

A Risk Prediction Model for Acute Kidney Injury in Pulmonary Tuberculosis Patients during Anti-tuberculosis Treatment

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Research Article

Keywords: Risk Prediction Model, Pulmonary Tuberculosis, Acute Kidney Injury, Nomogram

Posted Date: February 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-199862/v1>

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Version of Record: A version of this preprint was published at Renal Failure on April 4th, 2022. See the published version at <https://doi.org/10.1080/0886022X.2022.2058405>.

Abstract

Background Acute kidney injury (AKI) is not a rare complication during anti-tuberculosis treatment in some pulmonary tuberculosis (PTB) patients. We aimed to develop a risk prediction model to early recognize PTB patients at high risk of AKI during anti-TB treatment.

Methods In this retrospective cohort study, clinical baseline, and laboratory test data of 315 inpatients with active PTB from January 2019 and June 2020 were screened for predictive factors. The factors were analyzed by logistic regression analysis. A nomogram was established by the results of the logistic regression analysis. The prediction model discrimination and calibration were evaluated by the concordance index (C-Index), ROC Curve, and Hosmer-Lemeshow analysis.

Results 7 factors (Microalbuminuria, Hematuria, CYS-C, Albumin, eGFR, BMI and CA-125) are acquired to develop the predictive model. According to the logistic regression, Microalbuminuria (OR=3.038, 95% CI 1.168-7.904), Hematuria (OR=3.656, 95% CI 1.325-10.083), CYS-C (OR=4.416, 95% CI 2.296-8.491), CA-125 (OR=3.93, 95% CI 1.436-10.756) were risk parameter and ALB (OR=0.741, 95% CI 0.650-0.844) was protective parameter. The nomogram demonstrated a good prediction in estimating AKI. C-Index= 0.967, AUC=0.967, 95% CI (0.941-0.984) Sensitivity=91.04%, Specificity=93.95%, Hosmer-Lemeshow analysis SD=0.00054, Quantile of absolute error=0.049.

Conclusion Microalbuminuria, Hematuria, Albumin reduction, elevated CYS-C, and CA125 are predictive factors for AKI in PTB patients during anti-tuberculosis treatments. The predictive nomogram based on five predictive factors is achieved a good risk prediction of AKI during anti-tuberculosis treatments.

1. Introduction

Tuberculosis (TB) is a common infectious disease with a long history in China and is still one of the top 10 causes of death worldwide. The death rate of tuberculosis is still higher than that of HIV. According to the WHO global tuberculosis report, approximately 1.7 billion people are infected with *Mycobacterium tuberculosis* and 10 million people are diagnosed with tuberculosis each year, worldwide[1]. Although modern chemotherapy has played a pivotal role in combating TB, the occurrence of adverse drug events limits the completion rate of treatment[2].

Acute kidney injury (AKI) is not a single disease entity, it is defined as an abrupt decline in kidney function that occurs within 7 days or less. The epidemiological survey estimated that 2 million people worldwide die of AKI every year, whereas some AKI patients are at increased risk of developing chronic kidney disease (CKD)[3]. The retrospective study indicates that AKI is usually observed in patients who were admitted to the intensive care unit (ICU), and half of all such AKI were Septic AKI[4]. In other studies, only one-third of AKI patients were hospital-acquired, and the rest were community-acquired. Through statistical verification, creased GFR and proteinuria are independent risk factors for AKI[5].

AKI generally occurs in patients with acute or chronic diseases. In ICU patients, the predominant aetiological category of AKI is sepsis, and the most common cause of sepsis are Gram-negative bacteria, fungal etc[6]. A five-year retrospective study indicated that AKI is not a rare complication during anti-TB treatment in the elderly population[7]. Acute kidney injury (AKI), acute kidney disease (AKD), and chronic kidney disease (CKD) can form a process of continuous kidney injury. A diagnosis of AKI should evaluate the possible inducement of persistent kidney injury. Several studies have confirmed that the hypersensitivity reaction induced by rifampin is the main cause of AKI during anti-TB treatment. Serum creatinine usually develops within two months of anti-TB-treatment and resolves within three months. Whereas, approximately 27% of AKI patients will develop permanent kidney damage[8]. Even more importantly, AKI is generally asymptomatic, so screening and prediction for kidney injury during anti-TB treatment are particularly important. Kidney Disease: Improving Global Outcomes (KDIGO) recommends stratified screening of the occurrence of AKI based on the exposed and susceptible factors. However, there are few instruments to predict the occurrence of AKI[3].

In recent years, risk prediction models have been increasingly used to estimate the probability of occurrence (diagnostic models) or outcomes (prognostic models) of a particular disease[9]. In Guan Chen's study, predictive factors such as age, previous surgical history, cardiac arrhythmia are used to establish a prediction model to predict cardiac surgery-associated acute kidney injury (CSA-AKI). This model can improve the identification of patients at high risk of AKI before cardiac surgery[10]. Machine learning is used to develop risk prediction models in recent study[11]. Unfortunately, no prediction models have been developed to predict the risk of AKI during anti-tuberculosis treatment.

In this study, pulmonary tuberculosis patients (PTB) are divided into two groups according to the occurrence of AKI during anti-tuberculosis treatment. Clinical baseline and laboratory data are compared to obtain the different factors and establish a prediction model. We hope that the risk prediction model can effectively assess the risk of AKI before anti-tuberculosis treatment to prevent the occurrence of renal injury.

2. Materials And Methods

2.1 Study population

This was a retrospective observational study. This study obtained approval from the Clinical Research Ethics Committee of Taizhou People's Hospital TZRY-LL-AF/SQ-014-2.0 (Protocol number KY201803901). All tuberculosis diagnosis and treatments were conformed to the "Guidelines for the diagnosis and treatment of tuberculosis(2001)"[12].

724 individuals enrolled at the Department of Infectious Diseases, Taizhou People's Hospital, Jiangsu Province between January 2019 and June 2020. According to the inclusion and exclusion criteria, 315 primary pulmonary tuberculosis patients were eventually enrolled in the statistical comparison (Fig. 1).

Inclusion criteria: 1. According to the WHO guidelines, all pulmonary tuberculosis patients had typical imaging lesions, positive sputum smears, or sputum cultures of *Mycobacterium tuberculosis*; 2. Acute kidney injury (AKI) was diagnosed by the KDIGO criteria established in 2012, serum creatinine rises $\geq 0.3\text{mg/dl}$ ($\geq 26.5\mu\text{mol/L}$) within 48 hours or serum creatinine rises $\geq 50\%$ from the baseline value within 7 days or decrease in urine output [urine volume < 0.5] duration $\geq 6\text{h}$ [1, 13].

Exclusion criteria: 1. Patients who had received anti-tuberculosis treatment before admission were excluded; 2. Patients diagnosed with multi-drug resistant tuberculosis, tuberculous pleurisy, retreatment PTB, and non-tuberculous mycobacterial infection were excluded from enrollment; 3. PTB Patients who had underlying diseases such as hypertension, diabetes, and self Immune diseases, kidney diseases, malignant tumors et al. were excluded from enrollment;

All active PTB patients were given standardized anti-TB treatment consisting of oral rifampicin 10 mg/kg/d, isoniazid 5 mg/kg/d, pyrazinamide 25 mg/kg/d, and ethambutol 20 mg/kg/d for 2 months, followed by daily isoniazid and rifampicin for 4 months(2HRZE/4-6HRE). The regimen was modified by the infectious disease physician if necessary when there were adverse drug effects.

2.2 Data Collection and Study Design

The enrolled patients were divided into two groups, AKI-Group: pulmonary tuberculosis with Acute kidney injury; Control Group: pulmonary tuberculosis without Acute kidney injury.

The difference factors were obtained from the clinical baseline data and laboratory test data of the two groups. The clinical baseline including age, gender, occupation, place of residence, lung imaging characteristics, etc; Laboratory test data include urine routine (PH value, urine microalbumin, haematuria, etc.); The blood routine (RBC, NEU, etc.); liver function (TBIL, ALB, ALT, AST, etc.); kidney function (BUN, CREA, UA, B2MG, CYS-C, etc.). Tumor and inflammatory indicators were also included in the Laboratory test data. Predictive factors of AKI in PTB during anti-treatment were analyzed by logistic regression analysis. A prognostic nomogram was established by the results of the logistic regression analysis.

Immunological indices of the two groups were compared to explore the possible immunological mechanisms of AKI.

2.3 Statistical analysis

The data were expressed as the frequencies (n), percentages (%), means \pm standard deviations (SDs), median (inter-quartile range), and were analyzed with R version 4.0.2. Count data were analyzed with the chi-square test. If measurement data conformed to a normal distribution, the t-test was used to analyze. The Mann-Whitney U-test was used for comparing unorthodox distribution data. Before regression analysis, the factors are verified by multiple linear regression to verify independence. The nomogram was constructed on the results of logistic regression using the rms package in R software. The discrimination of the prediction model was verified by C-Index and the receiver-operating curve (ROC curve). The

correctness of the prediction model was verified by the Calibration curve. A difference with $P < 0.05$ was considered statistically significant.

3. Results

3.1 Characteristics of clinical baseline data.

315 initial treatment of pulmonary tuberculosis patients (PTB) were enrolled in this study. 67 (21.27%) PTB patients with acute kidney injury were set as AKI Group, and 248 (78.73%) PTB patients without AKI were included as Control Group; There was no statistical difference between the two groups in age, gender, occupation, and the extent of lesion involvement ($p > 0.05$);

The level of BMI in Control Group was $19.99 \pm 2.82\text{kg/m}^2$, which was significantly higher than that in AKI-Group $17.90 \pm 2.39\text{kg/m}^2$ ($p < 0.05$); The positive accounted of CA-125 were 35.89% in Control Group, which was significantly lower than that in AKI Group 83.87% ($p < 0.05$); There was no significant difference in T-SPOT, CEA, CA199, CRP, and ESR between the two groups. (Table 1)

Table 1
The clinical baseline data of PTB patients

Variable	Control Group	AKI Group	Total	Statistics(χ^2 /t/z)	P-value
n	248(78.73%)	67(21.27%)	315		
Age(year)	56.68 ± 18.77	58.36 ± 19.22	57.03 ± 18.85	0.647	0.518
Sex					
male	182(73.39%)	51(76.12%)	233(73.97%)	0.205	0.754
female	66(26.61%)	16(23.88%)	82(26.03%)		
BMI(kg/m²)	19.99 ± 2.82	17.90 ± 2.39	18.95 ± 2.61	5.544	0.000
Occupation					
individual	5(2.02%)	1(1.49%)	6(1.90%)	11.659	0.234
worker	17(6.85%)	3(4.48%)	20(6.35%)		
Medical staff	2(0.81%)	1(1.49%)	3(0.95%)		
Farmer	56(22.58%)	15(22.39%)	71(22.54%)		
retirement	61(24.60%)	20(29.85%)	81(25.71%)		
student	13(5.24%)	1(1.49%)	14(4.44%)		
Staff	40(16.13%)	6(8.96%)	46(14.60%)		
free	11(4.44%)	1(1.49%)	12(3.81%)		
other	4(1.61%)	2(2.99%)	6(1.90%)		
Unemployed	37(14.92%)	19(28.36%)	56(17.78%)		
Lesion site				1.741	0.419
Two lungs	182(80.60%)	54(80.60%)	236(74.92%)		
Left lung	26(5.97%)	4(5.97%)	30(9.52%)		
Right lung	40(13.43%)	9(13.43%)	49(15.56%)		
T-SPOT				0.645	0.422
(+)	142(57.26%)	42(62.69%)	184(58.41%)		
(-)	106(42.74%)	25(37.31%)	131(41.59%)		
CEA				2.928	0.087

*BMI body mass index; statistical method: chi-square test; t test; Mann-Whitney U-test.

Variable	Control Group	AKI Group	Total	Statistics(χ^2 /t/z)	P-value
(+)	12(10.45%)	7(10.45%)	19(6%)		
(-)	236(89.55%)	60(89.55%)	296(96.97%)		
CA-125				37.141	0.000
(+)	89(35.89%)	52(83.87%)	141(44.76%)		
(-)	159(64.11%)	15(16.13%)	174(55.24%)		
CA19-9				0.463	0.291
(+)	39(19.40%)	13(19.40%)	52(16.51%)		
(-)	209(80.60%)	54(80.60%)	263(83.49%)		
CRP(mg/l)	19.23(3.18–46.94)	47.23(11.73–86.54)	23.86(5.11–54.04)	1.816	0.178
ESR(mm/h)	32.68 ± 30.38	48.92 ± 34.70	40.08 ± 32.54	1.103	0.294
*BMI body mass index; statistical method: chi-square test; t test; Mann-Whitney U-test.					

3.2 Characteristics of blood routine and urine routine.

The positive proportion of microalbuminuria (UM) was 17.74% in Control Group, which was significantly lower than that in AKI Group 61.19% ($p < 0.05$); The number of patients with hematuria in Control Group was 26 (10.48%), which was significantly lower than 33(49.25%) in AKI Group ($p < 0.05$). (Table 2)

Table 2
The characteristics of blood routine and urine routine in PTB patients

Variable	Control Group	AKI Group	Total	Statistics($\chi^2/t/z$)	P-value
n	248(78.73%)	67(21.27%)	315		
RBC($10^9/L$)	4.22 ± 2.43	3.89 ± 0.71	4.148 ± 2.186	1.080	0.281
HB(g/L)	118.54 ± 21.23	122.58 ± 19.45	120.56 ± 20.34	1.406	0.161
NEU($10^9/L$)	5.05 ± 2.59	5.55 ± 2.18	5.30 ± 2.39	1.435	0.152
LYM($10^9/L$)	1.025(0.74–1.5)	0.95(0.62–1.25)	0.99(0.73–1.44)	1.814	0.700
MON($10^9/L$)	0.52(0.37–1.5)	0.55(0.39–0.83)	0.52(0.37–0.72)	0.829	0.407
PLT($10^9/L$)	232.5(182.00–303.00)	219.00(171.00–327.00)	232.00(178.00–307.00)	0.100	0.921
USG	1.02(1.013–1.025)	1.02(1.015–1.025)	1.02(1.014–1.025)	0.680	0.497
PH	6.24 ± 0.7	6.16 ± 0.72	6.22 ± 0.706	0.856	0.393
UM				50.549	0.000
(+)	44(17.74%)	41(61.19%)	85(26.98%)		
(-)	204(82.26%)	26(38.81%)	230(73.02%)		
UCR(g/L)	1.00(0.5–4.4)	1.00(1.00–5.00)	1.00(0.5–4.4)	1.146	0.252
Hematuria				52.088	0.000
(+)	26(10.48%)	33(49.25%)	59(18.73%)		
(-)	222(89.52%)	34(50.75%)	256(81.25%)		
*AKI = Acute kidney injury; USG = Urine specific gravit;UM = microalbuminuria;UCR = Urine creatinine;Statistical methods: independent sample t test, nonparametric test, chi-square test.					

3.3 Characteristics of liver and kidney function.

In liver and kidney function, the level of ALB in the AKI group was 28.94 ± 3.46 g/l, which was significantly lower than 35.17 ± 4.8 g/l in the control group ($P < 0.05$); The level of Cys-C in the AKI group was 1.66 ± 0.51 mg/l, which was significantly higher than 0.8 ± 0.43 mg/l in the control group ($P < 0.05$); The eGFR level in AKI group was 83.50 ± 36.98 ml/min per $1.73m^2$, which was lower than 94.61 ± 35.34 ml/min per $1.73m^2$ in the control group; There was no significant difference in other indexes between the two groups (Table 3).

Table 3
The characteristics off liver and kidney function in PTB patients

Variable	Control Group	AKI Group	Total	Statistics(t/z)	P-value
n	248(78.73%)	67(21.27%)	315		
TBIL(umol/L)	10.15(7.60-13.25)	10.30(8.10-13.10)	10.30(7.70-13.10)	1.001	0.317
DBIL(umol/L)	2.62 ± 1.11	2.89 ± 0.94	2.76 ± 1.03	1.829	0.069
TP(g/L)	66.34 ± 9.31	65.63 ± 12.33	66.19 ± 10.01	0.511	0.609
ALB(g/L)	35.17 ± 4.8	28.94 ± 3.46	33.85 ± 5.21	4.959	0.000
ALT(U/L)	12.00(8.00-20.00)	12.00(8.00-20.00)	12.00(8.00-20.00)	0.467	0.641
AST(U/L)	22.04 ± 10.62	22.31 ± 8.09	22.18 ± 9.36	0.193	0.847
ALP(U/L)	95.27 ± 37.12	104.61 ± 56.09	97.62 ± 41.96	1.621	0.106
GGT(U/L)	24.00(16.00-24.00)	25.00(18.00-46.00)	24.00(17.00-42.00)	1.612	0.107
LDH(U/L)	183.03 ± 48.28	193.31 ± 71.56	185.22 ± 54.35	1.376	0.170
CK(U/L)	42.5(30.00-65.75)	41.00(28.00-83.00)	42.00(30.00-66.00)	0.499	0.618
ACE(U/L)	31.89 ± 12.62	33.4 ± 17.25	32.21 ± 13.72	0.800	0.424
HCY(umol/L)	12.21 ± 5.59	14.2 ± 11.13	12.63 ± 7.16	2.030	0.161
BUN(mmol/L)	4.81 ± 2.00	5.26 ± 2.58	4.91 ± 2.14	1.544	0.124
CREA(umol/L)	63.81 ± 29.87	69.73 ± 54.60	65.07 ± 36.52	1.179	0.239
UA(umol/L)	287.87 ± 108.07	269.62 ± 96.54	283.99 ± 105.84	1.253	0.184
β ₂ MG(mg/L)	2.38 ± 0.83	2.48 ± 0.82	2.43 ± 0.83	0.894	0.372
CYS-C(mg/L)	0.8 ± 0.43	1.66 ± 0.51	0.98 ± 0.57	14.110	0.000
eGFR(ml/min per 1.73m ²)	94.61 ± 35.34	83.50 ± 36.98	89.06 ± 36.16	2.259	0.025
*eGFR estimated glomerular filtration rate;CYS-C = cystatin C; Statistical methods: independent sample t test, nonparametric test					

3.4 The characteristics of renal function of PTB-AKI patients before and after treatment

In 67 patients with AKI-TB, the five renal function BUN, CREA, UA, B2MG, and CYS-C were significantly increased after anti-tuberculosis treatment compared with before treatment. (Table 4)

Table 4
The characteristics of the renal function of PTB-AKI patients before and after treatment

Values	Before-T	After-T	Statistics(t)	P-value
n	67	67		
BUN(mmol/L)	5.26 ± 2.58	10.61 ± 5.00	9.107	0.000
CREA(umol/L)	69.74 ± 54.60	165.88 ± 104.83	11.698	0.000
UA(umol/L)	269.62 ± 96.54	457.94 ± 136.32	9.637	0.000
β ₂ MG(mg/L)	2.48 ± 0.82	6.34 ± 8.03	3.899	0.000
CYS-C(mg/L)	1.66 ± 0.51	2.15 ± 0.53	2.638	0.010

*Before-T = Before treatment; After-T = After treatment; Statistical methods: iPaired sample t test.

3.5 Independence verification of different factors

7 different factors are obtained through the above comparison. Spearman correlation analysis was used to verify the independence of the 7 factors (Fig. 2). In positive correlation, the correlation between BMI and ALB was the highest, $r = 0.41$; In a negative correlation, the correlation between ALB and CYS-C was the highest, $r = -0.36$; The correlation between all variables was low, $r < \pm 0.5$. 4 continuous variables (BMI, CYS-C, ALB, eGFR) are independent of each other (Table 5). There is no significant multicollinearity between 4 continuous variables ($VIF < 5$, $R^2 < 1$).

Table 5
The result of multicollinearity analysis

Factors	UStd.Coefficients		Std.Coefficients	Statistics		R ²	Durbin-Watson
	β	S.E	β	Tol	VIF		
BMI	-0.024	0.006	-0.167	0.875	1.143	0.479	0.908
CYS-C	0.190	0.019	0.437	0.862	1.160		
ALB	-0.028	0.003	-0.351	0.910	1.099		
eGFR	0.000	0.000	-0.020	0.922	1.084		

*UStd.Coefficients = Unstandardized Coefficients; Std.Coefficients = Standardized Coefficients; Tol = tolerance; VIF = variance inflation factor; eGFR estimated glomerular filtration rate; CYS-C = cystatin C; Statistical methods: Multicollinearity analysis.

3.6 Logistic regression analysis of the different factors between the two groups

To determine the predictors for the incidence of AKI in PTB patients during anti-tuberculosis treatments, 7 parameters (microalbuminuria; Hematuria; CYS-C, ALB, eGFR, BMI, CA-125) were included in the binary logistics regression.

According to the OR, 4 parameters were high-risk factors for AKI in PTB patients during anti-tuberculosis treatments: UM-microalbuminuria (OR = 3.038, 95% CI 1.168–7.904), URBC-Hematuria (OR = 3.656, 95% CI 1.325–10.083), CYS-C (OR = 4.416, 95% CI 2.296–8.491), CA-125 (OR = 3.93, 95% CI 1.436–10.756). On the other hand, ALB (OR = 0.741, 95% CI 0.650–0.844) was a protective parameter against AKI development(Table 6).

Table 6
Logistic regression analysis of the difference factors

<i>Factors</i>	<i>β</i>	<i>S.E</i>	<i>Waldχ²</i>	<i>P-value</i>	<i>OR</i>	<i>95%CI</i>	
						low	up
UM	1.111	0.488	5.187	0.023	3.038	1.168	7.904
URBC	1.296	0.518	6.271	0.012	3.656	1.325	10.083
CYS-C	1.485	0.334	19.821	0.000	4.416	2.296	8.491
ALB	-0.3	0.067	20.243	0.000	0.741	0.650	0.844
eGFR	-0.012	0.007	2.791	0.095	0.989	0.975	1.002
BMI	-0.135	0.102	1.74	0.187	0.874	0.716	1.068
CA-125	1.369	0.514	7.097	0.008	3.93	1.436	10.756

*BMI body mass index; UM = microalbuminuria; URBC = Hematuria; eGFR estimated glomerular filtration rat;Statistical methods: Binary logistics regression analysis.OR = odds ratio; CI = confidence interval.

The risk of AKI in PTB patients during anti-tuberculosis treatments was calculated by the following the binary logistics regression equation: $\ln(p/1 - p) = 8.244 + 1.111(\text{with microalbuminuria}) + 1.296*(\text{with Hematuria}) + 1.485*(\text{CYS-C value}) + 1.369*(\text{with positive CA-125}) - 0.3*(\text{ALB value})$. In the equation, p represents the probability of AKI in PTB patients during anti-tuberculosis treatments.

3.7 Nomogram construction and validation

A prognostic nomogram for early recognition of AKI in PTB patients before anti-tuberculosis treatment was constructed using the binary logistics regression results, and points were assigned to the predictive factors according to their regression coefficients (Fig. 3). As shown in the nomogram plot, PTB patients with microalbuminuria, hematuria, the higher value of CYS-C, and CA-125 were more likely to develop AKI during anti-tuberculosis treatment. Nevertheless, PTB patients who had higher ALB were at a lower risk in AKI development. By summing the total score and locating the score on the total point scale, the development of AKI can be predicted for PTB patients before anti-tuberculosis treatment.

To evaluate the discrimination of the prediction model, C-Index was calculated by the bootstrapping technique. The ROC Curve was plotted by the predicted values of the model. The C-Index was 0.967, and the AUC of ROC Curve was AUC = 0.967, 95%CI=(0.941 to 0.984) Youden index J = 0.850, Sensitivity = 91.04%, Specificity = 93.95%.(Fig. 4)

To evaluate the Calibration of the prediction model, the calibration curve was plotted by Hosmer-Lemeshow analysis. The prediction model has good Calibration (Fig. 5).

3.8 Characteristics of immunological data of 63 PTB patients.

The immunological data of 19 PTB patients with AKI and 49 patients without AKI were measured in this study. The numbers of CD3⁺ T cell in AKI Group were significantly higher than those in the Control Group; The value of CD4⁺ T cell/CD8⁺ T cell in the AKI Group were significantly higher than those in Control Group. The value of IgG and IgA in AKI the Group were also significantly higher than those in Control Group (p < 0.05). (Table 7)

Table 7
The immunological data of 63 PTB patients

Variable	Control Group	AKI Group	Total	Statistics(t)	P-value
n	49	19	68		
CD3 ⁺	66.07 ± 14.06	73.15 ± 10.01	68.05 ± 13.37	2.004	0.049
CD3 ⁺ /CD8 ⁺	24.22 ± 9.31	25.15 ± 12.04	24.48 ± 10.06	0.339	0.735
CD3 ⁺ /CD4 ⁺	39.26 ± 13.49	45.58 ± 14.48	41.03 ± 13.96	1.697	0.094
CD16 ⁺ /CD56 ⁺	14.22 ± 9.64	13.60 ± 9.22	14.05 ± 9.46	0.242	0.809
CD19 ⁺	11.81 ± 7.13	8.49 ± 5.80	10.88 ± 6.90	1.807	0.075
CD4 ⁺ /CD8 ⁺	2.00 ± 1.14	3.16 ± 1.73	2.32 ± 1.42	3.230	0.002
IgG	11.49 ± 2.76	19.15 ± 11.91	13.63 ± 7.46	4.262	0.000
IgA	2.36 ± 0.91	3.02 ± 1.4	2.54 ± 1.10	2.295	0.025
IgM	1.01 ± 0.43	1.08 ± 0.73	1.03 ± 0.52	0.460	0.647
C3	1.03 ± 0.23	0.95 ± 0.24	1.00 ± 0.23	1.295	0.200
C4	0.26 ± 0.09	0.23 ± 0.07	0.25 ± 0.09	1.113	0.270

4. Discussion

Acute kidney injury (AKI) is not a rare complication during anti-TB treatment in some special population[7]. Renal function impairment failure to recover within 7 days will progress to acute kidney disease (AKD)[14]. Therefore, the prediction model to identify the risk for AKI is of great significance.

Chronic diseases such as diabetes, hypertension, viral hepatitis are common causes of kidney function damage[15]. More importantly, diabetes mellitus is a major risk factor for the infection of latent tuberculosis[16]. To avoid mixed effects, 184 PTB patients with the underlying disease were not included in our study. After comparing the clinical data of 371 PTB patients, 7 factors (Microalbuminuria, Hematuria, CYS-C, Albumin, eGFR, BMI and CA-125) are acquired to develop the predictive model. The independence of factors is verified before the logistic analysis. According to the binary logistic regression, 4 parameters (Microalbuminuria, Hematuria, CYS-C, CA-125) were high-risk factors for AKI in PTB patients during anti-tuberculosis treatments, and ALB is a protective parameter against AKI development.

Urine microalbumin is considered an important marker of preclinical nephropathy[17]. Patients with increased urine microalbumin have a higher risk of long-term eGFR reduction[18]. In this study, approximately 50% of PTB patients with AKI have to find haematuria before anti-tuberculosis treatment. According to the AUA guideline, haematuria is generally secondary to the potential underlying risk of the clinical syndrome, including tumor, urolithiasis, and nephropathy[19]. Compared with serum creatinine or eGFR (creatinine-based glomerular filtration rate estimates), cysteine protease inhibitor C (CYS-C) has a higher sensitivity to predict early renal injury. CYS-C is useful to differentiate types of AKI and is strong predictors for acute renal injury[20]. As an endogenous inhibitor of cysteine proteinases, CYS-C has the characteristics of non-adhesion to plasma proteins and low molecular weight and is freely filtered by the glomeruli. Cysteine protease inhibitors belong to a group of proteins with characteristic tertiary structure and the ability to bind closely but reversibly to the active site of cysteine protease (cathepsin) and thereby inhibit its activity. Cysteine protease inhibitor C plays an important role in controlling protease activity in immune system regulation, antiviral, and antimicrobial activities[21]. Eventually, CYS is partially reabsorbed and decomposed in the proximal tubular cells[22]. While studies have confirmed that the value of CA-125 is related to the severity of pulmonary tuberculosis[23]. Serum CA-125 is beneficial in the differentiation between active and inactive pulmonary tuberculosis[24]. However, the mechanism of CA-125 elevation after TB infection is still unclear. Tuberculosis can lead to malnutrition and poor nutritional status may predispose to tuberculosis. ALB(albumin) and BMI(body mass index) are the direct indicators to reflect the nutritional status of patients. Cell-mediated immunity is the key host defense against *Mycobacterium tuberculosis*. Malnutrition is an important risk factor of immune system abnormality in tuberculosis patients[25]. Both innate immune and adaptive immune play specific roles in the development of AKI[26]. In consequence, severely malnourished PTB patients have a higher risk of developing AKI.

Nomograms are introduced to the medical field by J.L. Henderson in 1928. Nomograms can be used to predict the probability of the outcome of the regression model[27]. As shown in the nomogram plot (Fig. 3), PTB patients with microalbuminuria, hematuria, a higher value of CYS-C, and CA-125 are more likely to develop AKI during anti-tuberculosis treatment. Nevertheless, PTB patients who had higher ALB

are at a lower risk in AKI development. By summing the total score and locating the score on the total point scale, the development of AKI can be predicted for PTB patients before anti-tuberculosis treatment. PTB patients with a total score of 132 have 50% risk of developing AKI after the start of anti-tuberculosis. The prediction model discrimination and calibration are evaluated by ROC Curve, and Hosmer-Lemeshow analysis. According to the above-mentioned analysis, we believe that the initial treatment of PTB patients with malnutrition, microalbuminuria, hematuria, CA-125 positive, and high value of Cystatin-C should not be received anti-tuberculosis immediately. If patients with pulmonary tuberculosis fail to improve their nutritional status and take measures to protect kidney function in advance, they have a greater risk of AKI after the start of anti-tuberculosis.

After comparing the immunological indexes, we confirmed that PTB patients with AKI have high numbers of CD3⁺ T cells, and the value of CD4⁺T cell/CD8⁺ T cell, IgG and IgA in AKI Group are significantly higher than those in the control Group. The natural infection process of Mycobacterium tuberculosis is complex. Firstly, Mycobacterium tuberculosis invades alveolar macrophages, replicates in macrophages, and spreads to macrophages, myeloid dendritic cells, and neutrophils recruited from the surrounding areas, and finally triggers adaptive immunity[28]. The tubercle bacillus produces excessive tumor necrosis factor after infection, and produces excessive mitochondrial reactive oxygen species (ROS) through the mitochondrial-endoplasmic reticulum circuit, triggering the programmed necrosis of macrophages[29]. Acute kidney injury is associated with increased oxidative damage, superoxide radical anion, peroxide, and hydroxyl radical can oxidize biomolecules and membrane, affect organelle function, and eventually induce renal tubular cell injury[30]. Active TB is frequently associated with a substantial increase in serum IgA levels. Besides, the ratio of T cells is positively correlated with serum IgA level. The deposition of immune complexes in the kidney leads to renal dysfunction[31]. Confusingly, we do not yet know the exact cause of AKI in PTB patients, whether the deposition of immune complexes produced by tuberculosis infection damages the glomerulus, or whether anti-tuberculosis drugs such as rifampicin can damage the tubular or interstitial substance AKI, or whether both play an important role[7]. At present we can make it clear that some PTB patients have a higher risk of AKI during anti-tuberculosis treatment, and nephrotoxic drugs and special tests such as coronary angiography need to avoid[32].

Limitations

The proportion of AK in PTB patients in this study is higher than that reported in relevant clinical studies. The individuals included in our study are hospitalized patients with more severe pulmonary lesions, which may lead to statistical bias. This study failed to collect the long-term outcomes of AKI patients, and the relevant factors affecting the long-term outcomes of patients will be statistically verified in the future. The mechanism of AKI in PTB patients needs to be further studied to provide a theoretical basis for clinical prevention and treatment.

Conclusions

Microalbuminuria, Hematuria, Albumin reduction, elevated CYS-C, and CA125 are predictive factors for AKI in PTB patients during anti-tuberculosis treatments. Through the predictive nomogram based on five predictive factors, the risk of PTB patients with AKI during anti-tuberculosis treatments could be determined earlier and such an application is helpful for timely intervention to improve the patient's prognosis.

Declarations

Ethical approval

All subjects were treated with standard care without intervention from this study. All data were obtained via electronic medical records and a database review and were de-identified (the patient's name was replaced with an identification code, and the patient's private information was deleted before the analysis) to protect patient privacy. This study obtained approval from the Clinical Research Ethics Committee of Taizhou People's Hospital TZRY-LL-AF/SQ-014-2.0 (Protocol number KY201803901). The informed consent of human clinical data was obtained from all subjects.

Consent for publication

Not applicable.

Competing interests

The authors declared no competing interests.

Authors' contributions

Zx Du, Fq C, Zj W: study concept and design, analysis of data, and drafting of manuscript.

Dm Z,Y L: Drafting the work or revising it critically for important intellectual content. Zx Du and Jh Y: review of manuscript and agreement to be accountable for all aspects of this work. All of the authors have seen and approved the final version of the manuscript.

Acknowledgements

The authors thank Dr. Yang Jianghua, for his guidance on the design and writing of this paper.

Funding

None

Data availability statements

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

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Figures

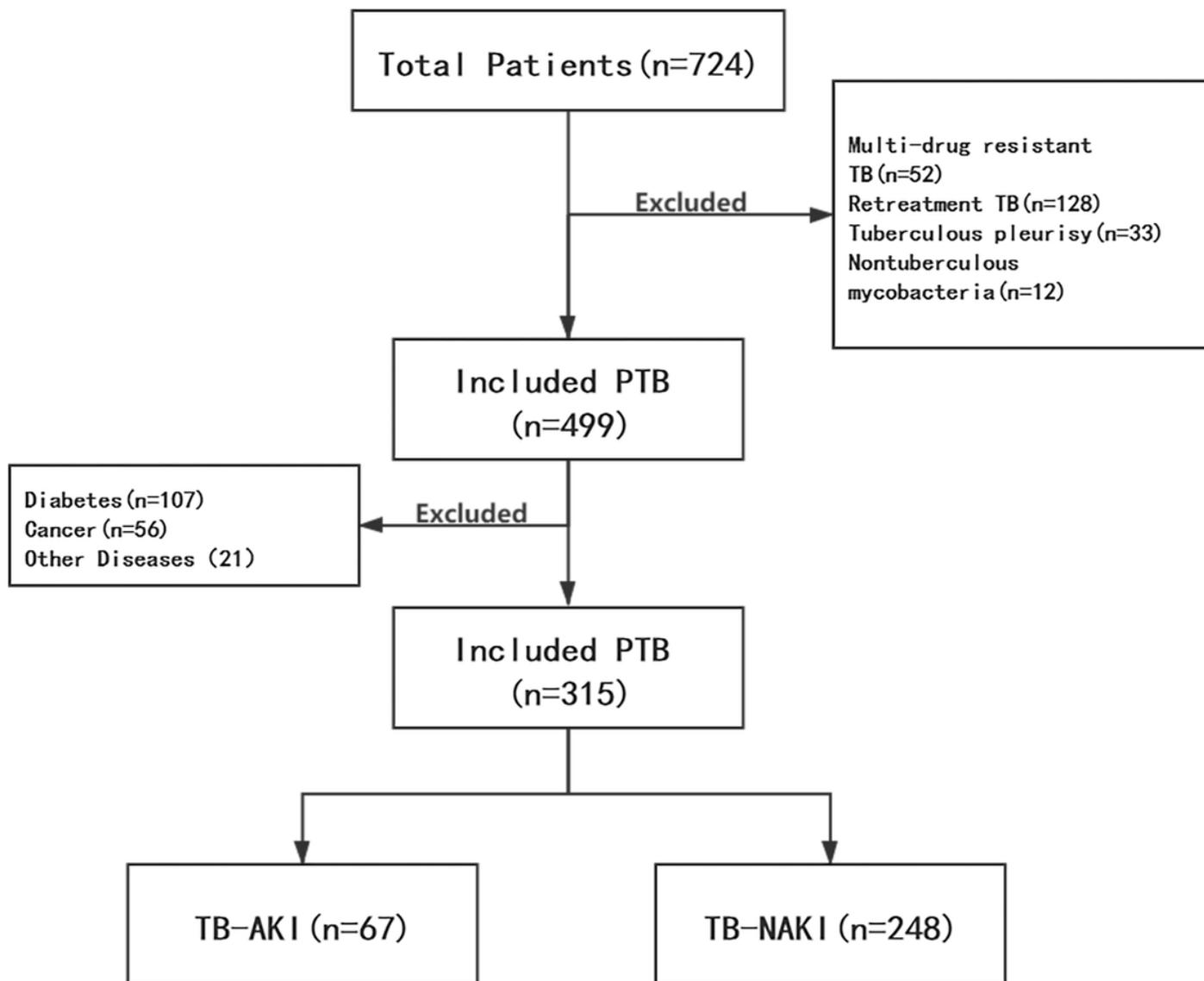


Figure 1

Flow chart of patient inclusion and exclusion. (PTB:pulmonary tuberculosis; TB-AKI:pulmonary tuberculosis with Acute kidney injury; TB-NAKI: :pulmonary tuberculosis without Acute kidney injury)

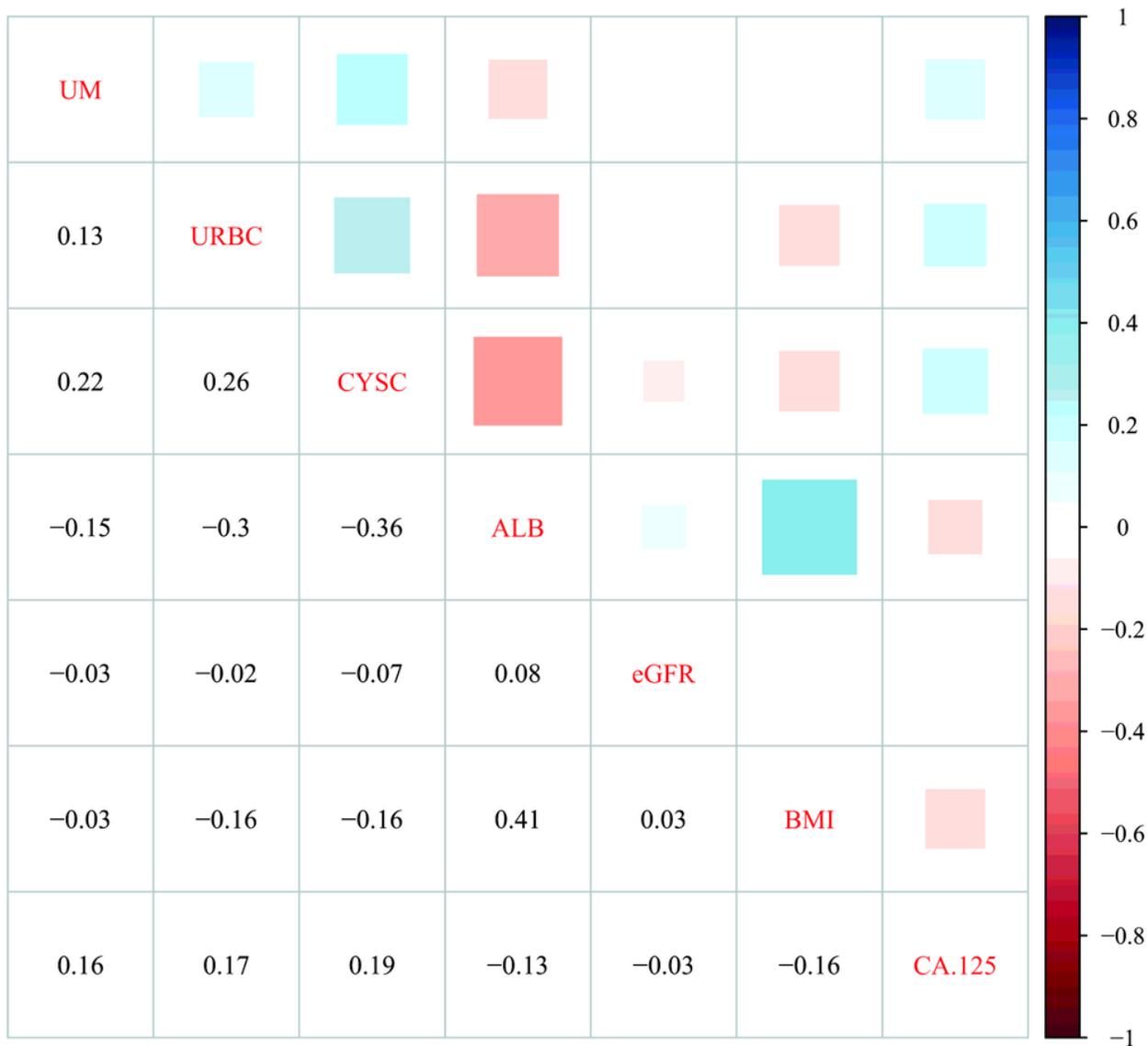


Figure 2

Independence verification of different factors.(UM=microalbuminuria; URBC=Hematuria; CYS-C=cystatin C; BMI body mass index;)

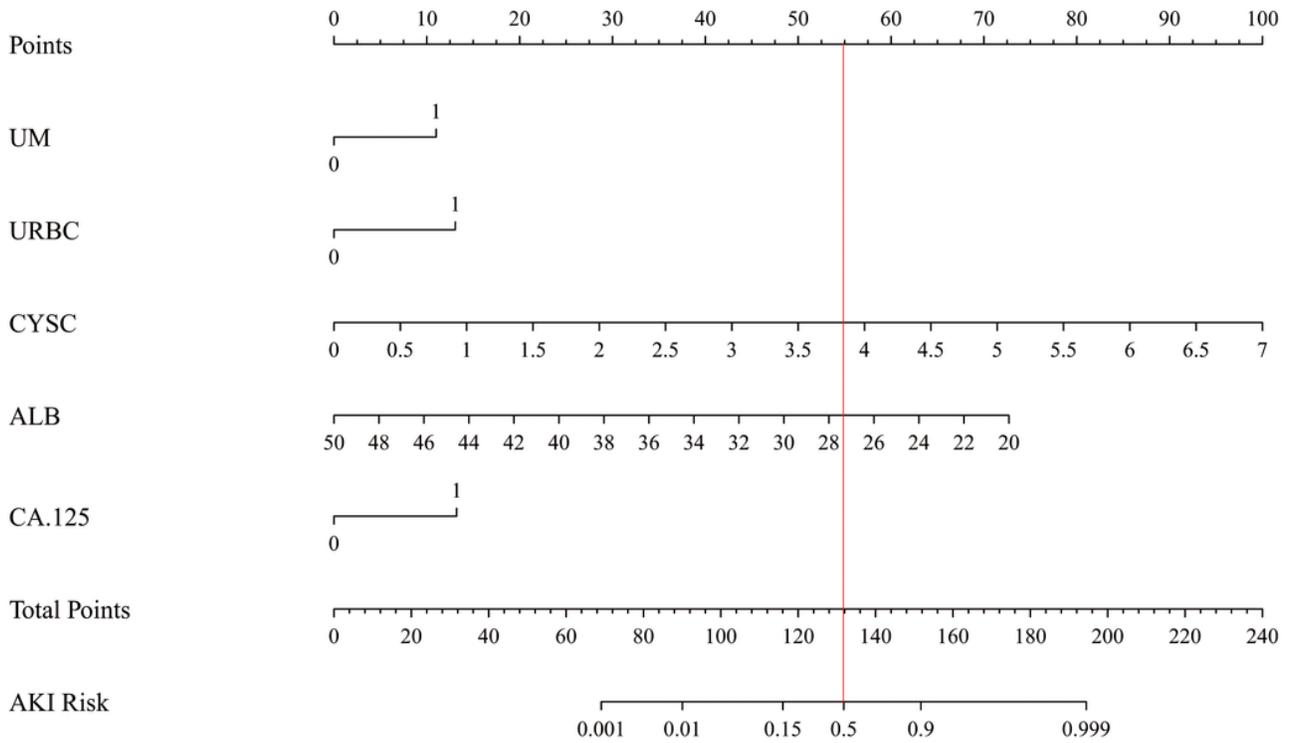


Figure 3

The Nomogram plot of logistic regression. (UM=microalbuminuria; URBC=Hematuria; ALB=Albumin; 1=positive;0=negative).

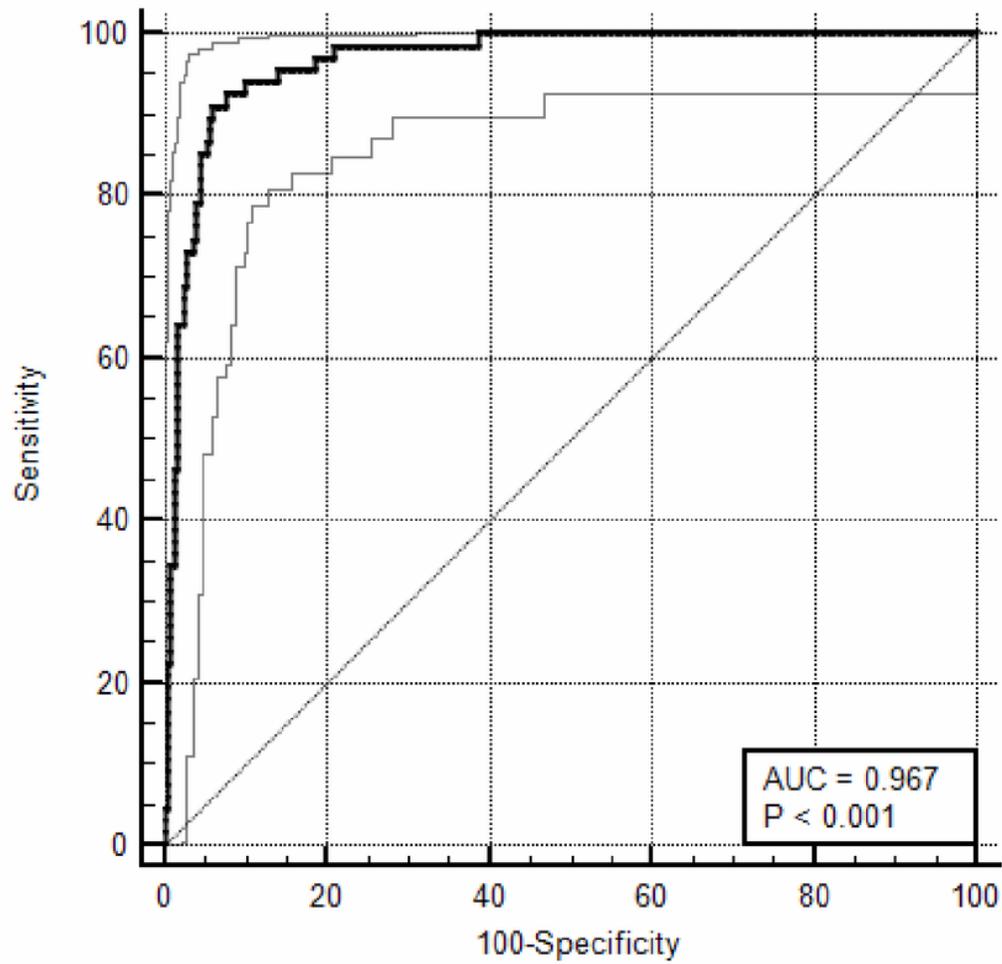


Figure 4

The ROC Curve of the discrimination. (AUC=0.967, 95%CI=(0.941 to 0.984), Youden index J=0.850, Sensitivity=91.04%, Specificity=93.95%.)

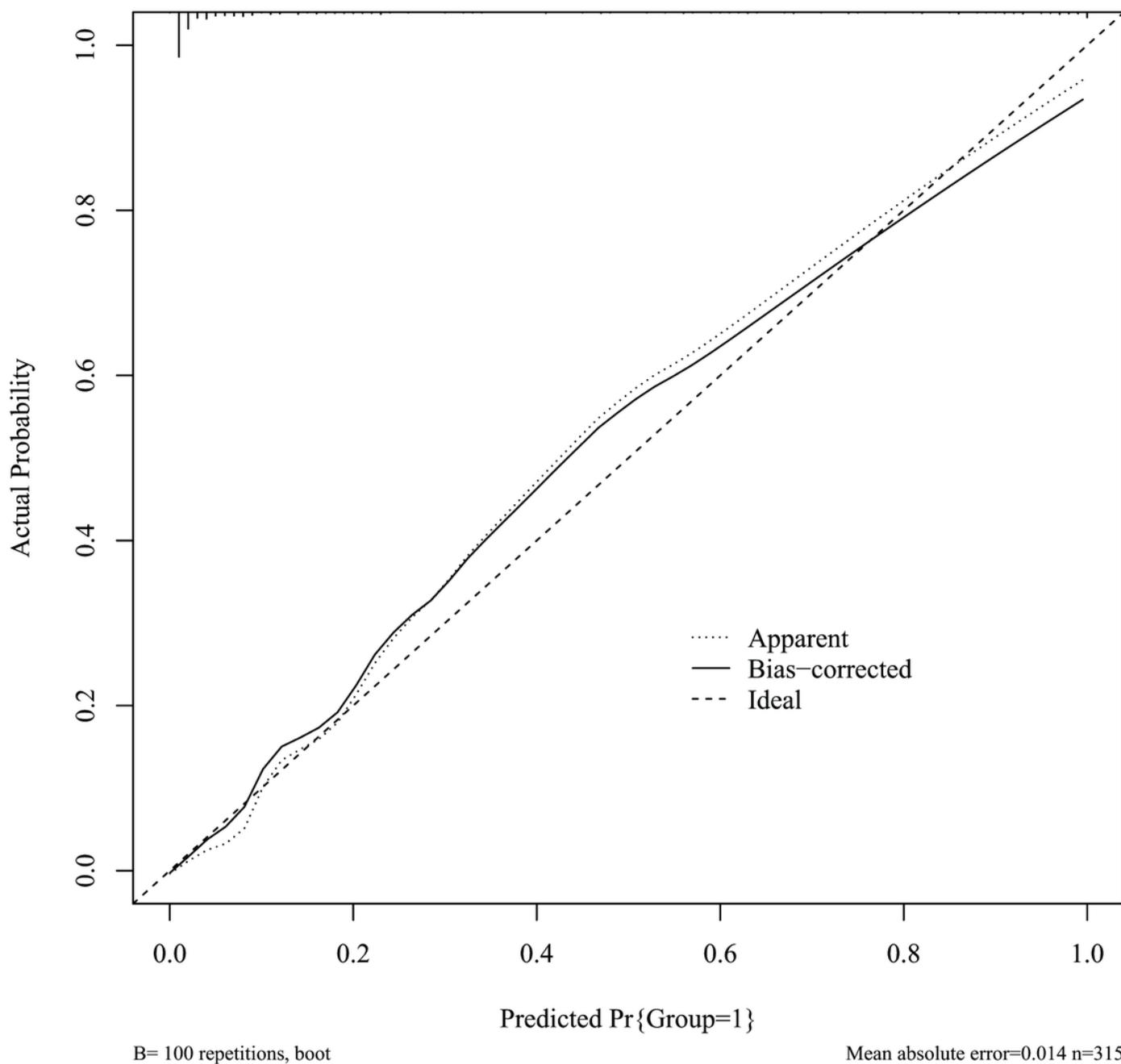


Figure 5

The Calibration curve of the prediction model. (Mean absolute error=0.014; Mean squared error=0.00054, Quantile of absolute error=0.049.)

Supplementary Files

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