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ORIGINAL RESEARCH

Predictive Factors for Progression to Severe Pulmonary Tuberculosis in Patients with Concurrent HIV/AIDS and Type 2 Diabetes Mellitus: A Single-Center Retrospective Study

Bennan Zhao[1], Jun Kang[1], Qing Du[2], Dafeng Liu[1]

[1]The First Ward of Internal Medicine, Public Health Clinical Center of Chengdu, Chengdu, Sichuan, People's Republic of China; [2]The Second Ward of ICU, Public Health Clinical Center of Chengdu, Chengdu, Sichuan, People's Republic of China

Correspondence: Dafeng Liu, The First Ward of Internal Medicine, Public Health Clinical Center of Chengdu, Chengdu, Sichuan, 610061, People's Republic of China, Tel +86-13094494836, Email ldf312@126.com; Qing Du, The Second Ward of ICU, Public Health Clinical Center of Chengdu, Chengdu, Sichuan, 610061, People's Republic of China, Tel +86-18780082858, Email 1031176534@qq.com

Purpose: The concurrent of HIV/AIDS, type 2 diabetes mellitus (T2D), and pulmonary tuberculosis (PTB) is a considerable public health challenge. This study aims to develop and validate a predictive model for the progression to severe PTB in patients with these three specific comorbidities.

Patients and Methods: A total of 114 patients with all three conditions—HIV/AIDS, T2D, and newly diagnosed PTB—who were admitted to the Public Health Clinical Center of Chengdu between 2018 and 2025, were enrolled as study subjects. We collected general demographic information of the research subjects, as well as laboratory indicators, TB etiological test results, and lung CT scans. First, subjects were divided into severe and non-severe PTB groups according to diagnostic criteria met during hospitalization, the Least Absolute Shrinkage and Selection Operator (LASSO) analysis was used to screen for predictors. Second, a multivariate logistic regression was used to build the predictive model. The model was evaluated using the receiver operating characteristic (ROC) curve, and calibration curve.

Results: Binary logistic regression revealed that admission ALB, NLR, and D-Dimer were independently associated with progression to severe PTB. ALB (*OR*=0.906, 95% *CI*: 0.822–0.998) served as a protective factor, while NLR (*OR*=1.234, 95% *CI*: 1.075–1.417) and D-Dimer (*OR*=1.500, 95% *CI*: 1.113–2.021) were risk factors. The area under the curve (AUC) of the model incorporating three variables was 0.892 (95% *CI*: 0.830–0.955). Internal validation using Bootstrap resampling (1000 iterations) yielded a concordance index of 0.892 (95% *CI*: 0.825–0.946), confirming the robustness of its discriminative power.

Conclusion: This study established a predictive model for progression to severe PTB in patients with these three specific comorbidities. Due to the lack of external validation, the clinical utility of this model remains to be further validated by multicenter studies.

Keywords: severe pulmonary tuberculosis, HIV/AIDS, type 2 diabetes mellitus, risk factor, predictive model

Introduction

As of the end of December 2024, there were 40.8 million people living with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) globally.[1] According to the global diabetes mellitus (DM) map released by *The Lancet*, the number of adult DM patients in China in 2022 was approximately 148 million, representing 18% of the total adult DM population worldwide and ranking second globally.[2] Among them, patients with type 2 diabetes (T2D) accounted for the largest proportion. The coexistence of T2D and HIV/AIDS presents a significant public health challenge, especially in low- and middle-income countries.[3] Whether the risk of DM increases in HIV-infected individuals remains controversial. However, a recent systematic review involving nearly 500,000 HIV-infected

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individuals demonstrated an association between HIV infection and increased odds of T2D (*OR*: 1.61; 95% *CI*: 1.09–2.38).[4] A Chinese study reported that from 2013 to 2022, the proportion of HIV-infected individuals diagnosed with DM after confirmation exhibited a significant upward trend ($P<0.001$).[5] Evidence from the above studies suggests a projected increase in the number of patients with HIV/AIDS and concurrent T2D, a trend that calls for heightened clinical vigilance.

Pulmonary tuberculosis (PTB) is a disease that poses a serious threat to human health and places a significant burden on society and the global economy. In 2023, there were 10.8 million new tuberculosis (TB) cases worldwide. In China, the number of new cases was 741,000, accounting for 6.8% of the global incidence, ranking third among the 30 countries with the highest TB burdens.[6] TB is both preventable and treatable; however, once it progresses to severe PTB, the mortality rate becomes very high. Currently, the impact of HIV/AIDS and DM on the risk and adverse outcomes of TB has been well established.[7,8] However, studies that take the triple comorbidity of HIV/AIDS, T2D, and newly diagnosed PTB as the baseline population and analyze the risk factors for progression to severe PTB remain extremely scarce. In recent years, research on severe PTB has been increasing annually. However, the diagnosis and treatment of severe PTB still face challenges, including unclear definitions and inconsistent diagnostic criteria. Severe PTB in previous retrospective studies has generally been defined as TB necessitating intensive care unit (ICU) admission for the management of major complications such as respiratory failure, septic shock, massive hemoptysis, and multiple organ dysfunction syndrome (MODS).[9–11] It is well known that admission to the ICU often indicates a poor prognosis and a high risk of mortality. Studies have shown that, even with active treatment, the mortality rate among patients with severe PTB admitted to the ICU remains as high as 24.7% to 74.0%,[10,12,13] and the average mortality rate is 52.9%.[14] Consequently, outdated diagnostic criteria have hindered the early detection and intervention of severe PTB cases, significantly impacting patient outcomes. Therefore, it is urgent to re-evaluate the definitions and diagnostic criteria for severe PTB.

The Guidelines for Definition and Diagnosis of Severe Pulmonary Tuberculosis in Adults in China (2023)[15] represents the first Chinese expert consensus to re-examine and standardize the diagnosis of severe PTB. Based on this guideline, this study aims to identify risk factors for progression to severe PTB in patients with concurrent HIV/AIDS, T2D, and newly diagnosed PTB using clinical data, and to develop an exploratory diagnostic prediction model to assist clinicians in formulating individualized intervention strategies.

Materials and Methods

Study Population and Grouping Standards

This retrospective cross-sectional study focused on patients with the tri-comorbidity of HIV/AIDS, T2D, and newly diagnosed PTB. These patients were primarily treated for TB and hospitalized at Public Health Clinical Center of Chengdu, with discharge dates ranging from January 2018 to December 2025. Based on whether the diagnostic criteria for severe PTB were met during hospitalization, the study subjects were divided into severe PTB and non-severe PTB groups. The inclusion criteria were as follows: 1. Patients over 18 years of age; 2. Infection with active PTB; 3. Newly diagnosed TB infection and no anti-tuberculosis medication treatment had been initiated. The exclusion criteria included: 1. Inactive PTB; 2. Within 24 hours of admission, the patient was diagnosed with severe PTB or was admitted to the ICU for treatment; 3. Besides TB, also accompanied by other HIV-related opportunistic infections; 4. The final pathogen culture confirmed the diagnosis of Non-tuberculous mycobacterial (NTM) disease; 5. Pregnant women; 6. Individuals with compromised immunity, including those with autoimmune diseases, cancer, or those on immunosuppressant/immunomodulator therapies; 7. Individuals with chronic organ dysfunction. Ultimately, this study enrolled 114 patients with triple comorbidity. Among them, 52 patients were classified into the severe PTB group and 62 into the non-severe PTB group. The selection process of the study subjects is shown in Figure 1.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Public Health Clinical Center of Chengdu (No.: YJ-K2025-34-01). The Ethics Committee waived the need for informed consent from patients because of the retrospective and anonymous nature of the study.

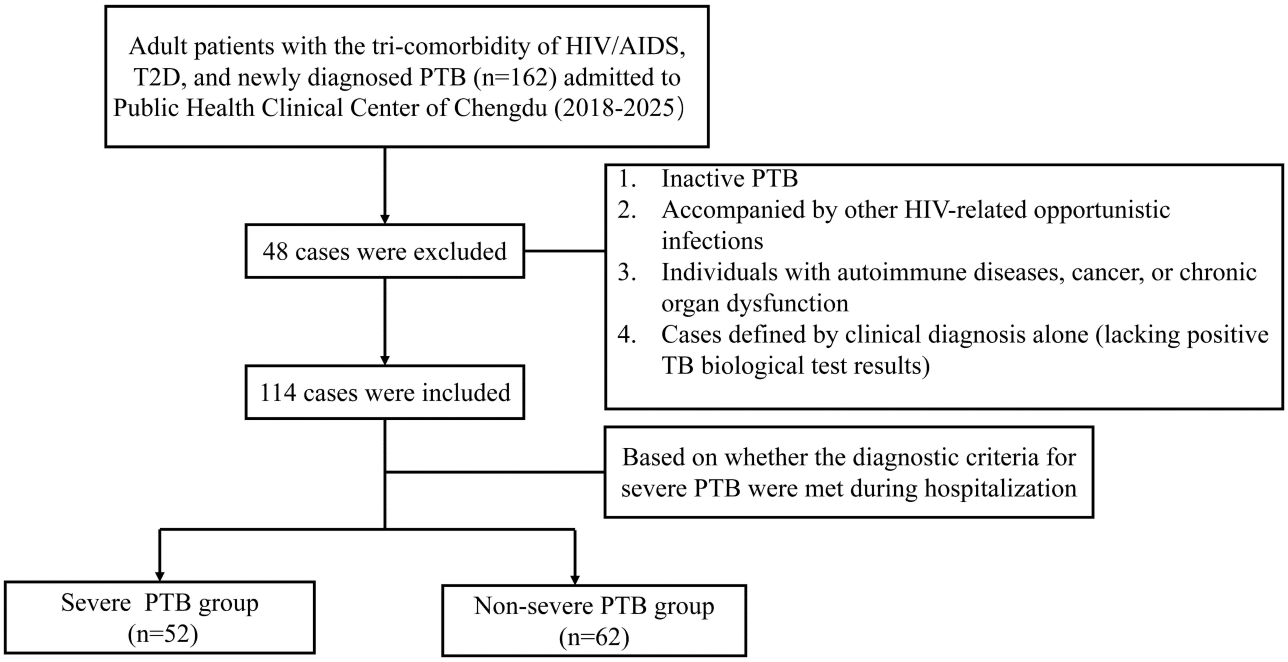

Figure 1 Selection process for the study subjects.
Abbreviations: TB, tuberculosis; PTB, pulmonary tuberculosis.

Disease Diagnostic Criteria

The diagnostic criteria for the diseases are as follows: 1. HIV/AIDS: Diagnosed using the Chinese Guidelines for HIV/AIDS Diagnosis and Management.[16] 2. TB using the Chinese Guidelines for TB Diagnosis and Management.[17] It should be emphasized that all PTB patients included in this study had confirmed evidence of Mycobacterium TB infection. This confirmation was based on positive results from sputum or fiberoptic bronchoscopy specimen smears, cultures, or molecular biological tests. Additionally, patients with confirmed Mycobacterium TB infection in extrapulmonary tissues or organs, accompanied by inflammatory lesions in the lungs, were included. Patients diagnosed solely by positive TB immunological tests or clinical diagnosis without positive biological test results were excluded from this study. 3. The diagnosis of T2D was confirmed by endocrinologists based on established diagnostic criteria[18,19] or documented use of antidiabetic medications. For newly diagnosed diabetic patients, TB infection was first controlled, followed by confirmation of T2D through venous blood glucose levels, oral glucose tolerance test (OGTT), and insulin release test results.

Data Collection

Referring to factors potentially associated with the progression to severe PTB in other studies,[10–12] this study retrospectively collected the following data from enrolled subjects via electronic medical records: population demographic data (including age, gender, ethnicity, number of children, current smoking status, BMI, weight changes since the onset of the illness, NRS2002 score, and underlying diseases), duration of HIV infection or T2D, time from symptom onset to hospital visit, venous blood laboratory indicators (white blood cell count, neutrophil-to-lymphocyte ratio, neutrophil percentage, hemoglobin, platelet count, albumin, C-reactive protein, erythrocyte sedimentation rate, sodium concentration, D-Dimer, lactic acid, Hemoglobin A1c, random blood glucose, count of T lymphocyte subsets, HIV-RNA viral load). In addition, the findings of lung CT imaging were included in this study for exploratory analysis. It should be noted that, with the exception of HIV-RNA and TB pathogenological test results, all other data were collected within 24 hours of hospital admission. Furthermore, all records reflect the baseline period prior to the commencement of TB treatment. The research team strictly controlled the accuracy, completeness and authenticity of all data.

Smoking status was defined as smoker (cumulative smoking of ≥100 cigarettes or current smoking) or non-smoker (cumulative smoking of <100 cigarettes and no current smoking). Sputum-positive TB was defined as the detection of acid-fast bacilli on at least two sputum smears or the growth of Mycobacterium TB in Löwenstein-Jensen medium or the Mycobacteria Growth Indicator Tube system. For patients newly diagnosed with HIV/AIDS or T2D during this hospitalization, the duration of the illness was recorded as zero.

Estimation of the Minimum Sample Size

In our cohort, based on data collected from 2018 to 2021, the incidence of severe PTB among patients with comorbidity of three diseases was 37% (23/62). Due to the lack of similar studies for reference, the anticipated sample size was considered potentially small. Therefore, following the method proposed by Riley et al[20] we used the pmsampsize package in R to calculate the minimum sample size required for developing a prediction model. The study had a binary outcome, and the parameters were set as follows: anticipated C-statistic (AUC) = 0.8, number of candidate predictors = 5, outcome prevalence = 0.37, and shrinkage factor = 0.9. The calculation indicated that a minimum total sample size of 110 study subjects, including 41 outcome events, is required.

The Process of Diagnosing Severe PTB

The diagnostic criteria for severe PTB are based on the Guidelines for definition and diagnosis of severe pulmonary tuberculosis in adults in China (2023).[15] The major diagnostic criteria include: requirement for mechanical ventilation treatment; combined with one or more organ failures. The secondary diagnostic criteria include: respiratory rate > 30 breaths per minute; oxygenation index≤250 mmHg (1 mmHg = 0.133 kPa); arterial partial pressure of oxygen≤60 mmHg; blood urea nitrogen≥7.14 mmol/L; systolic blood pressure < 90 mmHg; presence of central nervous system symptoms (such as confusion, delirium, hallucinations, or headache); pulmonary lesions involving three or more lung fields or covering≥50% of the lung area; suffering from severe malnutrition. A diagnosis of severe PTB can be made if the patient meets one major criteria or three or more secondary criteria. The diagnostic criteria for severe malnutrition are based on the GLIM Criteria for the Diagnosis of Malnutrition.[21] The specific steps are as follows: First, use the Nutrition Risk Screening 2002 (NRS 2002) scale to assess patients for nutritional risk. Patients with a nutritional risk (NRS 2002 score≥3) who also meet at least one phenotypic indicator (including unintentional weight loss, low BMI, or reduced muscle mass) and one etiological indicator (including reduced food intake or absorption, disease, or inflammation) are diagnosed as malnourished. Finally, the severity of malnutrition is determined based on the phenotypic indicators. Patients with significant weight loss (a decrease of more than 10% within the past 6 months or more than 20% over 6 months) or a low Body Mass Index (BMI) (BMI < 18.5 $kg/m^2$for individuals under 70 years old; BMI < 20 $kg/m^2$for those aged 70 or older) are diagnosed with severe malnutrition.

To determine whether study subjects met the diagnostic criteria for severe PTB, we conducted a comprehensive review of all relevant data from the current hospitalization. This included arterial blood gas analyses, venous laboratory results, lung CT scans, and specific clinical indicators extracted from the complete electronic medical records (such as central nervous system symptoms, respiratory rate, blood pressure, ICU admission, and the use of invasive mechanical ventilation).

Statistical Analysis

SPSS (version 26.0, Chicago, IL, USA) and R (version 4.5.2) were used for statistical analysis. Missing data were handled using multiple imputation, assuming data were missing at random. Continuous variables of normal distribution were expressed as mean ± standard deviation, and comparisons between two groups were performed using an independent-sample *t*-test. Continuous variables of skew distribution were expressed as the median and interquartile range (25th to 75th percentiles), and comparisons between two groups were conducted using the Mann–Whitney *U*-test. Categorical variables were expressed as frequencies with percentages, and comparisons of these data were performed using the chi-square test or consecutive correction chi-square test. Initially, all parameters were compared between the severe and non-severe PTB groups to identify potential variables. These candidate variables were further refined using Least Absolute Shrinkage and Selection Operator (LASSO) regression combined with 10-fold cross-validation, selecting significant

predictors associated with severe PTB at the minimum(min) λ value. Subsequently, these selected variables were incorporated into a multivariate logistic regression model to develop a predictive model. Finally, the Bootstrap resampling method was used for internal validation with 1000 iterations of sampling with replacement. The model was evaluated using the receiver operating characteristic (ROC) curve, and calibration curve (Hosmer-Lemeshow test). $P<0.05$ was considered to define statistical significance.

Results

Patient Characteristics

This study included 114 patients with concurrent HIV/AIDS, T2D, and newly diagnosed PTB. The cohort had a mean age of 54.09 years (range: 26–84), comprised 105 males and 9 females, and included 93 individuals of Han ethnicity and 21 from ethnic minority groups. Sputum or bronchoalveolar lavage fluid cultures were positive for Mycobacterium TB (human-type) in 74 patients. Among these culture-positive cases, nine demonstrated drug resistance.

Comparison of Clinical Data Between the Severe and Non-Severe PTB Groups

Compared to patients with non-severe PTB, those with severe PTB were older (mean age of 56.77±11.72 years vs 51.84 ±11.63 years, $P=0.027$); they also presented with higher NRS2002 scores at the time of admission (median score of 5 vs 3, $P<0.001$) (Table 1). No significant differences were observed in the rate of sputum-positive TB or pulmonary imaging findings between the severe and non-severe PTB groups (Table 2).

Table 1 Comparison of Sociodemographic Characteristics, Underlying Diseases, and Nutrition Screening Results Between the Severe and Non-Severe PTB Groups (n=114)

Items	Severe PTB Group (n=52) 【n(%)/mean ± SD/*M*(P_{25}, P_{75})】	Non-severe PTB Group (n=62) 【n(%)/mean ± SD/*M*(P_{25}, P_{75})】	x^2t/Z	*P*
Age (years)	56.77±11.72	51.84±11.63	2.246	0.027
Gender			0.076[a]	0.783
Male	47(90.4)	58(93.5)		
Female	5(9.6)	4(6.5)		
Ethnic Han			0.079	0.779
Yes	43(82.7)	50(80.6)		
No	9(17.3)	12(19.4)		
Children's situation			0.852	0.356
Having children	42(80.8)	54(87.1)		
Having no children	10(19.2)	8(12.9)		
Current smoking status			1.227	0.268
Yes	30(57.7)	42(67.7)		
No	22(42.3)	20(32.3)		
BMI (kg/m^2)	20.45±3.33	21.60±2.69	−1.851	0.067
NRS2002 score at admission	5.00(4.00, 5.00)	3.00(2.00, 4.00)	−7.269	<0.001
The time elapsed from the onset of respiratory symptoms to seeking medical treatment (months)	1.00(0.50, 2.00)	1.00(0.50, 3.00)	−0.339	0.734
Duration of T2D (years)	1.00(0.00, 5.75)	1.00(0.00, 8.00)	−0.729	0.466
Duration of HIV infection (months)	0.00(0.00, 24.00)	12.00(0.00, 36.00)	−1.754	0.079
Consistent adherence to ART			2.472	0.116
Yes	16(30.8)	28(45.2)		
No	36(69.2)	34(54.8)		

(*Continued*)

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Table 1 (Continued).

Items	Severe PTB Group (n=52) 【n(%)/mean ± SD/*M*(P_{25}, P_{75})】	Non-severe PTB Group (n=62) 【n(%)/mean ± SD/*M*(P_{25}, P_{75})】	x^2t/Z	*P*
Hypertension			3.494	0.062
Yes	15(28.8)	9(14.5)		
No	37(71.2)	53(85.5)		
Hepatitis B or Hepatitis C			1.548	0.213
Yes	5(9.6)	11(17.7)		
No	47(90.4)	51(82.3)		
Liver cirrhosis			1.041[a]	0.308
Yes	0	3(4.8)		
No	52(100.0)	59(95.2)		
COPD			0.024[a]	0.877
Yes	2(3.8)	1(1.6)		
No	50(96.2)	61(98.4)		
Fatty liver disease			3.693	0.055
Yes	2(3.8)	9(14.5)		
No	50(96.2)	53(85.5)		
Cerebral infarction			2.703	0.100
Yes	14(26.9)	9(14.5)		
No	38(73.1)	53(85.5)		

Note: [a]Denotes the use of the consecutive correction chi-square test.
Abbreviations: PTB, pulmonary tuberculosis; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease.

Comparison of Venous Blood Indicators Between the Severe and Non-Severe PTB Groups

Patients with severe PTB had significantly higher levels of Neutrophil-to-Lymphocyte ratio (NLR), neutrophil percentage (Neu%), C-reactive protein (CRP), D-Dimer, and HIV viral load, but lower levels of hemoglobin (HGB), albumin (ALB), and $CD4^+$ T count compared to those with non-severe PTB. All of the differences mentioned above were statistically significant (all $P<0.05$, Table 3).

Multivariate Binary Logistic Regression Analysis

The statistical significance variables of the differences in Table 1 and Table 3 were standardized and normalized through 10 - fold cross - validation (Figure 2A and B). First, LASSO regression was used to preliminarily screen predictors of severe PTB. The results show that when the penalty parameter λ_min was set to 0.0174, the model selects five variables: Age, ALB, NLR, D-Dimer, and $CD4^+$ T cell count. Subsequently, a multivariate logistic regression analysis was performed using these five variables, with the development of severe PTB as the dependent variable. The forward selection method based on likelihood ratio (LR) was used for variable entry. The analysis results identified that higher NLR levels (*OR*=1.234, 95% *CI*: 1.075–1.417, *P*=0.003) and elevated D-Dimer levels (*OR*=1.500, 95% *CI*: 1.113–2.021, *P*=0.008) in early stage of hospitalization as independent risk factors, and a higher ALB level at admission (*OR*=0.906, 95% *CI*: 0.822–0.998, *P*=0.045) as an independent protective factor, for progression to severe PTB among patients with concurrent AIDS, T2D, and PTB (Table 4). It should be emphasized that, since the NRS2002 score is closely associated with severe malnutrition and serves as an indicator for diagnosing severe PTB, the NRS2002 variable was excluded from the LASSO regression screening.

Table 2 Comparison of the Rate of Sputum-Positive TB and Pulmonary Imaging Findings Between the Severe and Non-Severe PTB Groups (n=114)

	Severe PTB Group (n=52) 【n(%)】	Non-Severe PTB Group (n=62) 【n(%)】	x^2	*P*
Combined Extrapulmonary Tuberculosis			0.005	0.942
Yes	23(44.2)	27(43.5)		
No	29(55.8)	35(56.5)		
Sputum-positive TB			2.168	0.141
Yes	23(44.2)	36(58.1)		
No	29(55.8)	26(41.9)		
Cavity lesions			2.875	0.090
Yes	17(32.7)	30(48.4)		
No	35(67.3)	32(51.6)		
Distribution of pulmonary lesions			0.000[a]	1.000
Single-sided lung	3(5.8)	3(4.8)		
Both lungs	49(94.2)	59(95.2)		

Note: [a]Denotes the use of the consecutive correction chi-square test.
Abbreviations: TB tuberculosis; PTB, pulmonary tuberculosis.

Table 3 Comparison of Laboratory Indicators in Venous Blood Between the Severe and Non-Severe PTB Groups (n=114)

Laboratory Parameter	Severe PTB Group (n=52) 【mean ± SD/ *M*(P_{25}, P_{75})】	Non-severe PTB Group (n=62) 【mean ± SD/ *M*(P_{25}, P_{75})】	*t*/*Z*	*P*
WBC count, 10^9/L	5.86 (4.06, 8.76)	5.38 (4.21, 7.30)	−0.313	0.754
NLR	9.56 (6.57, 20.46)	3.95 (2.75, 6.52)	−5.786	<0.001
Neu %, %	82.50±12.04	71.66±10.93	5.037	<0.001
HGB, g/L	104.58±29.45	118.08±20.08	−2.896	0.005
PLT count, 10^9/L	205.21±117.85	211.23±103.27	−0.291	0.772
ALB level, g/L	26.17±5.71	33.48±6.33	−6.394	<0.001
CRP, mg/L	92.64 (43.02, 114.76)	49.78 (10.88, 83.97)	−3.629	<0.001
ESR, mm/h	77.25±32.62	69.14±34.35	1.231	0.221
Na^+, mmol/L	133.65±5.51	134.89±4.99	−1.264	0.209
D-Dimer level, μg/mL	3.09 (2.28, 5.89)	0.98 (0.47, 1.75)	−5.957	<0.001
Lac, mmol/L	1.96 (1.40, 2.50)	1.78 (1.48, 2.36)	−0.689	0.491
HbA1c, %	8.48±2.35	9.00±2.61	−1.093	0.277
RBG, mmol/L	9.72 (6.32, 12.97)	9.62 (7.25, 15.86)	−1.078	0.281
$CD4^+$ T count, cells/μL	67.00 (25.00, 139.00)	196.00 (89.75, 314.25)	−4.313	<0.001
$CD4^+$ T/$CD8^+$ T	0.25 (0.14, 0.51)	0.39 (0.18, 0.60)	−1.331	0.183
HIV-RNA, copies/mL	46500 (259, 586,500)	4425 (40, 145,000)	−2.272	0.023

Abbreviations: PTB, pulmonary tuberculosis; WBC, white blood cell; NLR, Neutrophil-to-Lymphocyte ratio; Neu %, neutrophil percentage; HGB, hemoglobin; PLT, platelet; ALB, albumin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Lac, Lactic acid; HbA1c, Hemoglobin A1c; RBG, Random blood glucose.

Nomogram and ROC Curve Construction

Using these three factors, we developed a preliminary risk prediction model for severe PTB in newly diagnosed patients with concurrent AIDS and T2D. The model demonstrated good performance, with a Brier score of 0.123 (Figure 3). ROC curve analysis demonstrated that the model incorporating three variables achieved an area under the curve (AUC) of 0.892 (95% *CI*: 0.830–0.955) with a specificity of 90.2%. Its predictive ability was superior to that of any individual variable (Table 5 and Figure 4). Internal validation via the Bootstrap method with 1000 resamples demonstrated a concordance index (C-index) of

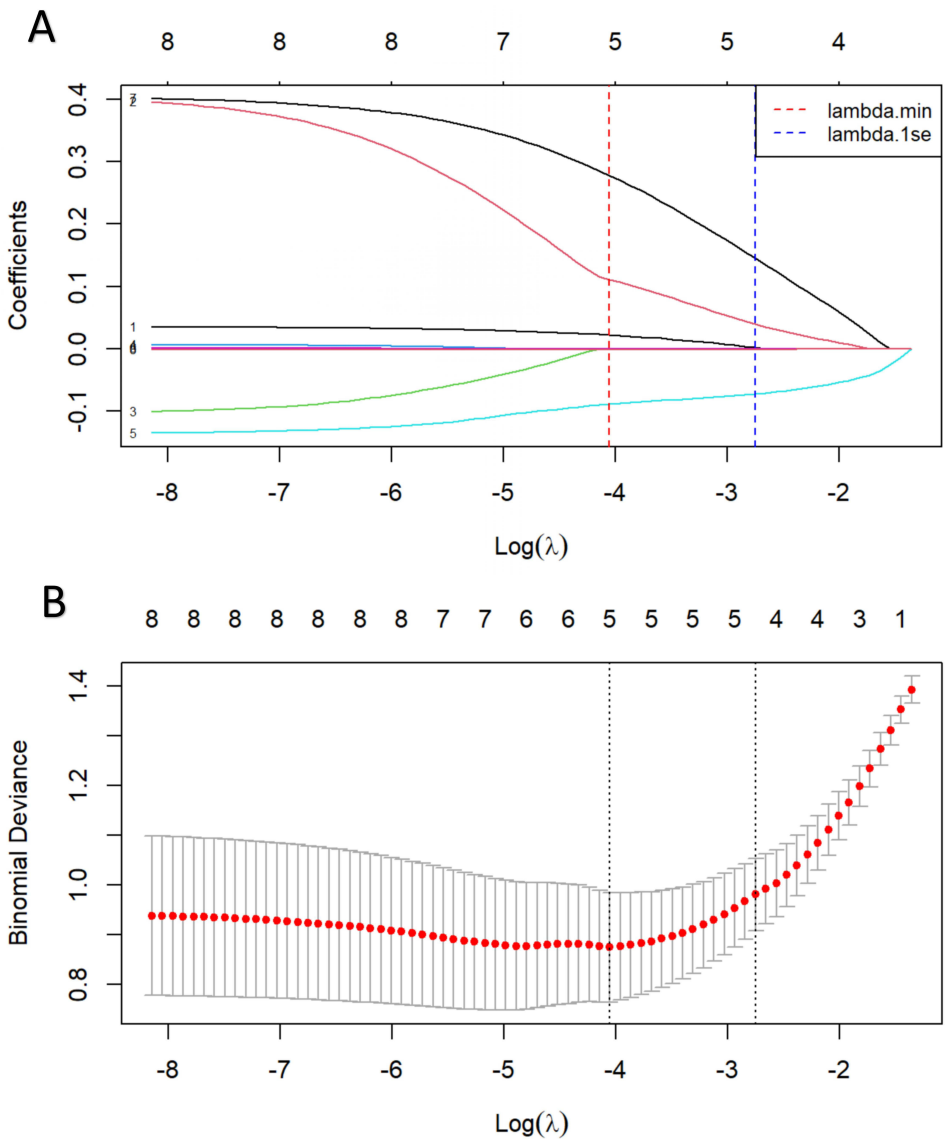

Figure 2 Identification of risk factors for severe pulmonary tuberculosis (PTB) in newly diagnosed PTB patients with concurrent HIV/AIDS and type 2 diabetes using LASSO regression. (**A**) Profiles of variable coefficients using the least absolute shrinkage and selection operator. (**B**) After verifying the optimal parameter (λ) in the least absolute shrinkage and selection operator model, a dashed vertical line was plotted according to the minimum criterion likelihood deviance (binomial) curve and log (λ).

0.892 (95% *CI*: 0.825–0.946), indicating that the model had good discriminatory ability. The calibration curve demonstrated good model fit, with mean and maximum calibration errors of 0.0275 and 0.0522, respectively. The Hosmer-Lemeshow test yielded a non-significant result (χ^2=7.812, *P*=0.452), further confirming adequate model calibration (Figure 5).

Table 4 Results of Binary Logistic Regression Analysis

Variables	*β*	*Wald*	*OR*	95% CI		*P*
				Lower	Upper	
ALB	−0.099	4.010	0.906	0.822	0.998	0.045
NLR	0.210	8.951	1.234	1.075	1.417	0.003
D-Dimer	0.405	7.107	1.500	1.113	2.021	0.008
Constant	0.079	0.002	1.082			0.963

Note: *β* denotes regression coefficient; *OR* denotes odds ratio; 95% CI denotes 95% confidence interval.
Abbreviations: ALB, albumin; NLR, Neutrophil-to-Lymphocyte Ratio.

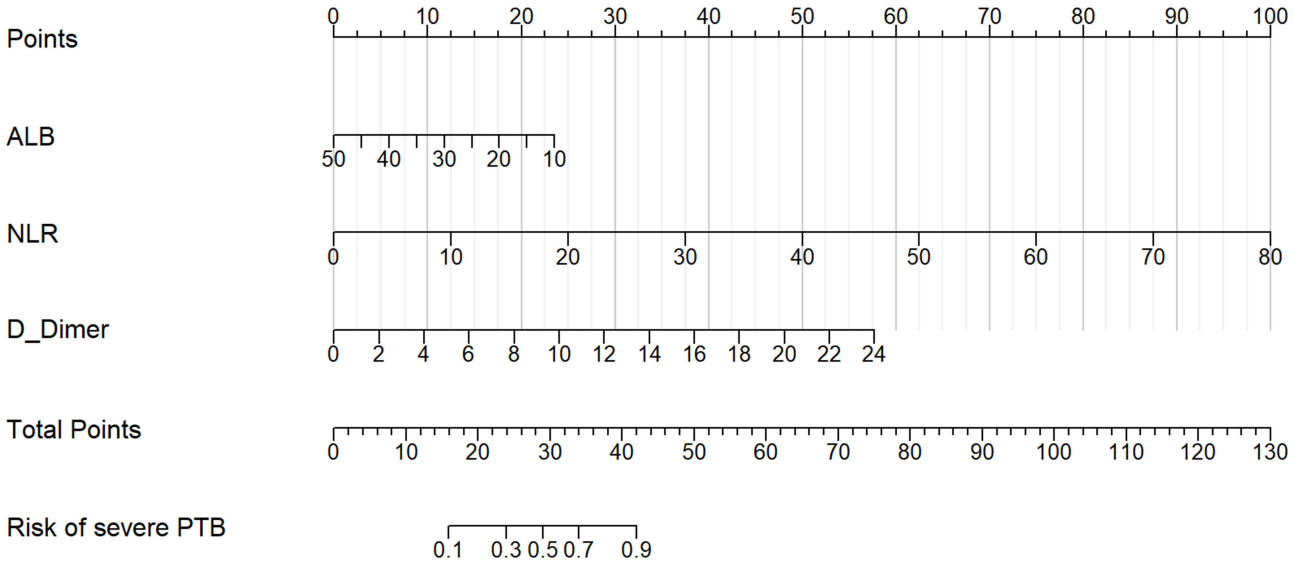

Figure 3 Nomogram for the severe PTB prediction model in newly diagnosed PTB patients with concurrent HIV/AIDS and T2D.

Discussion

The prevalence of PTB in the DM population is 2–3 times that in the general population.[22] Among DM-PTB patients receiving anti-TB treatment, rates of treatment failure are notably higher, TB recurrence is significantly increased, and the incidence of multidrug-resistant TB is also elevated.[22–24] Immunodeficiency is one of the risk factors for severe PTB. In cases of TB with HIV/AIDS, increased age and female gender are independently associated with a higher risk of death.[25] The research conducted by Griesel et al[26] indicates that an inability to walk unaided, low BMI, and low CD4 count were independently associated with death occurring within 56 days post-discharge in seriously ill HIV-infected inpatients with suspected TB. However, studies that take the triple comorbidity of HIV/AIDS, DM, and newly diagnosed PTB as the baseline population and analyze the risk factors for progression to severe PTB remain extremely scarce. In our cohort, severe PTB accounted for 45.6% (52/114) of cases, suggesting that among individuals with initial TB infection, those with comorbid HIV/AIDS and DM are at increased risk for progression to severe PTB.

We propose that early intervention can be implemented for populations with triple comorbidity of HIV/AIDS, DM, and newly diagnosed PTB in the following aspects to reduce the risk of progression to severe PTB or ICU admission. 1. Studies have shown that DM not only increases the incidence of infections, but also that hyperglycemia is associated with a higher risk of progression to critical illness and ICU mortality in infected patients.[27] Patients with DM-PTB should carefully manage their blood sugar levels during hospitalization. 2. In our cohort, the median NRS2002 score was 4, suggesting that the incidence of malnutrition is high among patients with triple comorbidity. Malnutrition is an independent risk factor for poor prognosis and mortality in adult patients with severe PTB.[28,29] Accordingly, following nutritional screening, patients with triple comorbidity should receive timely and appropriately graded nutritional support. 3. Delayed TB treatment is independently associated with increased in-hospital mortality in severe PTB,[10] according to

Table 5 Analysis of the ROC Curve for Risk Factors of Patients with Newly Diagnosed Severe PTB

Variables	AUC (95% *CI*)	Cut-off value	Sensitivity	Specificity
ALB	0.809 (0.729, 0.889)	28.450	76.9%	77.0%
NLR	0.815 (0.735, 0.896)	6.512	76.9%	75.8%
D-Dimer	0.835 (0.757, 0.913)	2.055	79.2%	83.3%
Combination of the three variables	0.892 (0.830, 0.955)	0.464	77.6%	90.2%

Abbreviations: ROC, receiver operating characteristic; PTB, pulmonary tuberculosis; AUC, area under the curve; CI, confidence interval; ALB, albumin; NLR, Neutrophil-to-Lymphocyte Ratio.

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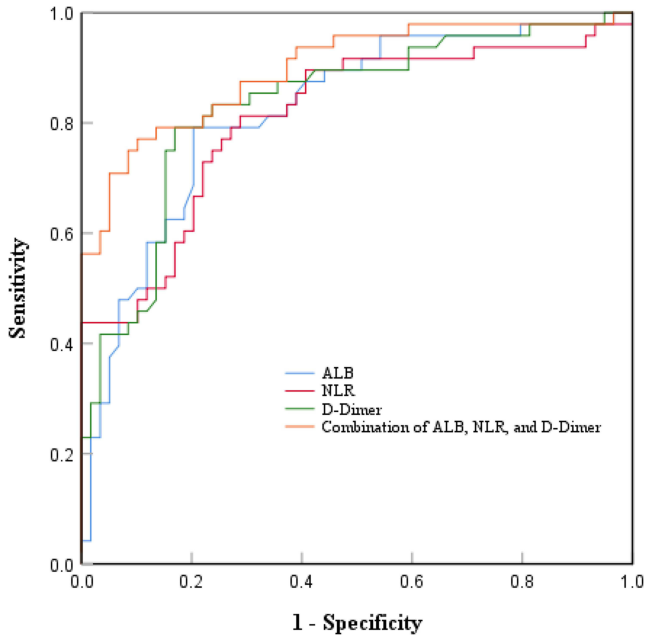

Figure 4 ROC curve of the severe PTB prediction model in newly diagnosed PTB patients with concurrent HIV/AIDS and T2D.

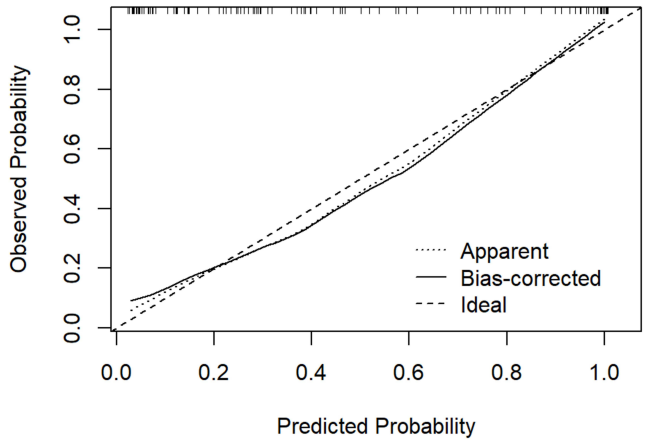

Figure 5 Calibration curve for the severe PTB prediction model in newly diagnosed PTB patients with concurrent HIV/AIDS and T2D.

a multicenter retrospective study. The prognosis of severe PTB hinges on timely anti-TB therapy and adequate drug exposure.[13] Intestinal mucosal edema, dysbiosis, and reduced absorptive area in severe disease delay drug uptake.[30] Additionally, extensive cavitary lesions may substantially lower the AUC of linezolid.[31] Therefore, for patients with triple comorbidity, anti-TB therapy should be initiated promptly when the condition permits. In those with severe PTB and gastrointestinal dysfunction, early intravenous administration is recommended, along with therapeutic drug monitoring to guide dosing. 4. According to WHO recommendations,[32] ART should be initiated as soon as possible, ideally within two weeks of starting anti-TB treatment, for newly diagnosed HIV/AIDS patients.

Multivariate regression analysis in this study revealed that lower ALB, higher NLR, and elevated D-Dimer at admission were independent predictors of disease progression to severe PTB in patients with triple comorbidity (all $P < 0.05$). The decline of ALB in infectious diseases is driven by cytokine-mediated downregulation of hepatic synthesis, capillary leakage, and increased catabolism.[33] Hypoproteinemia is an independent predictor of poor prognosis in patients with infectious diseases,[33–35] as demonstrated in multiple studies. NLR is an emerging marker of inflammation. An elevated NLR indicates a dynamic imbalance characterized by increased neutrophils and decreased lymphocytes,

reflecting a strong inflammatory response in the body. Studies have demonstrated that this ratio is closely associated with the systemic inflammatory response induced by Mycobacterium TB infection.[36,37] An increase in D-Dimer is a significant indicator reflecting the activation of the body's coagulation-fibrinolysis system and the intensification of the inflammatory response. D-Dimer levels may differentiate between active PTB and latent PTB.[38] To evaluate the model's predictive accuracy, we performed ROC curve analysis. The combined panel of ALB, NLR, and D-Dimer was a strong predictor of initial severe PTB, with an AUC of 0.892. At a sensitivity of 77.6% and a specificity of 90.2%, this model demonstrates high discriminatory ability. This simple, three-marker panel may provide robust support for clinical triage and early decision-making.

The present study has certain limitations. As a single-center study, the number of patients with concurrent HIV/AIDS, T2D, and active PTB was relatively limited, despite the inclusion of data spanning from 2018 to 2025. This limited sample size may increase the risk of overfitting in the prediction model. Although the LASSO method and Bootstrap resampling were employed to minimize overfitting, this issue cannot be completely ignored. Consequently, our model should be regarded as a preliminary prediction tool that requires external validation, which has not yet been conducted. Therefore, the findings of this study need to be further validated using larger and more diverse patient samples.

Conclusion

Patients with coexisting HIV/AIDS, T2D, and newly diagnosed PTB are at a high risk of developing severe PTB. This exploratory study was conducted using single-center clinical data from patients with comorbid diseases. We developed a three-variable model (ALB, NLR, and D-Dimer) to predict progression to severe PTB. However, owing to the relatively small sample size and the absence of external validation, the findings require confirmation through future multicenter or prospective studies.

Data Sharing Statement

The datasets used during this study are available from the author (Bennan Zhao, E-mail: 993896436@qq.com) on reasonable request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Public Health Clinical Center of Chengdu (No.: YJ-K2025-34-01). The Ethics Committee waived the need for informed consent from patients because of the retrospective and anonymous nature of the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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