PD patients indicates a higher serum albumin level and good nutrition status, which prevent patient death or peritonitis[28]. It is not hard to infer that a higher serum albumin level is related to the cure of PDAP. Theoretically, a higher serum albumin level has a good remedial effect when antibiotics are bound onto the serum albumin and the drug metabolism is reduced. We found that a high serum albumin level was good for the cure of PDAP, and it was assumed that treatment strategies to improve albumin levels should be advocated to improve the treatment outcome of peritonitis.

Noteworthily, the causative organism was included in the prediction model. As a matter of fact, the causative organism is an important factor for the outcome of PDAP. However, the specific effects on outcome between some bacteria are unclear. Our constructed nomogram allowed to intuitively observe the concrete effects of different bacteria on cure. In our study, Enterococcus showed the highest score to cure, followed by other G-positive Corynebacteria. Then, Cocoagulase-negative Staphylococcus and culture-negative organisms had the same score. In Htay's study[29], causative organisms were related to the outcome of

PDAP; The authors divided pathogenic bacteria into Gram-positive, Gram-negative, Culture-negative, Polymicrobial organisms and others, and found that Culture-negative bacteria had a higher cure rate than Gram-positive ones. Another study indicated that less virulent causative organisms (coagulase-negative staphylococci, and culture-negative streptococci) were associated with a higher probability of cure[10]. The prognosis of gram-negative bacterial peritonitis was worse than that of Gram-positive bacterial peritonitis in our study, consistent with Fung's study[30]. In the present work, bacterial classification was more detailed according to the ISPD peritonitis guidelines, which overcame the problem of different prognosis of different Gram-positive or Gram-negative bacteria. Pathogenic bacteria contained in our model were specific and suitable for clinical applications.

To the best of our knowledge, this is the first nomogram that provides clinicians with a predictable assessment tool for the cure of peritonitis among PDAP patients. Our research has a few strengths. First, our findings serve as the useful reference for the management of PDAP episodes by physicians, which rely on comprehensive assessment rather than a single factor. The external utility of the model is good and can be generalized. Timely ceasing PD can reduce the length of hospital stay, medical costs, and occurrence of serious complications in patients with a low probability of PDAP cure. Furthermore, the nomogram is practical because all the variables included are the easily and routinely collected clinical factors, which offers an intuitive tool for individualized prediction using a small number of risk factors.

Nonetheless, several limitations should also be noted in this study. First, given the retrospective nature of this study, there might be potential selection bias. Second, we did not take into account new biomarkers such as IL-6, COX-2, RNase 3 and RNase 7[31, 32]. Future studies should develop or update the prediction model to include new biomarkers. Besides, a larger population size and prospective investigations are also warranted.

Conclusion

In conclusion, this study develops a practical and convenient nomogram with good accuracy in estimating the probability of peritonitis cure among PDAP patients, which assists in the clinical decision-making.

Declarations

Acknowledgement

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Competing interests

The authors declare no competing interests.

Authors' contributions

Lingfei Meng explored the data and wrote this manuscript. Xinyang Li, Siyu Cheng, Shizheng Guo, Xiaohua Zhuang and Hongbin Zou collected the data. Liming Yang, Xueyan Zhu and Xiaoxuan Zhang provided the data. Ping Luo organized the study. Wenpeng Cui designed this study and reviewed this manuscript.

Consent to participate

Informed consent was exempt, due to the retrospective and non-interventional design of this study.

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Baseline demographic and laboratory parameters of 806 peritoneal dialysis-associated peritonitis episodes in the training dataset.

Index	Training dataset (n = 806)
Demographic characteristics	
Age (yr)	60(48, 69)
Gender (male, *n*, %)	385(47.8)
No. of PDAP episodes	1(1, 2)
PD duration (year)	1.34(0.51, 2.62)
Antibiotics before admission (yes)	77(9.6)
Protopathy	
glomerulonephritis	314(39.0)
interstitial nephritis	37(4.6)
Diabetic nephropathy	197(24.4)
Hypertensive renal impairment	139(39.0)
other	119(14.8)
Hypertension	716(88.8)
DM	276(34.2)
CVD	306(38.0)
Laboratory test	
WBC (10^{12}/L)	8.38(6.15, 11.35)
Hb (g/L)	99(84, 112)
Al (g/dL)	28.46 ± 6.34
BUN (mmol/L)	15.62(11.99, 19.82)
Scr (μmol/L)	711.2(545.00, 895.20)
PD cell count on admission(/μL)	80(60, 130)
Organisms (*n*, %)	
Culture-negative	132(16.4)
Gram-positive	
Staphylococcus aureus	34(4.2)
Cocoagulase-negative Staphylococcus	190(23.6)
Corynebacterium	10(1.2)

Enterococcus	15(1.9)
others	109(13.5)
Gram-negative	
pseudomonas aeruginosa	11(1.4)
Escherichia coli	80(9.9)
Klebsiella Pneumoniae	21(2.6)
Enterobacter species	18(2.2)
others	70(8.7)
Polymicrobial	75(9.3)
Fungi or Mycobacterium tuberculosis	41(5.1)
ESI/tunnel infection	3□0.4□

DM: Diabetes mellitus; PD: Peritoneal dialysis; WBC: White cell count; Hb: Hemoglobin; Alb: Albumin; BUN: Blood urea nitrogen; Scr: Serum creatinine; PDAP: Peritoneal dialysis-associated peritonitis; CVD: Cardiovascular disease; ESI: Exit-site infection.

Table 2. Univariate and multivariable Logistic regression of cure in the training dataset.

	Univariate			Multivariable		
Variable	B	OR(95% CI)	P	B	OR(95% CI)	P
PD duration(every one year)	-0.13	0.88(0.81, 0.95)	0.00	-0.14	0.87(0.79, 0.95)	0.00
Albumin(every 5g/L)	0.18	1.20(1.05, 1.37)	0.01	0.22	1.24(1.06, 1.45)	0.01
Antibiotics before admission	-0.83	0.44(0.27, 0.71)	0.00	-0.89	0.41(0.23, 0.74)	0.00
Type of organisms						
Culture-negative	Reference					
Gram-positive						
Staphylococcus aureus	-1.18	0.31(0.13, 0.72)	0.01	-1.23	0.29(0.12, 0.70)	0.01
Cocoagulase-negative Staphylococcus	-0.03	0.97(0.52, 1.83)	0.93	0.00	1.0(0.53, 1.90)	1.00
Corynebacterium	0.41	1.51(0.18, 12.64)	0.70	0.32	1.38(0.16, 12.06)	0.77
Enterococcus	0.86	2.35(0.29, 18.96)	0.42	0.89	2.43(0.30, 19.83)	0.41
others	0.51	1.66(0.74, 3.75)	0.22	0.53	1.70(0.74, 3.92)	0.21
Gram-negative						
pseudomonas aeruginosa	-1.97	0.14(0.04, 0.51)	0.00	-1.95	0.14(0.04, 0.53)	0.00
Escherichia coli	-0.88	0.42(0.21, 0.83)	0.01	-0.82	0.44(0.22, 0.90)	0.02
Klebsiella Pneumoniae	-1.09	0.34(0.12, 0.94)	0.04	-1.05	0.35(0.12, 1.01)	0.05
Enterobacter species	-0.83	0.44(0.14, 1.37)	0.15	-0.87	0.42(0.13, 1.37)	0.15
others	-0.40	0.67(0.31, 1.44)	0.31	-0.51	0.60(0.27, 1.33)	0.21
Polymicrobial	-1.03	0.36(0.18, 0.71)	0.00	-1.14	0.32(0.16, 0.65)	0.00
Fungi or Mycobacterium tuberculosis	-4.75	0.01(0.00, 0.04)	0.00	-4.82	0.01(0.00, 0.04)	0.00

Figures

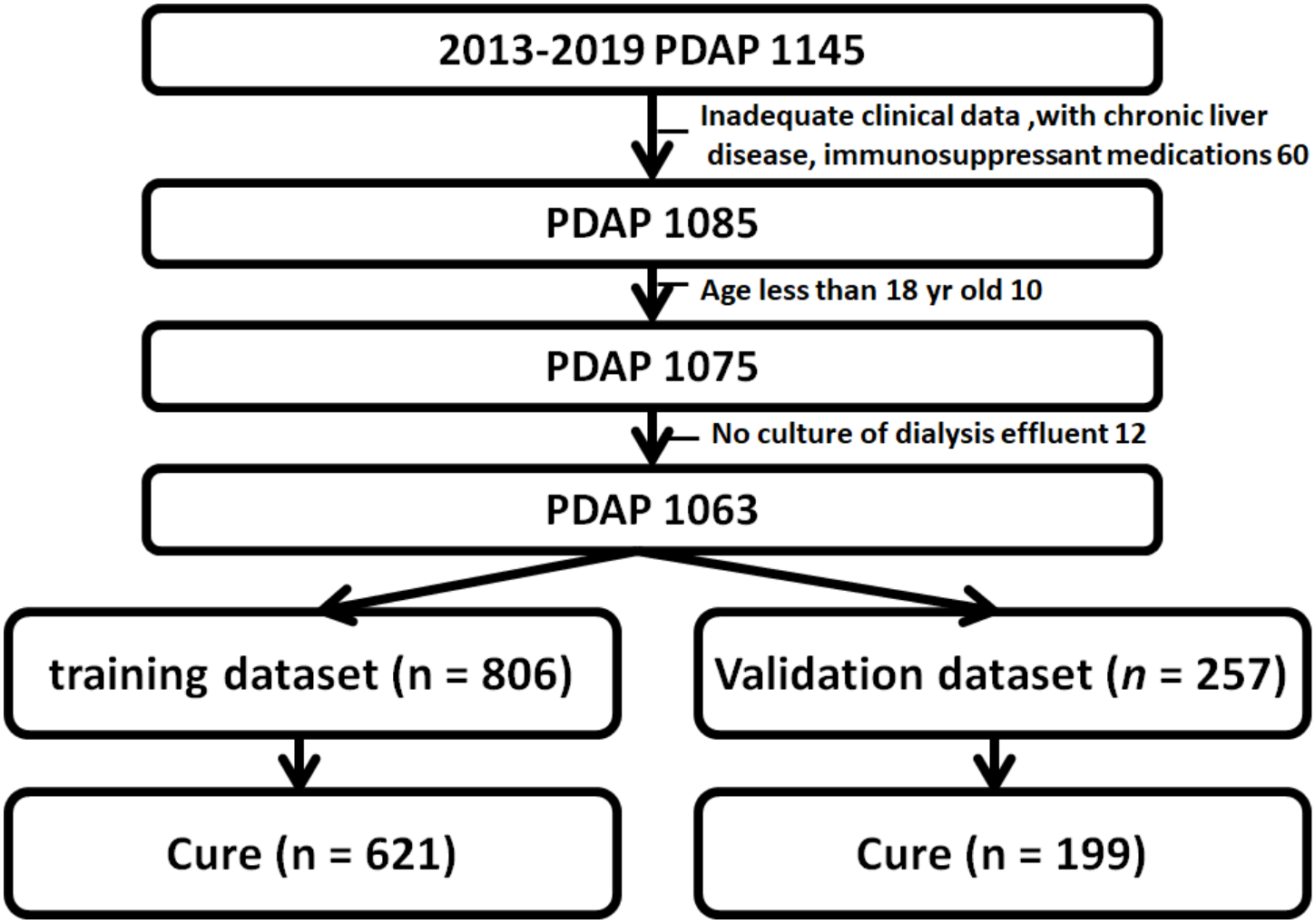

Figure 1

Flowchart of cohort establishment

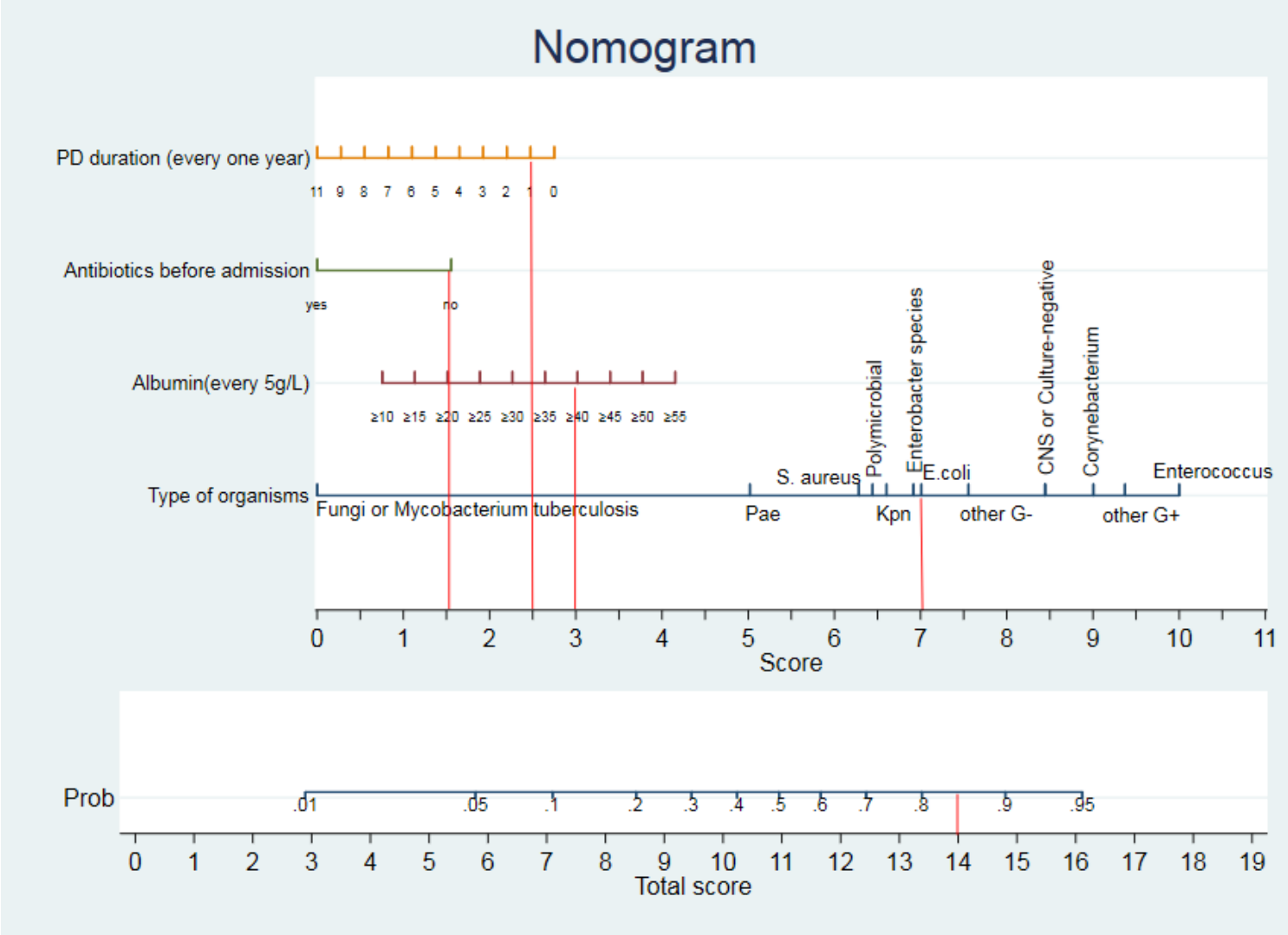

Figure 2

The nomogram for predicting cure of PDAP

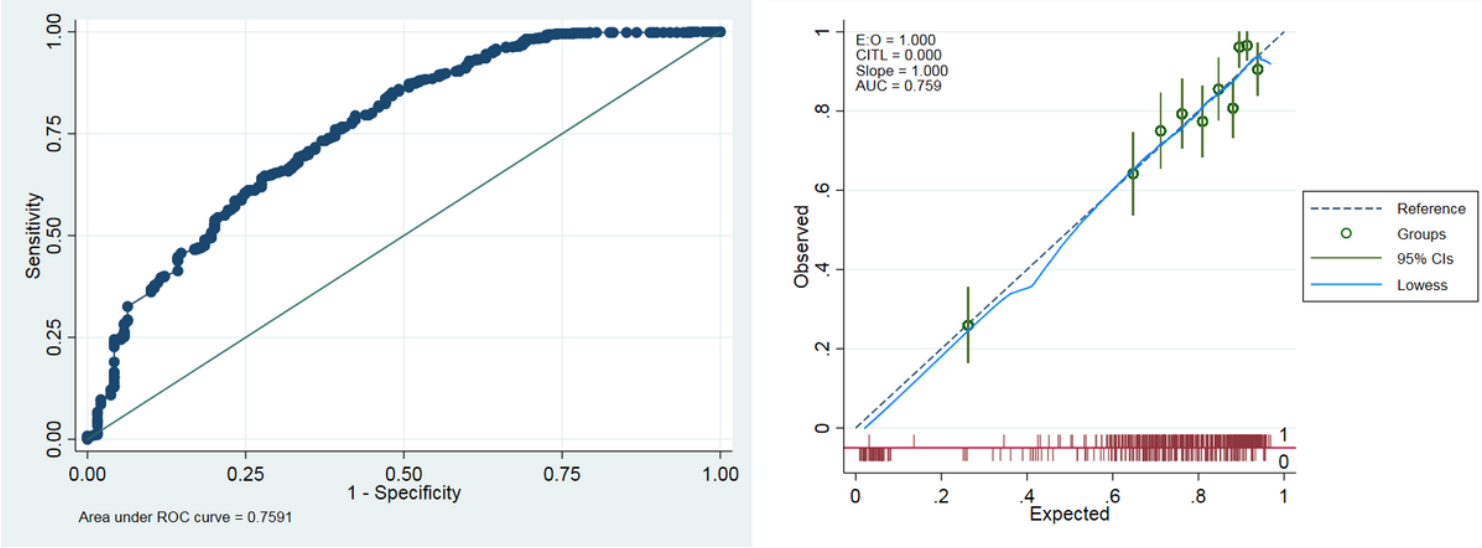

Figure 3

a. ROC curve for internal validation of cure

b. Calibration plot for internal validation of cure

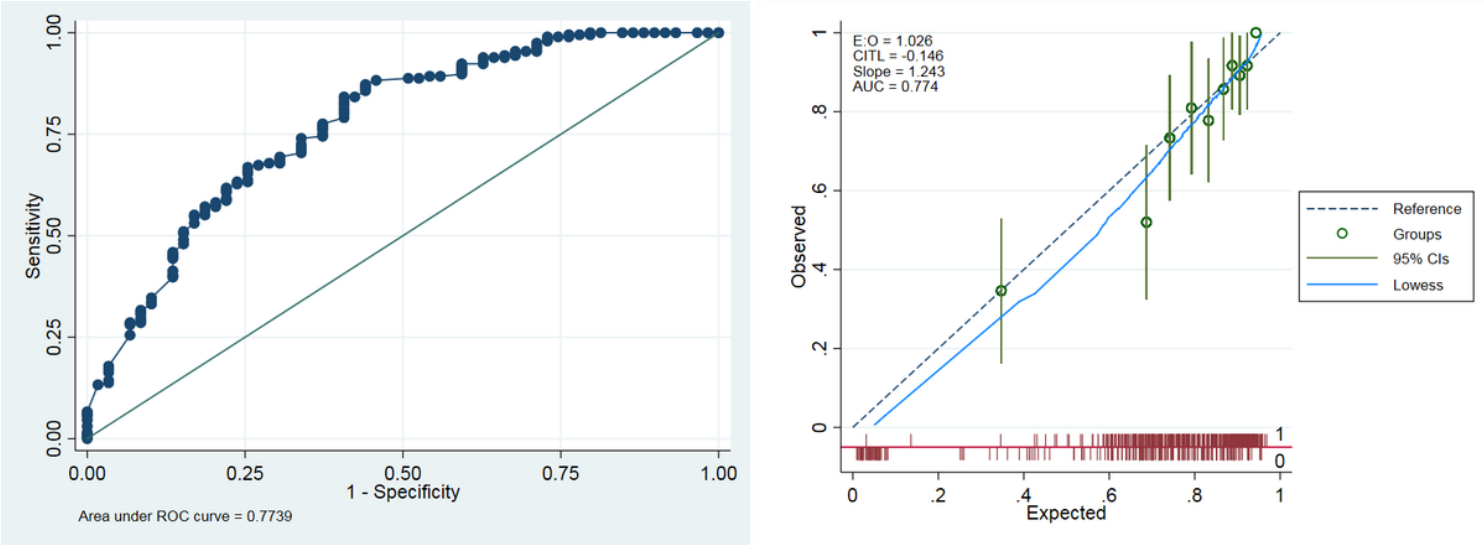

Figure 4

a. ROC curve for external validation of cure

b. ROC curve for external validation of cure

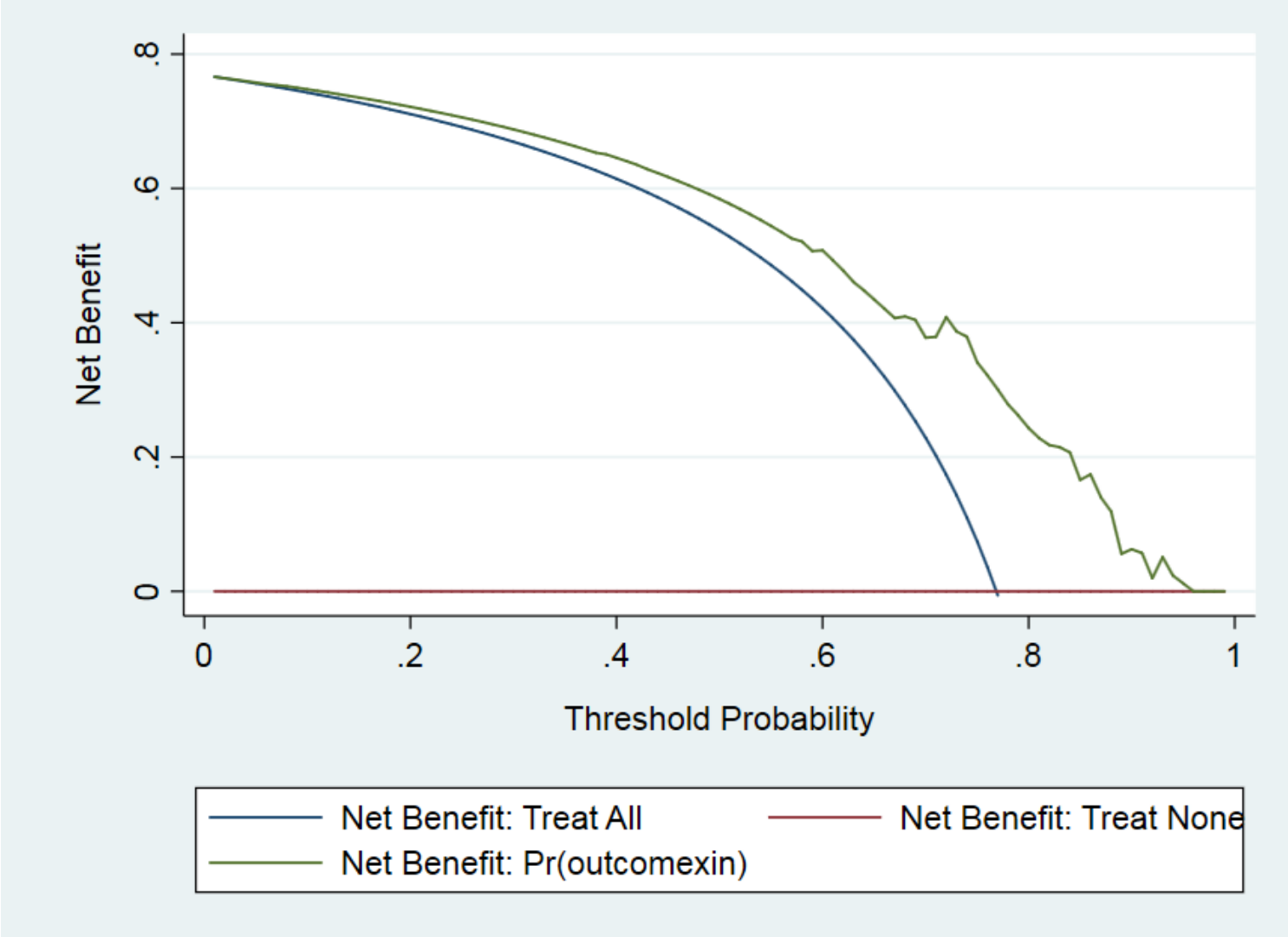

Figure 5

The decision curve for cure in the validation dataset.