Infection and Drug Resistance Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Applying a Combined Model to Evaluate the Risk of Poor Treatment Outcomes in Rifampicin Resistant Tuberculosis Patients: A Multicenter Retrospective Study

Yunbin Yang, Jinou Chen, Liangli Liu, Ling Li, Rui Yang, Kunyun Lu, Yubing Qiu, Xing Yang, Lin Xu

Division of Tuberculosis Control and Prevention, Yunnan Center for Disease Control and Prevention, Kunming, People's Republic of China

Correspondence: Lin Xu, Email xulinth@hotmail.com

Objective: Treating and managing rifampicin resistant tuberculosis (RR-TB) patients in Yunnan, China, are major challenges. This study aims to evaluate the risk of poor treatment outcomes in RR-TB patients, allowing clinical doctors to proactively target patients who would benefit from enhanced patient management.

Methods: Four RR-TB care facilities in different regions of Yunnan province as the data collection points were selected. A total of 524 RR-TB patients were included in this study and randomly assigned into a training set (n=366) and a validation set (n=158). In the training set, four significant factors were screened by using a random forest model and a Lasso regression model, and then included in a logistic regression model to construct a nomogram for internal validation.

Results: The successful treatment rate of RR-TB patients in training set was 42.6% (156/366), and the main poor treatment outcomes were loss to follow-up (66.7%) and death (18.1%). Low hemoglobin (HGB) (OR=0.977, 95% CI: 0.964–0.989), long-regime (OR=2.784, 95% CI: 1.634–4.842), poor culture results at the end of the 6th month (CR6TM) (OR=11.193, 95% CI: 6.507–20.028), pre-extensively drug-resistant tuberculosis (pre-XDR) (OR=3.736, 95% CI: 1.294–12.034) were risk factors for poor treatment outcomes in RR-TB patients. The Area Under Curve (AUC) of this model was 0.829 (95% CI: 0.787–0.870), and there was good consistency between the predicted probability and the actual probability. The DCA curve showed that when the threshold probability was 20–98%, the use of nomogram to predict the net benefit of poor treatment outcomes risk in RR-TB patients was higher.

Conclusion: We combined multiple models to develop a nomogram for predicting poor treatment outcomes in RR-TB patients. This would help clinical doctors identify high-risk populations and enable them to proactively target RR-TB patients who will benefit from strengthened patient management.

Keywords: drug resistance tuberculosis, poor treatment outcomes, prediction, model, nomogram

Introduction

Rifampicin resistant tuberculosis (RR-TB) is characterized by challenging diagnosis, long treatment duration, high treatment costs, more adverse reactions, and a high loss rate.[1,2] According to the World Health Organization (WHO), in China, there were approximately 30,000 RR-TB patients, accounting for 7.3% of the global total. In 2020, the successful treatment rate of RR-TB patients undergoing treatment was only 51%.[3] Ethiopian studies showed that 38–92% of TB patients reported income loss and 26–76% of TB patients lost their jobs due to unfavorable outcomes of RR-TB, further worsening the financial problem.[4] Yunnan, situated on China's southwestern border, is an economically underdeveloped province comprising 16 prefectures and 129 counties. The successful treatment rate for RR-TB patients in Yunnan was only about 50%~60%, with nearly 40%~50% of RR-TB patients experiencing poor treatment outcomes for various reasons, resulting in the continued spread of drug-resistant bacteria throughout the community.[5,6] Therefore, it is

Received: 12 September 2024
Accepted: 22 November 2024
Published: 29 November 2024

essential to analyze the factors associated with poor treatment outcome in RR-TB patients to prioritize intervention to improve outcomes among RR-TB patients with elevated risks.

Many risk factors associated with unsuccessful treat ment outcomes of RR-TB had been reported, including older age, baseline alcohol use, cavitary disease, culture-positive at baseline, relapsed TB, treatment non-compliance, previous TB treatment, longer treatment duration and history of second-line drug resistance.[7–9] The clinical characteristic data that clinicians pay more attention to were less included in previous studies. At the same time, the clinical data were collected from only one facility would inevitably lead to the unrepresentativeness and unrepeatability of the analysis results. In addition, when many variables with highly linear correlation were collected, only using logistic regression model was easy to cause equation over fitting, and the included variables needed to be controlled and limited. Considering the above factors, this study included the multi-dimensional data of multiple RR-TB care facilities in Yunnan, and applied multiple statistical models to screen and control variable for the construction of influencing factor models, aiming to evaluate the risk of poor treatment outcomes in RR-TB patients in Yunnan, allowing clinical doctors to proactively target patients who would benefit from enhanced patient management.

Methods

Sample Size Estimation

The method of epidemiological cluster sampling was adopted in this study. According to the preliminary work statistics, the average successful treatment rate of RR-TB patients in Yunnan Province was 60% from 2017 to 2023. Taking p=60% into the formula calculation, the design effect deff=2, at least 512 survey subjects should be included (Figure 1).

Data Collection

Based on the estimated sample size, this study collected diagnosis and treatment data of RR-TB patients from four RR-TB care facilities (Baoshan People's Hospital, Puer People's Hospital, Lincang People's Hospital, Gejiu Hospital of Infectious Disease) in different prefectures. These facilities had been enrolling RR-TB patients from 2017 to 2023, recording a large number of cases with high completeness and accuracy. The clinicians of these RR TB care facilities received intensive training from the Yunnan Provincial Center for Disease Control and Prevention (CDC) to ensure the unity of the entered patient clinical data definitions and units of measurement and other effective information. There were standardized protocols across all four centers. Eligible patients were those diagnosed with RR-TB, who received second-line anti-tuberculosis treatment in a TB care facility, and who had recorded treatment outcomes. Patients who met the following criteria were excluded: tuberculosis patients who were sensitive to rifampicin, tuberculosis patients with unknown rifampicin resistance, patients who did not participate in second-line anti-tuberculosis treatment, and patients who did not report treatment results.

Data were collected by doctors in the four participating facilities on various demographic and clinical characteristics of the participants. The data collection was divided into two rounds. Firstly, the author collected the first round of data, sorted out the missing data, and returned it to the clinical doctor. The doctor was asked to supplement and improve it by reviewing the patient's medical records, test result reports, etc. Secondly, if there were still missing data collected in the second round, in order to ensure the authenticity and accuracy of the research data, we directly remove them. Then the authors conducted secondary analysis on patient data contained in treatment databases in the four participating facilities. Demographic data included gender, age, ethnic, occupation, weight. Clinical data consisted of patient type (new, re-treatment), drug resistance type (rifampicin mono-resistance, multidrug resistance, pre-extensively drug

$$N = \frac{Z_\alpha{}^2 pq}{\delta^2} \times deff = \frac{Z_\alpha{}^2 p\ (1-p)}{\delta^2} \times deff$$

$$(Z_\alpha = 1.96, \alpha = 0.05, \delta = 0.1 \times p)$$

Figure 1 The formula for estimating the sample size of cluster sampling.

resistant), detection method (molecular test, conventional drug susceptibility test), treatment regimen (long-term, short-term), culture results at the end of the sixth month (CR6TM; negative, positive and unknown), treatment outcome (successful treatment outcome, STO; poor treatment outcome, PTO), baseline testing data at the start of treatment: red blood cell (RBC), white blood cell (WBC), hemoglobin (HGB), albumin (ALB), fasting blood glucose (FBG), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), glutamyl transpeptidase (GT), Alkaline phosphatase (ALP), silicon controlled rectifier (SCR), blood uric acid (BUA), kalium (K) and pulmonary cavity (yes, no). To ensure the accuracy and reliability of the data, standard operating guidelines were followed for data collection.

Definitions

Drug resistance type: Rifampicin mono-resistance refers to mycobacterium tuberculosis that is only resistant to rifampicin. Multidrug resistance (MDR) refers to mycobacterium tuberculosis that is resistant to at least two or more first-line anti-tuberculosis drugs, including isoniazid and rifampicin, simultaneously. pre-XDR refers to mycobacterium tuberculosis that is resistant to a fluoroquinolone (FQ) antibiotic on the basis of multidrug resistance. XDR refers to the resistance of mycobacterium tuberculosis to at least one of Bedaquiline (Bdq) and Linazolamide (Lzd) in addition to pre-XDR. RR-TB includes Rifampicin monoresistance, MDR, pre-XDR and XDR. Patient type: New patients refer to the patients who have never been exposed to anti-TB treatment or have not received anti-TB treatment for more than one month. Re-treatment refers to TB patients who had been exposed to anti-TB treatment in the past and who relapsed after cure or were retreated without reaching cure. Treatment regime: Long-regime refers to an 18–20 months treatment regime. Short-regime refers to a 9–12 months treatment regime. STO: The first outcome was defined as cured when patients completed the treatment regimen and had three consecutive negative cultures taken at least 30 days apart after the intensive phase. Second, "treatment completion" means patients who completed the treatment regimen, had three consecutive negative cultures and no evidence of treatment failure, STO included cure and treatment completion. PTO: PTO includes treatment failure, death, and loss to follow-up. Treatment failure refers to the termination of treatment for RR-TB patients due to the absence of sputum-negative conversion at the end of the enhancement phase, continued positive conversion after sputum-negative conversion, resistance to fluoroquinolones or second-line anti-tuberculosis drug injections, adverse drug reactions, or the need to switch to at least two anti-tuberculosis drugs. Death refers to the death of RR-TB patients due to any reason during the treatment process. Loss to follow-up refers to the interruption of treatment for RR-TB patients for two months or more.[10]

Data Analysis

Split the Training Set and Validation Set

524 RR-TB patients were randomly divided into training and validation sets in a 7:3 ratio. The training set consisted of 366 patients and was used to establish a predictive model, while the validation set consisted of 158 patients and was used to validate the established model.[11]

Screening of Predictors

A combination of two methods, namely random forest model (RFM) and least absolute shrinkage and selection operator (Lasso) regression model, was used to identify significant predictors. Compared with traditional regression methods, RFM has strong anti-interference capabilities and can avoid increased parameter estimation or reduced sensitivity to outliers when dealing with multi-level categorical variables. Lasso regression, on the other hand, can reduce the correlation between variables and ensure that the subsequent diagnostic plot is not overfit.

Establish a Predictive Model and Draw a Nomogram

The optimal predictors selected by the aforementioned models were incorporated into binary logistic regression analysis using the Backward-LR method. The dependent variable was the STO or PTO, represented by 0 and 1, where a PTO was coded as 1 and STO was coded as 0. Multiclass variables were represented by numbers from 1 to 3, while binary variables were coded as 1 and 2. These variables were entered into the model in the form of dummy variables, and a column line chart was plotted.

Nomogram is constructed based on the results of a multi-factor regression analysis, which combines multiple predictors to estimate the probability of an outcome event. The underlying principle involves assigning scores to each level of the influencing factors based on their contribution to the outcome variable (represented by the magnitude of the regression coefficient in the model). These scores are then summed to obtain a total score, which is subsequently used to calculate the predicted probability of the outcome event for an individual using a functional transformation relationship between the total score and the probability of the outcome event.[12]

Model Performance Evaluation

The model's performance is assessed in terms of its discrimination ability, calibration, and applicability. Discrimination ability is determined by calculating the area under the receiver operating characteristic curve (ROC, AUC). Model calibration is evaluated by comparing predicted values with actual results and visualizing the calibration curve. Applicability is assessed through decision curve analysis (DCA), which quantifies net benefit at different threshold probabilities[13] (Figure 2).

Statistical Analysis

The training and validation datasets were split using the sklearn function in Python. The RFM, Lasso regression model, and logistic regression model were implemented using the functions randomforrest, glmnet4, and logreg in R version 4.2.3, respectively. The logistic regression model was then built and a column line chart was plotted using the logreg function. ROC curves, calibration curves, and DCA curves were plotted using the pROC, rms and rmda functions. The Hosmer–Lemeshow goodness-of-fit test was employed to assess the model fit. Count data was described using "frequency" and "percentage composition (%)". Quantitative data was described using "mean" and "standard deviation". The chi-square test was used to compare differences between groups. The significance level was set at $\alpha=0.05$, and $P<0.05$ was considered statistically significant.

Results

Participant Characteristics

A total of 366 patients with RR-TB were enrolled in the training set. Among them, 301 (82.2%) were male and 65 (17.8%) were female. The age range of the patients was from 17 years to 80 years, with a median age of 49.0 (40.0–59.8) years. The average weight of patients was 48.0 (41.9–55.0) kg. The majority of patients (56.2%) belonged to a minority ethnicity, as opposed to being Han Chinese. Farmers constituted the largest occupational group (310 cases, 84.7%). The majority of RR-TB patients were retreatment (219 cases, 59.8%), with a long-course treatment as the main treatment option (230 cases, 62.8%). 307 cases (83.9%) of RR-TB patients had cavities in the lungs, with RBC of 4.5 (4.0–-4.9)×10^{12}/L, WBC of 7.6 (6.1–9.3)×10^{12}/L, HGB of 127.0 (112.3–140.0) g/L, ALB of 37.7 (34.3–40.7) g/L, TBIL of 7.2

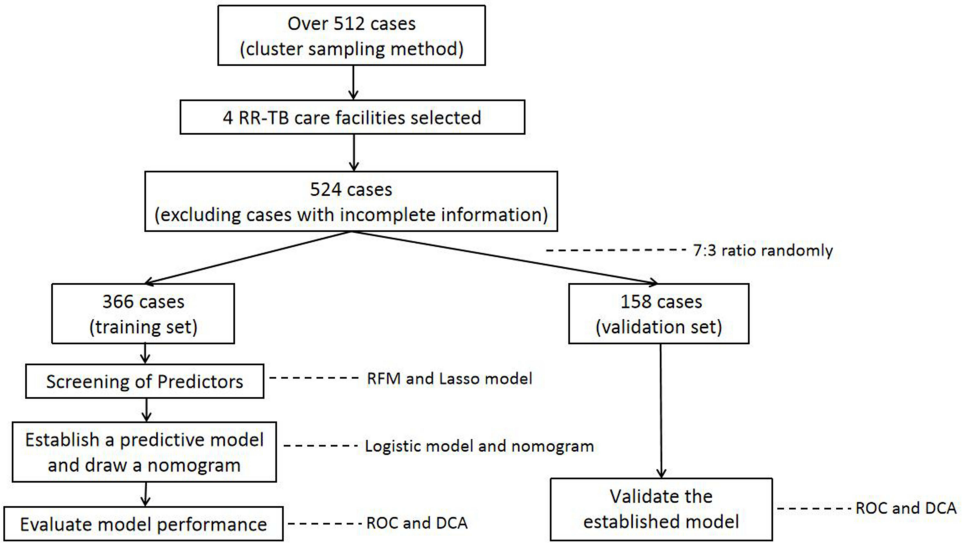

Figure 2 Flowchart in the study design and model establishment.

(5.0–10.5) μmol/L, DBIL of 2.9 (1.9–4.2) μmol/L, GT of 39.4 (25.2–67.0) U/L, ALP of 84.0 (68.7–104.8) U/L, AST of 19.9 (15.0–28.0) U/L, SCR of 64.7 (55.0–77.6) μmol/L, BUA of 392.2 (281.3–525.6) μmolL, FBG of 4.8 (4.4–5.3) mmol/L, K of 4.0 (3.7–4.3) mmol/L. The overall STO rate was 42.6%. The types for PTO were loss to follow-up (66.7%), death (18.1%) and treatment failure (15.2%) (Table 1).

Predictor Selection

Eleven variables (including age, RBC, WBC, HGB, weight, TBIL, ALB, gender, treatment region, CR6TM, drug resistance type) with statistical differences in univariate analysis were included in RFM. The RFM was utilized to conduct variable importance analysis, the factors were ranked based on their impact, including CR6TM, ALB, RBC,

Table 1 Univariable Analysis of Treatment Outcomes Related Variables in Training Set

Variable	Total (n=366)	STO (n=156)	PTO (n=210)	*P*-value
Age (years)	49.0 (40.0–59.8)	48.0 (38.5–56.5)	50.5 (41.0–61.0)	0.017*
RBC (10^{12}/L)	4.5 (4.0–4.9)	4.7 (4.2–5.0)	4.3 (3.9–4.8)	<0.001*
WBC (10^{12}/L)	7.6 (6.1–9.3)	7.1 (5.6–9.0)	8.1 (6.3–9.5)	0.011*
HGB (g/L)	127.0 (112.3–140.0)	133.5 (119.0–144.0)	123.0 (108.3–136.0)	<0.001*
Weight (kg)	48.0 (41.9–55.0)	50.0 (43.0–58.0)	47.9 (41.0–54.0)	0.036*
SCR (μmol/L)	64.7 (55.0–77.6)	66.0 (56.9–77.7)	63.6 (54.6–77.6)	0.303
BUA (μmol/L)	392.2 (281.3–525.6)	405.0 (277.9–525.2)	380.0 (282.3–527.3)	0.605
AST (U/L)	19.9 (15.0–28.0)	21.0 (16.0–31.0)	18.6 (15.0–27.0)	0.059
TBIL (μmol/L)	7.2 (5.0–10.5)	7.8 (5.9–10.7)	6.7 (4.7–10.3)	0.040*
DBIL (μmol/L)	2.9 (1.9–4.2)	2.9 (2.1–4.2)	2.8 (1.9–4.2)	0.403
GT (U/L)	39.4 (25.2–67.0)	36.0 (24.8–64.2)	43.0 (26.2–71.4)	0.129
ALP (U/L)	84.0 (68.7–104.8)	81.5 (68.3–99.9)	85.3 (70.2–107.5)	0.279
ALB (g/L)	37.7 (34.3–40.7)	39.3 (36.6–41.6)	36.3 (32.5–39.9)	<0.001*
FBG (mmol/L)	4.8 (4.4–5.3)	4.7 (4.4–5.3)	4.8 (4.4–5.3)	0.805
K (mmol/L)	4.0 (3.7–4.3)	4.0 (3.7–4.3)	3.9 (3.7–4.2)	0.418
Gender, n (%)				0.044*
Male	301 (82.2)	121 (77.6)	180 (85.7)	
Female	65 (17.8)	35 (22.4)	30 (14.3)	
Ethnic, n (%)				0.061
Han	160 (43.7)	77 (49.4)	83 (39.5)	
Others	206 (56.3)	79 (50.6)	127 (60.5)	
Occupation, n (%)				0.072
Farmer	310 (84.7)	126 (80.8)	184 (87.6)	
Others	56 (15.3)	30 (19.2)	26 (12.4)	
Patient type, n (%)				0.941
New	147 (40.2)	63 (40.4)	84 (40.0)	
Re-treatment	219 (59.8)	93 (59.6)	126 (60.0)	
Treatment regime, n (%)				0.001*
Short-term	136 (37.2)	73 (46.8)	63 (30.0)	
Long-term	230 (62.8)	83 (53.2)	147 (70.0)	
Detection method, n (%)				0.268
Molecular test	318 (86.9)	132 (84.6)	186 (88.6)	
Conventional drug susceptibility test	48 (13.1)	24 (15.4)	24 (11.4)	
CR6TM, n (%)				<0.001*
Negative	204 (55.7)	132 (84.6)	72 (34.3)	
Positive and unknown	162 (44.3)	24 (15.4)	138 (65.7)	
Drug resistance type, n (%)				0.015*
Rifampicin mono-resistance	118 (32.2)	59 (37.8)	59 (28.1)	
MDR	219 (59.8)	91 (58.3)	128 (61.0)	
pre-XDR	29 (8.0)	6 (3.9)	23 (10.9)	
Pulmonary cavity, n (%)				0.163
No	59 (16.1)	30 (19.2)	29 (13.8)	
Yes	307 (83.9)	126 (80.8)	181 (86.2)	

Notes: *: The difference is statistically significant when the *P*-value is less than 0.05.

TBIL, WBC, HGB, age, weight, drug resistance type, treatment regime, gender. Subsequently, these 11 factors underwent Lasso regression analysis, resulting in the selection of 4 factors after applying a minimum distance standard error of λ=0.051. The final selected factors included HGB, drug resistance type, CR6TM, treatment regime (Figure 3).

Building and Validating a Predictive Model

A predictive model was developed using the training set data, where the 4 most significant predictors were included in a stepwise logistic regression analysis. The final results indicated that HGB (*OR*=0.977, *95% CI*: 0.964–0.989), treatment regime (*OR*=2.784, *95% CI*: 1.634–4.842), CR6TM (*OR*=11.193, *95% CI*: 6.507–20.028), and drug resistance type (*OR*=3.736, *95% CI*: 1.294–12.034) were associated with PTO of RR-TB patients (Table 2). A nomogram was used to display the model, where each variable option corresponded to a score, and the total score was obtained by adding the scores of all 4 variables. At the bottom of the nomogram, the probability prediction for different total scores was given. Higher total scores corresponded to higher probabilities of PTO (Figure 4).

The internal validation results revealed that the AUC values of the model developed from the training set and the validation set were 0.829 (*95% CI*: 0.787–0.870) and 0.881 (*95% CI*: 0.829–0.932), respectively. In both datasets, the calibration curve demonstrated consistency between the predicted probability and the actual probability, closely resembling the ideal straight line. Furthermore, the Hosmer–Lemeshow test indicated a good fit for the model, and the DCA curve illustrated that the use of the nomogram to predict the risk of PTO in RR-TB patients provided a high net benefit

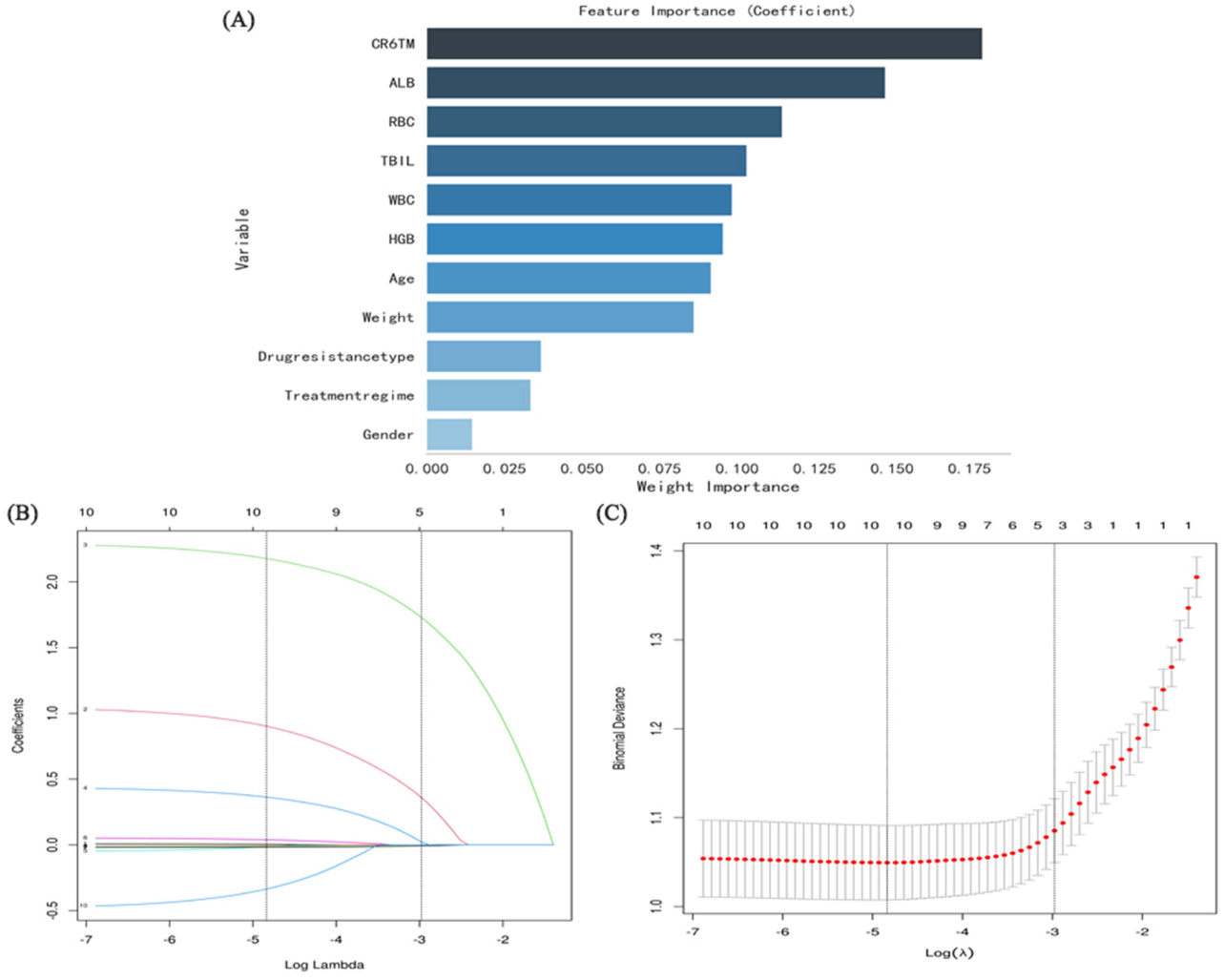

Figure 3 RFM and coefficients of the Lasso model. (**A**) Coefficients of importance: CR6TM, ALB, RBC, TBIL, WBC, HGB, age, weight, drug resistance type, treatment regime, gender. (**B**) Lasso coefficient profiles of the candidate features. (**C**) Lasso coefficient profiles of the four factors. A coefficient profile plot was produced against the log λ sequence. Lasso, least absolute shrinkage and selection operator.

Table 2 Univariate Logistic Regression for PTO of RR-TB Patients

Variables	Beta	S.E	Z	*P*-value	aOR (95% CI)
HGB	−0.024	0.007	−3.597	<0.001	0.977 (0.964–0.989)
Treatment regime					
Short-term					1.00 (Reference)
Long-term	1.024	0.276	3.707	<0.001	2.784 (1.634–4.842)
CR6TM					
Negative					1.00 (Reference)
Positive and unknown	2.415	0.286	8.448	<0.001	11.193 (6.507–20.028)
Drug resistance type					
Rifampicin mono-resistance					1.00 (Reference)
pre-XDR	1.318	0.562	2.344	0.019	3.736 (1.294–12.034)

Abbreviations: aOR, Adjusted Odds ratio; CI, Confidence Interval.

when the threshold probability ranged from 20% to 98%. These findings suggest that the nomogram developed in this study exhibits favorable discrimination, calibration, and clinical applicability (Figure 5).

Discussion

Treating RR-TB patients is a daunting challenge, with a significantly lower STO rate than rifampicin-sensitive patients.[14,15] The STO rate of RR-TB patients in this study was only 42.6%, significantly lower than the national

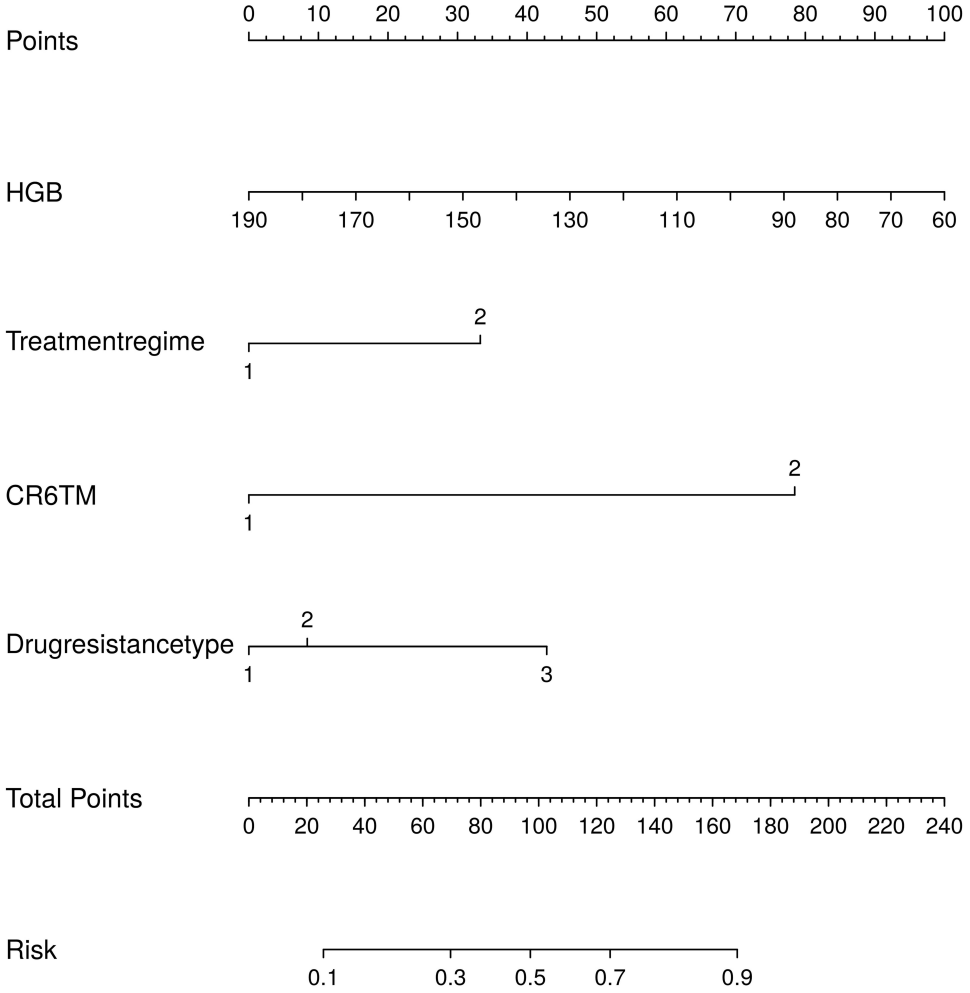

Figure 4 Nomogram for PTO of RR-TB patients. Treatment regime: 1 = Short-term, 2 = Long-term; CR6TM: 1 = Negative, 2 = Positive and unknown; Drug resistance type: 1 = Rifampicin mono-resistance, 2 = MDR, 3 = pre-XDR; logistic regression.

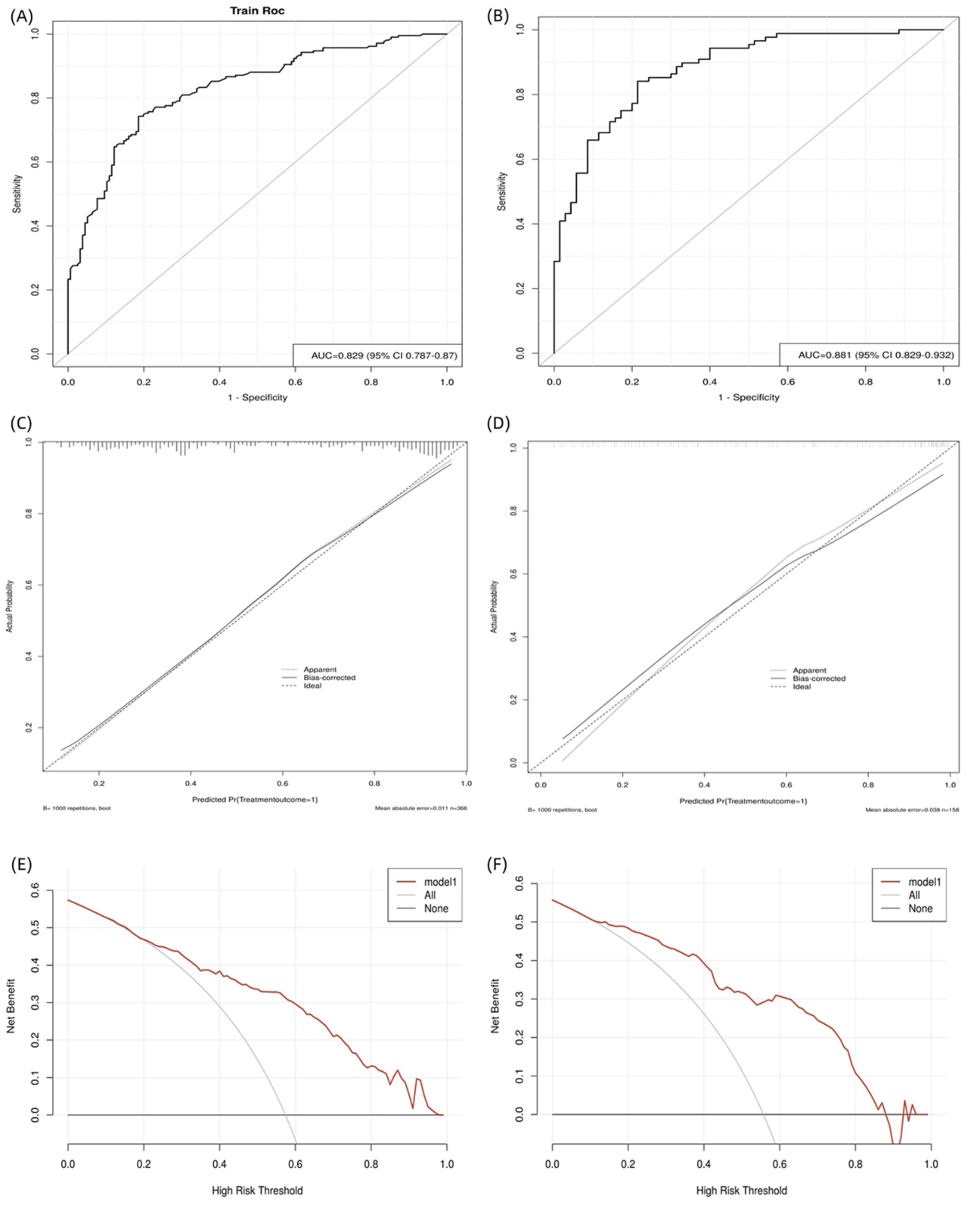

Figure 5 Three evaluation curves for training and validation sets. (**A**) ROC curves of nomogram for training sets. (**B**) ROC curves of nomogram for validation sets. (**C**) Calibration curves of the nomogram for training sets. (**D**) Calibration curves of the nomogram for validation sets. (**E**) DCA of the model for training sets. (**F**) DCA of the model for validation sets.

average of 51%[1] and the level of 61.4% in coastal areas of China.[16] Nearly 55%RR-TB patients still exhibit PTO.[17] Excluding deaths, these patients continue to spread drug-resistant bacteria in the community and at home, leading to an increase in the number of RR-TB patients receiving initial treatment.[18]

In recent years, logistic regression analysis had been widely employed to construct disease risk prediction models, demonstrating good discriminative value.[19,20] Compared to other network models, logistic regression is simpler and easier to use.[21] Unlike previous research designs, this study utilized a combination of three models to construct the prediction model. The RFM was responsible for sorting potential predictors according to their contribution and further screened the top four predictors using the Lasso regression model. The selected predictors were then incorporated into the logistic regression model, and a nomogram was drawn. Finally, the model was evaluated and validated.

The results demonstrated that the model's discrimination reached a good level, consistent with other studies.[22–24] The calibration curve showed good consistency between the predicted probability and the actual probability, while the DCA curve indicated that the model had certain value for identifying high-risk RR-TB patients with PTO at a threshold probability of 20% to 98%. The model can serve as a reference for relevant personnel in RR-TB designated care facilities and CDCs. For example, a RR-TB patient diagnosed with MDR had a baseline HGB of 150 g/L, received a long-term treatment regimen, and had a negative CR6TM test; in the bar chart, HGB earned 30 points, treatment regime earned 32 points, CR6TM earned 0 points, MDR earned 8 points and the total score was 70 points. This indicates that he may have a 31% risk of PTO.[25]

Logistic regression analysis showed that the lower HGB of RR-TB patients, the higher likelihood of PTO. HGB concentration is the most relevant indicator of anemia at the population level.[26,27] When hemoglobin levels decrease, the function of red blood cells was affected, which may lead to the occurrence of anemia. There are literature reports that HGB is an independent predictor of death among in-hospital patients initially diagnosed with primary TB.[28] The occurrence, progression, and prognosis of TB were all related to nutrition.[29,30] The metabolic disruptions caused by the disease, further exacerbate the body's inability to replenish sufficient protein and energy, ultimately affecting the TB patient's nutrition status.[31] And the efficacy of anti-TB drugs was reduced, thereby diminishing the overall success rate of treatment.[32] Consequently, it is imperative to proactively use nutrition risk screening tools (NRS 2002) upon RR-TB patients admission to identify individuals at risk of malnutrition by clinician. Identifying RR-TB patients at nutrition risk enables the provision of nutrition guidance or support.[33]. Due to the wide variety and high dosage of second-line anti-tuberculosis drugs taken by RR-TB patients, they are prone to vomiting, diarrhea, etc., which can lead to poorer nutritional status. Therefore, clinical doctors need to pay special attention to giving RR-TB patients more appropriate drugs and doses to help them better tolerate treatment plans. In this study, although ALB and weight were not included in the predictive model, we can see that the median values of baseline ALB and weight for RR-TB patients were only 37.7 g/L (below 40.9 g/L in some studies)[28] and 48.0 kg (the average weight of males was only 50.2 kg), indicating that the nutritional status of RR-TB patients was not very good. The malnutrition is a risk factor for immunodeficiency and an important risk factor for TB poor outcomes.[34] Drug resistance type was also an important influencing factor. Patients with pre-XDR type had significantly poorer prognosis, and pre-XDR had developed resistance to the most effective second-line anti-tuberculosis drug FQ. Pedersen pointed out, the strongest risk factors for an unsuccessful outcome were pre-XDR.[35–39] The strength of this association may be due to the long treatment period, many adverse effects related to historical treatment regulations.[40] Due to the fact that the investigation agency has not yet conducted drug sensitivity tests for Bdq and Lzd, XDR data were not involved in this study.

In addition, the presence of positive and unknown CR6TM was associated with a higher incidence of PTO. Previous studies have demonstrated that CR6TM serve as an important indicator for evaluating the effectiveness and efficacy of RR-TB treatment regimens, playing a crucial role in providing early warnings throughout the treatment process.[41,42] If the results are positive, it indicates treatment ineffectiveness and an increased risk of treatment failure. However, for those with unknown results, it could imply a failure to return to the designated RR-TB care facilities for timely follow-up examinations or that they had already dropped out of treatment or died. The incidence of PTO in RR-TB patients undergoing short-term treatment was lower, possibly due to the shortened duration of the treatment by nearly 9 months. RR-TB patients are more able to persist in completing the course of treatment, and the cost is relatively low. According to a previous survey in Yunnan Province, the median direct medical cost of short-term treatment decreased by 15,380 yuan

over long-term.[43] A safe and effective short-term treatment plan for RR-TB could improve treatment compliance, reduce costs, and improve the STO rate of treatment, benefiting both doctors and patients.[44] Some studies had also shown that pulmonary activity has a certain impact on the treatment outcomes of tuberculosis patients.[25] This study indicated that 83.9% of the study subjects had pulmonary activity, indicating that the detection of RR-TB patients was delayed, leading to a more severe condition of RR-TB patients by enrollment. It was recommended to implement an active detection strategy and detect RR-TB early and enroll.

The limitation of this study was that although multicenter data from four RR-TB care facilities in different regions were included, it lumped several outcomes that may had different influencing factors–loss to follow-up, death, treatment failure–into a single category. If different types of PTO were disassembled and analyzed separately, different influencing factors might be obtained. In this way, we could better provide more targeted clinical support for RR-TB patients of different PTO types. In the future, the research team needs to further analyze the influencing factors of different PTO, in order to provide more specific reference basis for clinical practice.

Conclusion

We combined multiple models to create a nomogram for predicting PTO in RR-TB patients. Clinical doctors could use the nomogram in this study as the RR-TB patient score in future diagnosis and treatment work to quantitatively evaluate the probability of possible prospective outcomes for different RR-TB patients in the form of scores, to proactively target RR-TB patients who will benefit from strengthened patient management, such as pre-XDR, long-term treatment, poor CR6TM, and baseline low HGB. In the future, multicenter research, different types of PTO should be classified and refined, to better tailor interventions for different types of PTO of RR-TB patients.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data Sharing Statement

In order to protect the privacy of RR-TB cases, we will not share the original copies of information from the database. We would like to share statistical results of this study. If anyone needs these data, please contact the corresponding author for a soft copy.

Ethics Approval

This study was consulted to "the ethics committees of Yunnan Center for Disease Control and Prevention" (Ethical review approval document 2023-34). A waiver for patient informed consent was granted by the Institutional Review Board/Ethics Committee of Yunnan Center for Disease Control and Prevention because of the study did not include any data of patients' personal information, including name, identity information, address, telephone number, etc. Our study complies with the Declaration of Helsinki.

Acknowledgments

We thank the four RR-TB care facilities (Baoshan People's Hospital, Puer People's Hospital, Lincang People's Hospital, Gejiu Hospital of Infectious Disease) gave permission for the use of their data, tireless contributions of the staff in RR-TB care facilities and other related health-care workers for undertaking this hard study in Yunnan. Special thanks go to FHI 360 China/Kunming Office for their technical support to this study.

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.

Funding

This work was funded by the Yunnan Provincial High-Level Talent Incubator Program. The funders had no role in study design, data collection and analysis, writing of the manuscript and decision to publish.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lu S, Yang HY, Chen YB. Risk factors and intervention measures for multidrug-resistant tuberculosis. *Nursing Pract Res*. 2020;17(3):51–53.
2. Pooran A, Pieterson E, Davids M, Theron G, Dheda K. What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa. *PLoS One*. 2013;8(1):e54587. doi:10.1371/journal.pone.0054587
3. World Health Organization. *Global Tuberculosis Report 2023*. Geneva: World Health Organization; 2023.
4. World Health Organization. Ethiopia launched new guideline for reaching missed tuberculosis cases; 2018.
5. Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med*. 2017;5:291–360.
6. Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug-resistance in epidemics of tuberculosis: a transmission modelling analysis. *Lancet Respir Med*. 2015;3(12):963e72. doi:10.1016/S2213-2600(15)00458-0
7. Alemu A, Bitew ZW, Worku T. Poor treatment outcome and its predictors among drug-resistant tuberculosis patients in Ethiopia: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;98:420–439. doi:10.1016/j.ijid.2020.05.087
8. Girum T, Tariku Y, Dessu S. Survival status and treatment outcome of multidrug resistant tuberculosis (MDR-TB) among patients treated in treatment initiation centers (TIC) in South Ethiopia: a retrospective cohort study. *Ann Med Health Sci Res*. 2017;7(5):1.
9. Arroyo LH, Ramos ACV, Yamamura M. Predictive model of unfavorable outcomes for multidrug-resistant tuberculosis. *Revista de Saúde Pública*. 2019;53:77. doi:10.11606/s1518-8787.2019053001151
10. Liu JJ, Zhao YL. *Technical Guidelines for Tuberculosis Prevention and Control in China [M]*. People's Health Publishing House.
11. Yan J, Liu Y, Yu J, et al. Establishment and validation of a nomogram for suicidality in Chinese middle school students. *J Affective Disord*. 2023;330:148–157. doi:10.1016/j.jad.2023.02.062
12. Chen D, Lin S, Dai Zhisong ZY, Chen K. Construction and validation of a nomogram for predicting unfavorable treatment outcomes among rifampicin-sensitive tuberculosis. *Chin J Antituberculosis*. 2023;45(10):957.
13. Xi L, Xiang M, Wu C, et al. Adverse events after repair of tetralogy of Fallot: prediction models by machine learning of a retrospective cohort study in western China. *Transl Pediatr*. 2023;12(2):125–136. doi:10.21037/tp-22-246
14. Liang D, Zhao XY, SHang Y, et al. Analysis of influencing factors and Bayesian network model study of treatment outcome in tuberculosis patients in Qinghai. *Dis Surveillance*. 2022;37(2):210–213.
15. Chaves Torres NM, Quijano Rodriguez JJ, Porras Andrade PS, et al. Factors predictive of the success of tuberculosis treatment: a systematic review with meta-analysis. *PIoS One*. 2019;14(12):e0226507. doi:10.1371/journal.pone.0226507
16. Chen B, Chen X, Ren Y, et al. Treatment cascade for patients with multidrug- or rifampicin-resistant tuberculosis and associated factors with patient attrition in southeastern China: a retrospective cohort study. *J Infection Public Health*. 2023;16(7):1073–1080. doi:10.1016/j.jiph.2023.05.012
17. Naidoo P, Theron G, Rangaka MX, et al. The South African tuberculosis care cascade: estimated losses and methodological challenges. *J Infect Dis*. 2017;216(7):S702–13. doi:10.1093/infdis/jix335
18. Jia XJ, Hu YL, Zhang DY, et al. Investigation of pulmonary tuberculosis cluster in a boarding school. *J Tuberculosis Lung Dis*. 2023;4(1):18.
19. Jiang SF, Di J, Wang YY, et al. Risk prediction model for ICU patients with lower respiratory tract CRKP nosocomial infection. *Chinese J Nosocomiol*. 2022;32(6):930–935.
20. Yuan XP, Cheng ZT, Liu GX, et al. Construction of risk prediction model of catheter-related bloodstream infection for long-term hemodialysis patients. *Chinese J Nosocomiol*. 2022;32(1):61–65.
21. Akbar G, Liu YJ. Causal effect of the treatment of pulmonary tuberculosis in the elderly based on Bayesian network, Urumqi. *Mod Preventive Med*. 2020;47(5):788–794.
22. Li BC, Wang YJ, Cao XY. Establishment of prediction model of medication compliance in patients with pulmonary tuberculosis. *Mod Med J*. 2022;50(5):529–535.
23. Li YL, Chen J, Xu MY, et al. Development and validation of a risk prediction model for unsuccessful treatment of patients with pulmonary tuberculosis. *China Preventive Med*. 2023;1–9.
24. Peetluk LS, Ridolfi FM, Rebeiro PF, Liu D, Rolla VC, Sterling TR. et a1. Systematic review of prediction models for pulmonary tuberculosis treatment outcomes in adults. *BMJ Open*. 2021;11(3):e044687. doi:10.1136/bmjopen-2020-044687
25. Ma J-B, Zeng L-C, Ren F, et al. Development and validation of a prediction model for unsuccessful treatment outcomes in patients with multi-drug resistance tuberculosis. *BMC Infect Dis*. 2023;23(1):289. doi:10.1186/s12879-023-08193-0
26. Du ZX, Chang FQ, Wang ZJ, Zhou DM, Li Y, Yang JH. A risk prediction model for acute kidney injury in patients with pulmonary tuberculosis during anti-tuberculosis treatment. *Ren Fail*. 2022;44(1):625–635. doi:10.1080/0886022X.2022.2058405
27. Khan JR, Awan N, Misu F. Determinants of anemia among 6-59 months aged children in Bangladesh evidence from nationally representative data. *BMC Pediatr*. 2016;16(1):3. doi:10.1186/s12887-015-0536-z
28. Dan L, Tang S-Y, Lei S, et al. A nomogram for predicting mortality of patients initially diagnosed with primary pulmonary tuberculosis in Hunan province, China a retrospective study. *Front Cell Infect Microbiol*. 2023;13:1179369. doi:10.3389/fcimb.2023.1179369
29. Martin SJ, Sabina EP. Malnutrition and associated disorders in tuberculosis and its therapy. *J Diet Suppl*. 2019;16(5):602–610. doi:10.1080/19390211.2018.1472165
30. Semba RD, Darnton-Hill I, de Pee S. Addressing tuberculosis in the context of malnutrition and HIV coinfection. *Food NutrBull*. 2010;31(4 suppl):S345–S364.

31. Maulahela H, Simadibrata M, Nelwan EJ, et al. Recent advances in the diagnosis of intestinal tuberculosis. *BMCGastroenterol*. 2022;22(1):89.
32. Sinha P, Davis J, Saag L, et al. Undernutrition and tuberculosis: public health implications. *J Infect Dis*. 2019;219(9):1356–1363. doi:10.1093/infdis/jiy675
33. Li Z, Wang P, Ma J, Chen Y, Pan D. Analyzing nutrition risks and blood biomarkers in hospitalized patients with tuberculosis: insights from a 2020 hospital-based study. *Nutr Clin Pract*. 2024;39(6):1464–1474. doi:10.1002/ncp.11223
34. Ma L, Chen X, Gao M. Analysis on the risk factors of malnutrition in type 2 diabetes mellitus patients with pulmonary tuberculosis. *Infect Drug Resist*. 2022;15:7555–7564. doi:10.2147/IDR.S381392
35. Pedersen OS, Butova T, Kapustnyk V, et al. Treatment outcomes and risk factors for an unsuccessful outcome among patients with highly drug-resistant tuberculosis in Ukraine. *Clin Microbiol Infect*. 2024;30(3):360–367. doi:10.1016/j.cmi.2023.12.001
36. Butov D, Lange C, Heyckendorf J, et al. Multidrug-resistant tuberculosis in the Kharkiv Region, Ukraine. *Int J Tuberc Lung Dis*. 2020;24(5):485–491. doi:10.5588/ijtld.19.0508
37. Yesypenko Y, Grigoryan R, Sereda Y, et al. Treatment outcomes of drug-resistant tuberculosis in people living with HIV in Odesa province, Ukraine, 2014-2016. *J Infect Dev Ctries*. 2020;14(11.1):88–93. doi:10.3855/jidc.11979
38. Aibana O, Bachmaha M, Krasiuk V, et al. Risk factors for poor multidrug-resistant tuberculosis treatment outcomes in Kyiv Oblast, Ukraine. *BMC Infect Dis*. 2017;17(1):129. doi:10.1186/s12879-017-2230-2
39. Lytvynenko N, Cherenko S, Feschenko Y, et al. Management of multi- and extensively drug-resistant tuberculosis in Ukraine: how well are we DOIng?. *Public Health Action*. 2014;4(Suppl 2):67–72. doi:10.5588/pha.14.0035
40. Motta I, Boeree M, Chesov D, et al. Recent advances in the treatment of tuberculosis. *Clin Microbiol Infect*. 2023;30(9):1107–1114. doi:10.1016/j.cmi.2023.07.013
41. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi and extensively drug-resistant pulmonary TB. *Eur Respir J*. 2014;33(5):1085–1094. doi:10.1183/09031936.00155708
42. Li L, Sun JS, Wu YL. Influencing factors of treatment outcome of MDR-TB patients that completed the whole-process treatment of Global Fund MDR-TB Project in Xuzhou. *Pract J Cardiac Cerebral Pneumal Vasc Dis*. 2015;23(7):50–54.
43. Ly T. *Analysis of Economic Burden and Its Influencing Factors Among Rifampin-Resistant Tuberculosis in Yunnan Province[D]*. Kunming Medical University; 2022.
44. Feng Z, Tongxin L, Song Y, Shenjie T. Progress on short-course regimens for the treatment of tuberculosis. *Chinese J Antituberculosis*. 2023;45(3):311–317.