A simple-to-use nomogram for the individualized prediction of multidrug-resistant tuberculosis among individuals with previous tuberculosis history

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Research

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Abstract

Background: So far, there are few studies that have investigated the risk of incident multidrug-resistant tuberculosis (MDR-TB) among individuals with previous tuberculosis history (PTBH), let alone developed a nomogram so as to comprehensively estimate an individualized risk of incident MDR-TB in this population. The present study was to construct a comprehensive nomogram for providing simple and precise personalized prediction of incident MDR-TB risk among individuals with PTBH.

Methods: A matched case–control study (1: 2 ratios) was performed between 2005 and 2018 in Hangzhou City, China. A multivariable Cox proportional hazard regression was used to evaluate independent predictors of incident MDR-TB in individuals with PTBH. A comprehensive nomogram was developed based on the multivariable Cox model.

Results: Overall, 1, 836 participants were included in this study. We developed a simple-to-use nomogram for predicting the individualized risk of incident MDR-TB by using the parameters of age < 60 years, a history of direct contact, passive mode of TB case finding, human immunodeficiency virus infection, re-treated TB history, unsuccessful treatment, 3HRZES/6HRE, duration of pulmonary cavities, and duration of positive sputum culture in individuals with PTBH. The concordance index of this nomogram was 0.833 [95% confidence interval (CI): 0.807-0.859] and 0.871 (95% CI 0.773-0.969) for the training and validation sets, respectively, which indicated adequate discriminatory power. The calibration curves for the risk of incident MDR-TB showed an optimal agreement between nomogram prediction and actual observation in the training and validation sets, respectively. The high sensitivity and specificity of nomogram was indicated by using a receiver operating characteristic curve analysis.

Conclusions: We developed and validated a novel nomogram for predicting and preventing the risk of incident MDR-TB in individuals with PTBH. Through this clinic tool, TB control executives could more precisely monitor, estimate and intervene the risk of incident MDR-TB among individual PTB patients.

Introduction

The prevalence of multidrug-resistant tuberculosis (MDR-TB) is increasing rapidly in the world [1]. According to the latest indication given by the World Health Organization (WHO), there were about 500,000 new cases of drug-resistant TB (DR-TB) (of which 78% had the MDR-TB) worldwide in 2018 [2]. With 500,000 patients with DR-TB, China has the second highest number of cases of this disease worldwide [2]. The MDR-TB remains a serious public health issue globally, causing severely social, familial and economic dysfunctions [1].

Continuous monitoring indicated that some individuals with previous tuberculosis history (PTBH) evolved into the MDR-TB after a definite period of time. According to our investigation, we found that the surveillance and management were insufficient among individuals with PTBH in China. Although several studies have revealed that a number of clinical and environmental factors (such as acquired infections, prior irregular treatment, and inadequate treatment management of TB) may affect the prevalence of

MDR-TB in TB patients [3–6], the most recent MDR-TB epidemic seems to reveal a different increased risk of morbidity in individuals with PTBH.

To reduce the morbidity and mortality of MDR-TB, it is urgent that the government and researchers take measures to explore preventive strategies of MDR-TB risk among individuals with PTBH. Recently investigators have proved the significance of early prediction and assessment on the MDR-TB risk [7, 8]. A white paper on the predictive, preventive and personalized medicine [9] suggested that a central component of preventive strategies is the identification of individuals at risk for development of a disease. Although previous studies have established several models based on predicting the outcome of TB infection and showed certain application value [10, 11], there is currently no model available for the prediction and assessment of MDR-TB risk in individuals with PTBH.

To date, in the research field of MDR-TB control, though some variables, such as sociodemographic, clinical, and microbiological predictors [12–14], have been well recognized as determinants of incident MDR-TB risk in TB patients, few studies focused on the status of incident MDR-TB among individuals with PTBH, let alone integrated them so as to comprehensively assess a patient's specific risk of incident MDR-TB. It is now well established from a variety of studies, that the nomogram model is an algorithm with integrating predictors and has been identified as a practical tool of preventive interventions [15]. In addition, a nomogram can accurately predict and estimate the individualized risk of a disease and quantitatively demonstrate a personalized probability for predicting the incidence of disease outcome [15].

In the present study, based on a matched case – control study (1: 2 ratios), we selected a population with PTBH as participants and mainly aimed to (a) identify predictors of incident MDR-TB in individuals with PTBH, hoping to reduce the morbidity and mortality of MDR-TB; and (b) construct a comprehensive nomogram for providing simple and precise personalized prediction of incident MDR-TB risk among individuals with PTBH.

Materials And Methods

Workflow

This study workflow was summarized in Fig. 1. Two separate datasets were used to develop and validate the risk-prediction tool based on predictors of incident MDR-TB in individuals with PTBH. Data of a matched case – control study (1: 2 ratios) from January 1, 2005 to December 31, 2018 (n = 1719) were used as a training data set to derive the risk of MDR-TB among individuals with PTBH, while data from the National TB Surveillance System (NTSS) between January 1 and October 31, 2019 (n = 117) was used as an independent dataset to validate the prediction tool.

After the quantitative predictors were extracted from individuals with PTBH, univariate and multivariate Cox proportional hazard regression models were applied to select optimal risk factors to build a practical instrument for predicting the risk of incident MDR-TB in individuals with PTBH.

Sample Size Calculation

(see Supplementary Files for Sample Size Calculation)

Study Design And Settings

A matched case – control study (1: 2 ratios) was conducted in Hangzhou, China. This study was based on individuals with PTBH from 2005 to 2018. All subjects with drug resistance detection who were enrolled in this retrospective study between January 1, 2005 and December 31, 2018 constituted the case – control study.

For the present study, the MDR-TB cases were selected from all of TB designated hospitals in Hangzhou City. The cases were selected in this study using the 'all comers' principle [19], as long as they met inclusion and exclusion criteria, and the controls were selected by using a random sampling method from the same TB designated hospitals. In this study, the subjects were classified into 'incident MDR-TB' (i.e., the case group) and 'non-incident MDR-TB' groups (such as the control group) according to the ultimate outcome. The subjects were ultimately selected if they (a) had not a history of MDR-TB infection who were first examined with drug susceptibility testing (DST) before the previous TB treatment; (b)were surviving during the study; (c) had a history of TB treatment; (d) had a definite treatment outcome; and (e) could be followed up. The subjects were excluded if (a) they had a history of MDR-TB infection before the previous TB treatment; (b) no DST results were reported; (c) TB patients were being treated; (d) no treatment outcome could be obtained; (e) subjects who lost or died during the follow-up visit; and (f) the missing data was severe (Fig. 1).

The starting date of previous anti-TB treatment was defined as the starting time of the observation study; while we defined a patient's observation ending date as the end date of the study, which was the data of incident MDR-TB or December 31, 2018. Incident MDR-TB for all years were collected between January 1, 2005, and December 31, 2018. In this study, treatment regimens (TRs) were formulated on the basis of patients' PTBH.

Data Collection

All data in this retrospective observational study were collected from self-designed standard questionnaires and the NTSS, and were entered in duplicate into an electronic database. The NTSS was established in 2005 and used as one of data sources in our study. A self-designed standard questionnaire was used to collect patients' sociodemographic, clinical and laboratory test data. Sociodemographic data included age, gender, areas of residence, a history of direct contact, nationality, family income, occupational risk, education levels, and registered household of patients. Clinical data included mode of TB case finding, human immunodeficiency virus (HIV) infection, patients with severe infection, comorbidities, different PTBH including newly diagnosed TB history (NDTH) and re-treated TB history

(RTH), mode of TB case management, treatment outcomes, time from illness onset to the first medical visit (TIOFMV) and laboratory confirmation (TIOLC), TB treatment time, the status of using TRs, and chest radiological findings. Laboratory test data included sputum smear, culture, and DST results at baseline and follow-up visits.

Standard participant reporting included sociodemographic, clinical and microbiological information along with initial and follow-up visits. The sociodemographic, clinical and microbiological data of each participant were collected by trained investigators.

Variables And Definitions

The case definitions and classifications used in the present study were consistent with World Health Organization (WHO) revised TB definitions and reporting framework [20]. The main outcome variable was measured as incident MDR-TB or non-incident MDR-TB. Table 1 showed the definitions of this study. The main covariate variables were defined and classified based on the WHO and national guidelines [20, 21]. Sputum smear, culture, and DST results were defined according to the WHO guideline [20, 21].

Variables	Definitions
MDR-TB case	A patient infected with TB resistant to at least H and R.
Incident MDR-TB	A MDR-TB case was confirmed from previous TB treatment starting to the end date of the study.
Non-incident MDR-TB	The MDR-TB had not happened from previous TB treatment starting to the end date of the study.
Low-income level	The economy income of a family (i.e., below middle-income level) is less than RMB 150,000 Yuan during a year.
Middle level and above income	The economy income of a family is more than or equal to RMB 150,000 Yuan during a year.
High-risk occupation	Including migrant worker, worker, jobless and vagrant persons.
Non-high-risk occupation	Including farmers, teacher, pupils, business services, nurses and nannies, waiters, business services, hospital staffs, herdsmen, fisherman, seafarers and long-distance drivers, official staffs, and being retired.
Passive mode of TB case finding	Including physical examination, contact examination, and differential diagnosis of other diseases.
Active mode of case finding	Including initiatively clinical consultation, recommend based on symptoms, and referral and tracing of TB suspects reported.
Lost to follow-up	Treatment interrupted for at least two consecutive months.
A history of direct contact	Direct contact with MDR-TB patients during the 3 months before illness onset.
Different PTBH	Including NDTH and RTH [like individuals with initial treatment failure, relapse, returned (i.e., re-entry after abandonment), chronic, and other re-treated (such as loss to follow-up, discontinued therapy, and unknown or undocumented treatment outcome) TB history].
Successful treatment	TB patients are cured or have completed the treatment.
Unsuccessful treatment	Including loss to follow-up, discontinued therapy, and treatment failure for TB patients.
2HRZE/4HR	NDTPs were started on first-line drug therapy consisting of 2 months of R, H, E and Z, and followed by 4 months of R and H; the dosing frequency of TB treatment is a daily dosing throughout therapy.
FDC-2HRZE/4HR	NDTPs were started on first-line drug therapy consisting of 2 months of R, H, E and Z, and followed by 4 months of R and H; the dosing frequency of TB treatment is a daily dosing throughout therapy; FDC formulations were used.
2H3R3Z3/4H3R3	NDTPs were started on first-line drug therapy consisting of 2 months of R, H and Z, and followed by 4 months of R and H; the dosing frequency of TB treatment is three-times-weekly dosing throughout therapy.
2H3R3Z3E3/4H3R3	NDTPs were started on first-line drug therapy consisting of 2 months of R, H, E and Z, and followed by 4 months of R and H; the dosing frequency of TB treatment is three-times-weekly dosing throughout therapy.
2HREZ/4H3R3	NDTPs were started on first-line drug therapy consisting of 2 months of R, H, E and Z, and followed by 4 months of R and H; new PTB patients may receive a daily intensive phase followed by a three-times weekly continuation phase.
2HRZES/6HRE	RTPs without R resistance detected on Xpert were started on WHO guidelines, i.e., 2 months of R, H, E, Z and S, and followed by 6 months of R, H and E; the dosing frequency of TB treatment is a daily dosing throughout therapy.
3HRZE/6HRE	RTPs without R resistance detected on Xpert were started on WHO guidelines, i.e., 3 months of R, H, E and Z, and followed by 6 months of R, H and E; the dosing frequency of TB treatment is a daily dosing throughout therapy.
3HRZES/6HRE	RTPs without R resistance detected on Xpert were started on WHO guidelines, i.e., 3 months of R, H, E, Z and S, and followed by 6 months of R, H and E; the dosing frequency of TB treatment is a daily dosing throughout therapy.

2H3R3Z3E3S3/6H3R3E3	RTPs without R resistance detected on Xpert were started on WHO guidelines, i.e., 2 months of R, H, E, Z and S, and followed by 6 months of R, H and E; the dosing frequency of TB treatment is three-times-weekly dosing throughout therapy.
Individualized treatment regimens	Clinic doctors developed the individualized therapeutic schedule including 4–6 drugs (typically including a fluoroquinolone and/or injectable secondline drug and three or four first-line drugs therapy) based on clinical experience.

Table 1 Definitions of this study

Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *PTBH* previous TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *NDTPs* newly diagnosed TB patients, *RTPs* re-treated TB patients, *FDC* fixed-dose combination, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *WHO* World Health Organization

Variables	Training set (n= 1719)	Validation set (n= 117)	P Value
Age (mean ± SD, years)	48.90 ± 20.95	49.41 ± 21.84	0.799
	n (%)	*n* (%)	
Gender			
Male	1216 (70.74)	88 (75.21)	0.302
Female	503 (29.26)	29 (24.79)	
Nationality			
Han	1700 (98.89)	114 (97.44)	0.161
National minority	19 (1.11)	3 (2.56)	
Occupational risk			
High-risk	362 (21.06)	33 (28.21)	0.069
Non-high-risk	1357 (78.94)	84 (71.79)	
Education levels			
High school and below	1270 (73.88)	87 (74.36)	0.909
Universities and higher	449 (26.12)	30 (25.64)	
Residences			
Rural areas	554 (32.23)	36 (30.77)	0.744
Urban areas	1165 (67.77)	81 (69.23)	
Registered household			
Migrant individuals with PTBH	768 (44.68)	50 (42.74)	0.683
Resident individuals with PTBH	951 (55.32)	67 (57.26)	
Family income			
Low level	558 (32.46)	48 (41.03)	0.057
Middle level and above	1161 (67.54)	69 (58.97)	
Types of MDR-TB diagnosis			
Traditional susceptibility test	1212 (70.51)	81 (69.23)	0.770
Gene Xpert MTB/R	507 (29.49)	36 (30.77)	
Different PTBH			
NDTH	1411 (82.08)	97 (82.91)	0.822
RTH	308 (17.92)	20 (17.09)	
Treatment outcomes			
Unsuccessful treatment	257 (14.95)	21 (17.95)	0.381
Successful treatment	1462 (85.05)	96 (82.05)	

Table 2 Baseline characteristics of the study population (N = 1836)

Abbreviations: TB tuberculosis, *MDR-TB* multidrug-resistant tuberculosis, *PTBH* previous TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *SD* standard deviation, *MTB* mycobacterium tuberculosis, *R* rifampicin

Laboratory Methods

A case of MDR-TB was confirmed by using the DST in the TB designated laboratory. The DST was performed on all culture positive isolates against first line [isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) and streptomycin (S)] and second line anti-TB drugs (kanamycin and ofloxacin) [22]. The methods of DST include conventional microbiological DST and Gene Xpert Mycobacterium TB (MTB)/R.

The conventional microbiological DST is performed using solid or automated liquid culture media system (BACTEC MGIT 960; Becton Dickinson, Sparks, Maryland, USA) according to standard procedures [22]. The method of Gene Xpert MTB/R denotes that the resistance to R is detected by using Gene technology [22].

The DST detection were performed during the course of follow-up visits. For conventional microbiological DST and Gene Xpert MTB/R detections, samples collected were sent to the TB Program Laboratory of Hangzhou Center for Disease Control and Prevention (a biosafety level-3 laboratory with proficiency testing approved by National Reference Laboratory in China). MDR -TB cases of laboratory cross-contamination were excluded. Drugs with borderline resistance were considered to be resistant.

Statistical analysis

Outcome variable was categorized as a binary variable with incident MDR-TB and non-incident MDR-TB categories. Descriptive analyses were used to examine the distribution of characteristics of participants in the training and validation sets. Continuous variables were described by using mean with standard deviation while categorical data was analyzed by using percent (proportion). A Pearson Chi-square test was used for categorical variables and an independent sample *t*-test for continuous variables in both training and validation sets.

We used univariable and multivariable Cox regression models to analyze the risk of incident MDR-TB among individuals with PTBH. Patients who died, loss to follow-up visit and could not be evaluated were excluded from the analysis. Univariable Cox proportional hazard regression analysis was conducted to determine factors associated with incident MDR-TB. Variables were analyzed using hazard ratio (HR) generated by univariable Cox proportional hazards regression.

Subsequently, independent predictors associated with incident MDR-TB were evaluated using HR generated by a multivariable Cox proportional hazard regression model. All variables with *P* value of $\leq$ 0.10 were included into a multivariable Cox proportional hazard regression model using backward stepwise method based on the minimum statistics of the Akaike information criterion. Variables with *P* value of < 0.05 were considered statistically significant in the multivariable Cox proportional hazard regression model and were included in the final predictive model.

Based on the results of multivariate Cox regression analysis in the training set, a nomogram was developed and validated. Nomogram validation included two components. First, the internal validation of clinic nomogram was performed using a concordance index (C-index) by subjecting the nomogram to bootstrapping with 200 resamples [23]. The predictive accuracy of 1-, 5-, and 10-year probability of incident MDR-TB was evaluated by using the area under receiver operating characteristic (ROC) curve (AUC). Next, the calibration of nomogram was performed by comparing the predicted probability of incident MDR-TB with the observed probability of incident MDR-TB after bias correction (i.e., using a calibration curve). In addition, for external validation, we predicted the risk of incident MDR-TB using data from the other 117 individuals of validation set.

All statistical analyses were performed with R software (version i 386 3.6.1; www.R-project.org, 2019). The multivariable Cox proportional hazard regression model was created using the R software's 'survival' package, while the nomogram and calibration curves were plotted using the 'rms' package.

Results

Characteristics of the subjects

A flow diagram summarizing the identified eligible subjects and the study participants was shown in Fig. 1. The baseline characteristics of the study population were listed in Table 2.

We retrospectively studied 1,836 subjects with PTBH in Hangzhou from 2005 to 2018. Participants in the training set (n = 1719) and the external validation set (n = 117) were analyzed respectively. There was not a significant difference between the two sets (Table 2). The mean age was 48.90 ± 20.95 and 49.41 ± 21.84, and the ratio of males to females was 2.42 to 1 and 3.03 to 1 in the training and validation set, respectively. Notably, most of the subjects [1, 357 (73.91%)] were with the education level of high school and below (Table 2).

Predictor's Selection

Table 3 summarizes the results of the univariate analyses of the association between an individual covariate and the risk of incident MDR-TB in individuals with PTBH. Twenty of the 43 tested covariates were associated with a high risk of incident MDR-TB from this study population in the training set (P< 0.10). The significant covariates were (a) sociodemographic characteristics, including age < 60 years, a history of direct contact, family income of low level, high-risk occupation, high school and below, and rural areas, (b) clinical characteristics, including passive mode of TB case finding, HIV infection, RTH, unsuccessful treatment, TIOFMV, FDC-2HRZE/4HR, 2HRZES/6HRE, 3HRZES/6HRE, frequencies of chest X-ray examination, duration of pulmonary cavities (DPC), and duration of abnormal X-ray findings, and (c) microbiological characteristics, including frequencies of sputum culture, duration of positive sputum culture (DPSC), and duration of negative sputum culture. The remaining 23 covariates, including gender, nationality, a history of direct contact (e.g., unknown), registered household of patients, comorbidities, patients with severe infection, mode of TB case management, TB treatment time, TIOLC, 2H3R3Z3/4H3R3, 2H3R3Z3E3/4H3R3, 2HREZ/4H3R3, 2HRZE/4HR, 3HRZE/6HRE, 2H3R3Z3E3S3/6H3R3E3, individualized TRs, duration of pulmonary miliary tubercles, duration without radiological findings, duration without sputum culture, frequencies of sputum smear, duration of positive sputum smear, duration of negative sputum smear, and duration without sputum smear, were not associated with incident MDR-TB among individuals with PTBH (P> 0.10).

Table 3

Univariate Cox regression model showing risk factors associated with incident MDR-TB in the training and validation sets (N = 1836)

Variables	Training set (*n* = 1719)[a]		Validation set (*n* = 117)[a]	
	HR (95% CI)	*P* Value*	HR (95% CI)	*P* Value*
Sociodemographic characteristics				
Age (years)				
< 60	1.90 (1.57–2.31)	**<0.001**	2.74 (1.26-6.00)	**0.011**
≥ 60	Reference			
Gender				
Male	1.18 (0.85–1.42)	0.083	1.40 (0.64–3.06)	0.399
Female	Reference			
Nationality				
Han	1.03 (0.46–2.31)	0.940	0.98 (0.13–7.17)	0.986
National minority	Reference			
A history of direct contact				
Yes	3.25 (2.96–3.56)	**<0.001**	3.56 (2.38–5.33)	**<0.001**
Unknown	1.18 (0.76–1.84)	0.231	0.99 (0.46–1.69)	0.213
No	Reference			
Family income				
Low-income level	1.33 (1.13–1.58)	**0.001**	1.42 (0.76–2.68)	0.275

[a] Data are shown as hazard ratio (95% CI), *P* Value

* Bold values are those that reach statistical significance (*P* < 0.05)

Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *HIV* human immunodeficiency virus, *PTBH* previous TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *HR* hazard ratio, *TRs* treatment regimens, *FDC* fixed-dose combination, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *CI* confidence interval

Variables	Training set (n = 1719)[a]		Validation set (n = 117)[a]	
	HR (95% CI)	*P* Value*	HR (95% CI)	*P* Value*
Middle level and above	Reference			
Occupational risk				
High-risk	1.51 (1.26–1.80)	**0.001**	2.22 (1.18–4.18)	**0.013**
Non-high-risk	Reference			
Education levels				
High school and below	1.26 (1.04–1.54)	**0.022**	1.44 (0.69–3.15)	0.359
Universities and higher	Reference			
Residences				
Rural areas	1.32 (1.12–1.57)	**0.001**	1.45 (0.76–2.76)	0.265
Urban areas	Reference			
Registered household				
Migrant individuals with PTBH	1.133 (0.88–1.34)	0.143	1.29 (0.68–2.45)	0.445
Resident individuals with PTBH	Reference			
Clinical characteristics				
Mode of TB case finding				
Passive	2.76 1.59–4.78)	**0.001**	2.13 (1.12–4.05)	**0.022**
Active	Reference			
Comorbidities				

[a] Data are shown as hazard ratio (95% CI), *P* Value

* Bold values are those that reach statistical significance ($P < 0.05$)

Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *HIV* human immunodeficiency virus, *PTBH* previous TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *HR* hazard ratio, *TRs* treatment regimens, *FDC* fixed-dose combination, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *CI* confidence interval

Variables	Training set (n = 1719)[a]		Validation set (n = 117)[a]	
	HR (95% CI)	*P* Value*	HR (95% CI)	*P* Value*
Yes	0.80 (0.54–1.16)	0.240	0.93 (0.33–2.64)	0.892
No	Reference			
HIV infection				
Positive	3.96 (2.97–5.26)	**<0.001**	2.96 (1.16–7.61)	**0.024**
Negative	Reference			
Patients with severe infection				
Yes	1.07 (0.80–1.45)	0.660	1.20 (0.37–3.91)	0.763
No	Reference			
Mode of TB case management				
Family members' management or self-management	1.16 (0.93–1.44)	0.197	1.19 (0.49–2.89)	0.700
Community doctor management	Reference			
Different PTBH				
NDTH	Reference			
RTH	1.67 (1.38–2.02)	**<0.001**	3.66 (1.86–7.21)	**<0.001**
Treatment outcomes				
Unsuccessful treatment	5.14 (4.33–6.11)	**<0.001**	5.37 (2.54–11.34)	**<0.001**
Successful treatment	Reference			

[a] Data are shown as hazard ratio (95% CI), *P* Value

* Bold values are those that reach statistical significance ($P < 0.05$)

Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *HIV* human immunodeficiency virus, *PTBH* previous TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *HR* hazard ratio, *TRs* treatment regimens, *FDC* fixed-dose combination, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *CI* confidence interval

Variables	Training set (n = 1719)[a]		Validation set (n = 117)[a]	
	HR (95% CI)	*P* Value*	HR (95% CI)	*P* Value*
TB treatment time, days	0.99 (0.99-1.00)	0.130	1.05 (1.02–2.01)	**0.015**
Time from illness onset to the first medical visit, days	1.01 (1.00-1.02)	**0.025**	0.99 (0.98–1.01)	0.162
Time from illness onset to laboratory confirmation, days	0.99 (0.99-1.00)	0.945	0.99 (0.98–1.01)	0.100
TRs of PTBH				
2H3R3Z3/4H3R3	0.67 (0.32–1.43)	0.304	0.72 (0.22–2.36)	0.592
2H3R3Z3E3/4H3R3	0.82 (0.62–1.10)	0.185	0.74 (0.22–2.57)	0.640
2HREZ/4H3R3	0.85 (0.40–1.79)	0.611	0.97 (0.23–4.03)	0.963
2HRZE/4HR	0.87 (0.73–1.04)	0.114	1.03 (0.97–2.02)	0.596
FDC-2HRZE/4HR	0.57 (0.36–0.93)	**0.025**	0.73 (0.17–3.11)	0.674
2HRZES/6HRE	1.64 (1.12–2.40)	**0.011**	0.48 (0.07–3.51)	0.469
3HRZE/6HRE	1.25 (0.89–1.77)	0.196	1.84 (0.65–5.21)	0.251
3HRZES/6HRE	4.79 (2.47–9.29)	**<0.001**	2.44 (1.11–5.37)	**0.027**
2H3R3Z3E3S3/6H3R3E3	1.00 (0.53–1.87)	0.988	1.23 (0.43–3.47)	0.699
Individualized TRs	1.11 (0.93–1.33)	0.266	1.39 (0.71–2.75)	0.334

[a] Data are shown as hazard ratio (95% CI), *P* Value

* Bold values are those that reach statistical significance ($P < 0.05$)

Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *HIV* human immunodeficiency virus, *PTBH* previous TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *HR* hazard ratio, *TRs* treatment regimens, *FDC* fixed-dose combination, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *CI* confidence interval

Variables	Training set (n = 1719)[a]		Validation set (n = 117)[a]	
	HR (95% CI)	*P* Value*	HR (95% CI)	*P* Value*
Chest radiological findings				
Frequencies of X-ray examination	0.90 (0.85–0.96)	**0.001**	1.01 (0.83–1.23)	0.911
Duration of cavities, months	1.21 (1.14–1.28)	**<0.001**	1.53 (1.15–2.04)	**0.004**
Duration of miliary tubercles, months	1.08 (0.54–2.15)	0.836	0.77 (0.19–3.21)	0.720
Duration of abnormal findings, months	1.15 (1.09–1.21)	**<0.001**	0.98 (0.78–1.23)	0.852
Duration without radiological findings, months	0.81 (0.53–1.25)	0.337	0.72 (0.28–1.84)	0.492
Microbiological characteristics				
Frequencies of sputum culture	0.88 (0.83–0.93)	**<0.001**	0.77 (0.60-1.00)	**0.050**
Duration of positive sputum culture, months	1.14 (1.04–1.24)	**0.004**	0.99 (0.64–1.54)	0.968
Duration of negative sputum culture, months	0.77 (0.69–0.86)	**<0.001**	0.46 (0.22–0.97)	**0.042**
Duration without sputum culture, months	0.92 (0.79–1.06)	0.249	1.01 (0.33–3.11)	0.983
Frequencies of sputum smear	1.05 (0.95–1.18)	0.434	0.94 (0.87–1.02)	0.121
Duration of positive sputum smear, months	1.02 (0.98–1.06)	0.405	1.05 (0.86–1.28)	0.628
Duration of negative sputum smear, months	0.98 (0.81–1.20)	0.880	0.89 (0.80–0.99)	**0.030**

[a] Data are shown as hazard ratio (95% CI), *P* Value

* Bold values are those that reach statistical significance ($P < 0.05$)

Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *HIV* human immunodeficiency virus, *PTBH* previous TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *HR* hazard ratio, *TRs* treatment regimens, *FDC* fixed-dose combination, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *CI* confidence interval

Variables	Training set (n = 1719)[a]		Validation set (n = 117)[a]	
	HR (95% CI)	*P* Value*	HR (95% CI)	*P* Value*
Duration without sputum smear, months	0.62 (0.32–1.21)	0.161	0.83 (0.09–7.71)	0.869

[a] Data are shown as hazard ratio (95% CI), *P* Value

* Bold values are those that reach statistical significance ($P < 0.05$)

Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *HIV* human immunodeficiency virus, *PTBH* previous TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *HR* hazard ratio, *TRs* treatment regimens, *FDC* fixed-dose combination, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *CI* confidence interval

To further explore independent predictors of incident MDR-TB in individuals with PTBH, we performed a multivariate Cox proportional hazard regression analysis. Table 4 listed the multivariable Cox regression results for this study population. The analysis showed that age < 60 years, a history of direct contact, passive mode of TB case finding, HIV infection, RTH, unsuccessful treatment, 3HRZES/6HRE, DPC, and DPSC were significantly linked to the MDR-TB risk among individuals with PTBH (*P*□0.05). From this model, we could also see that the unsuccessful treatment (HR 2.72, 95% CI 2.20–3.37, *P*□0.001) was one of the strongest predictors for incident MDR-TB in this population (Table 4). These findings were used to create a practical clinical nomogram for predicting the probability of incident MDR-TB among individuals with PTBH (Fig. 2).

Table 4
Multivariate Cox regression model showing risk factors associated with incident MDR-TB in the training and validation sets (N = 1836)

Variables	Training set (*n* = 1719)[a]		Validation set (*n* = 117)[a]	
	HR (95% CI)	*P* Value*	HR (95% CI)	*P* Value*
Sociodemographic characteristics				
Age < 60 years	1.25 (1.01–1.57)	**0.049**	1.37 (0.51–3.71)	0.531
Family income of low level	1.05 (0.56–1.99)	0.867	NA	
High-risk occupation	0.98 (0.78–1.22)	0.833	1.90 (0.78–4.65)	0.160
High school and below	1.22 (0.95–1.58)	0.125	NA	
Rural areas	1.13 (0.64–1.97)	0.256	NA	
A history of direct contact	2.71 (2.42–3.04)	**<0.001**	2.34 (1.33–4.13)	**0.003**
Clinical characteristics				
Passive mode of TB case finding	2.38 (1.24–4.58)	**0.009**	1.28 (0.46–3.53)	0.639
HIV infection	2.36 (1.75–3.18)	**<0.001**	1.32 (0.42–4.16)	0.640
Re-treated TB history	1.36 (1.11–1.68)	**0.004**	1.83 (0.26–12.70)	0.540
Unsuccessful treatment	2.72 (2.20–3.37)	**<0.001**	2.65 (1.06–6.62)	**0.037**
TB treatment time, days	NA		1.03 (1.01–1.14)	**0.016**
Time from illness onset to the first medical visit, days	1.00 (0.99–1.01)	0.368	NA	
FDC-2HRZE/4HR	0.90 (0.52–1.54)	0.692	NA	
2HRZES/6HRE	0.71 (0.47–1.06)	0.09	NA	

Variables	Training set (n = 1719)[a]		Validation set (n = 117)[a]	
	HR (95% CI)	P Value*	HR (95% CI)	P Value*
3HRZES/6HRE	2.18 (1.31–3.62)	**0.003**	0.71 (0.26–1.96)	0.510
Chest radiological findings				
Frequencies of X-ray examination	0.71 (0.65–1.77)	0.149	NA	
Duration of cavities, months	1.18 (1.10–1.27)	**0.001**	1.51 (1.01–2.25)	**0.046**
Duration of abnormal findings, months	1.21 (0.91–1.34)	0.253	NA	
Microbiological characteristics				
Frequencies of sputum culture	1.00 (0.87–1.15)	0.978	0.71 (0.45–1.13)	0.148
Duration of positive sputum culture, months	1.26 (1.10–1.44)	**0.001**	NA	
Duration of negative sputum culture, months	0.90 (0.75–1.08)	0.997	0.95 (0.44–2.05)	0.896

[a] Data are shown as hazard ratio (95% CI), P Value

* Bold values are those that reach statistical significance (P < 0.05)

Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *HIV* human immunodeficiency virus, *HR* hazard ratio, *FDC* fixed-dose combination, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *CI* confidence interval, *NA* not available

Construction Of The Nomogram

A nomogram was developed to assess the risk of incident MDR-TB using significant factors from the 1719 patients' data in the training set. With 9 independent predictors of training set, it was possible to create a nomogram to predict the probability of incident MDR-TB among individuals with PTBH (Fig. 2). The top row of the nomogram corresponds to the general score. For each predictors listed on the left (including age < 60 years, a history of direct contact, passive mode of TB case finding, HIV infection, RTH, unsuccessful treatment, 3HRZES/6HRE, DPC, and DPSC), there is a corresponding row on the right indicating possible descriptors. After characterizing the patient for each variable, a perpendicular line toward the first row should be drawn to identify the value. This action should be performed for all 9 predictors, followed by tallying the final score. This final score should be identified in a total point row

and then a perpendicular line is drawn that corresponds to the probability of incident MDR-TB from individuals with PTBH.

Calibration And Validation Of The Nomogram

After internal validation using the bootstrap technique, the C-index of this nomogram is 0.833 (95% CI 0.807–0.859) and 0.871 (95% CI 0.773–0.969) for the training and validation sets, respectively, which indicates adequate discriminatory power. The calibration plots are also performed separately using the training and external validation sets. As shown in Fig. 3 (A), the calibration plots show that the predicted 1-, 5-, and 10-year probability of incident MDR-TB corresponded closely with the actual 1-, 5-, and 10-year probability of incident MDR-TB estimated in the training set. Figure 3 (B) illustrates that the nomogram appears well calibrated, and there is a strong correlation between predicted and observed outcomes across the spectrum of predictions in the external validation set.

For the training set, the AUCs of the nomogram predicting the 1-, 5- and 10-year incidence of MDR-TB were 0.904, 0.921, and 0.908, respectively [Fig. 4 (A)]. Regarding the external validation set, the AUCs of the nomogram for predicting the 1-, 5- and 10-year incidence of MDR-TB were 0.954, 0.970, and 0.919, respectively [Fig. 4 (B)]. As Fig. 4 shows, the nomogram demonstrated the superior prediction ability of incidence of MDR-TB.

Predicting An Individual Patient's Risk

To make it easier to interpret our results, we represented the final reduced model with a nomogram that can be used to calculate a prognostic score and estimate the risk of incident MDR-TB for an individual with PTBH (Fig. 2). The nomogram produced the following mathematical predictive model for the presence of incident MDR-TB risk in the training set, with $h\,(t, x)$ denoting the probability of incident MDR-TB among individuals with PTBH [24]:

$h\,(t, x) = h_0\,(t) \exp\,(\beta_1 x_1 + \ldots + \beta_i x_i + \ldots + \beta_k x_k) = h_0\,(t) \exp$ *[0.9975×(a history of direct contact) + 0.2253×(age < 60 years) + 0.2544 × RTH + 0.8685×(passive mode of TB case finding) + 0.8596×(HIV infection) + 1.0023×(unsuccessful treatment) + 0.7779 × (3HRZES/6HRE) + 0.1682 × DPC + 0.2308 × DPSC]*

where $h\,(t, x)$ is the hazard at time t after a defined starting point for an individual with variables $x = (x_1 \ldots x_i \ldots x_k)$ is being predicted by $h_0\,(t)$, the so-called underlying hazard at time t, and the predictor variables x_1 to x_k (recorded at time zero), each variable x_i being multiplied by a corresponding regression coefficient β_i. Here, exp stands for exponential function, e.g., $\exp\,(\beta x) = e^{\beta x}$, and the underlying hazard $h_0\,(t)$ is the hazard at time t of an individual whose x_i's are all zero.

The predicted probabilities associated with each factor are mapped into points on a scale from 0 to 100. The presence or the level of each predictive factor is associated with a point system, allowing summing

up the points for all the factors. The total points accumulated by the various covariates correspond to the predicted probability of incident MDR-TB. For example, for an individual with the characteristics of age < 60 years, a history of direct contact, RTH, unsuccessful treatment, 3HRZES/6HRE, DPC (such as 3 months), and DPSC (such as 2 months) in individuals with PTBH (see Table 5).

Table 5
Predicting an individual patient's MDR-TB risk

Risk factor	Value	Points
Age < 60 years	Yes	12.5
A history of direct contact	Yes	100
Passive mode of TB case finding	No	0
HIV infection	No	0
Re-treated TB history	Yes	14.0
Unsuccessful treatment	Yes	51.5
3HRZES/6HRE	Yes	18.0
Duration of pulmonary cavities, months	3	15.0
Duration of positive sputum culture, months	2	24.0
Total points	235.0	
Estimate of MDR-TB risk, %		
1-year probability of incident MDR-TB	74.5	
5-year probability of incident MDR-TB	84.0	
10-year probability of incident MDR-TB	90.5	
Abbreviations: TB tuberculosis, *MDR-TB* multidrug-resistant tuberculosis, *HIV* human immunodeficiency virus, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin		
Abbreviations: MDR-TB multidrug-resistant tuberculosis, *TB* tuberculosis, *DST* drug susceptibility		
Abbreviations: MDR-TB multidrug-resistant tuberculosis, *MTCF* mode of TB case finding, *HIV* human immunodeficiency virus, *PRTH* previous re-treated TB history, *NDTH* newly diagnosed TB history, *RTH* re-treated TB history, *TO* treatment outcome, *H* isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin, *DPC* duration of pulmonary cavities, *DPSC* duration of positive sputum culture		
Abbreviations: PTBH previous tuberculosis history, *MDR-TB* multidrug-resistant tuberculosis		

Discussion

Up to now, far too little attention has been paid to monitoring and managing the risk of incident MDR-TB among individuals with PTBH, let alone developed a nomogram so as to comprehensively estimate an individualized risk of incident MDR-TB in individuals with PTBH. In the present study, we performed a matched case – control study (1: 2 ratios) to explore the predictors of MDR-TB in individuals with PTBH. According to results of this study, we constructed a comprehensive nomogram for providing simple and precise personalized prediction of incident MDR-TB among individuals with PTBH. Our findings may provide more reliable evidences in developing prevention and control strategies of MDR-TB and guiding TB control executives decision-making regarding the most effective surveillance, assessment and intervention measures for this population. We anticipate that these results will be useful in reducing the incidence of MDR-TB, the monitoring and management of individuals with PTBH, and the design of clinical interventions for preventing MDR-TB.

The significance of this study is that it offers a few important features. First, this is the first nomogram for predicting MDR-TB risk in individuals with PTBH that has collected enough risk factors to allow authentic forecast and assessment analyses. Second, in the validation analyses, whether internal (e.g., the C-index is 0.833 and 0.871 for the training and validation sets, respectively) or external, the comprehensive model outputted both sufficient accuracy and satisfied uniformity in predicting incident MDR-TB. Third, this tool would be easy to use in clinical practice, mainly because the applying of nomogram is very simple, convenient, and economical (i.e., an accurate evaluation is made by just using 10 dominant predictors of incident MDR-TB). Moreover, we observe that the running cost of this model is low, which lies primarily in developing a practice tool (i.e., a risk assessment scale) and incorporating this tool into the treatment information system of TB designated hospital. Fourth, comparing with the logistic regression model (e.g., it may not consider the impact of time effect for predicting the risk of MDR-TB), our study specifically considers estimating the risk of MDR-TB by using a semi-parametric model (i.e., Cox proportional hazard model) to maximize the Wald χ^2 statistic.

In the present study, we found that 9 independent predictors were associated with the increased risk of MDR-TB in individuals with PTBH. Similar results have been described in many previous studies on TB patients [3–6]. For example, regarding the unsuccessful treatment, it is still a key predictor for the control of incident MDR-TB. Thus, to monitor and manage the risk of MDR-TB, we not only focused on TB patients, but also concentrated on individuals with PTBH.

Compared with risk factors of incident MDR-TB in TB cases, there were some different features on predictors of incident MDR-TB among individuals with PTBH. A notable finding in this study was that a mild association was only found between RTH and incident MDR-TB. This is inconsistent with previous studies [3, 25], which suggested that re-treatment TB patients was significantly associated with MDR-TB risk. One possible explanation is that the difference is originated from a low susceptibility of drug resistance for re-treatment TB patients after the end of treatment. To understand the cause further, the causal mechanism needs to be verified. Unlike a study conducted by Zhang et al [26], we observed that gender was not associated with MDR-TB risk. The present study also suggested that older age (≥ 60 years) did not correlate with the risk of MDR-TB. This had important public health implications for

younger TB patients. Flora et al [27] reported that HIV infection was not strongly associated with MDR-TB risk. In this study, HIV infection was significantly associated with MDR-TB on the multivariate analysis. According to these data, we can infer that the early prediction and risk assessment of MDR-TB will be crucial among individuals with PTBH. Resorting to this tool, we can comprehensively predict an individual with PTBH's personalized risk of MDR-TB.

Interestingly, our study identified passive modes of TB case finding (like physical examination, contact examination, and differential diagnosis of other diseases) as a strong risk factor for incident MDR-TB in individuals with PTBH. The delayed diagnosis and treatment of TB, as we all know, potentially increased the risk for MDR-TB [12]. If the TB case finding was delayed, the TB case would develop into a serious TB leading to the course of treatment extended, it might become a risk factor associated with MDR-TB [12]. Thus, this finding has an important implication that the government should vigorously promote and develop the active finding mode of MDR-TB among individuals with PTBH. Additionally, a TB control scheme including this nomogram should be formulated by our government.

It is worth mentioning that this study identified the association between 3HRZES/6HRE and the MDR-TB risk among individuals with PTBH. According to the 2017 WHO guideline [28], the category II regimen should no longer be prescribed during the treatment of re-treatment TB patients. Our finding might elucidate a key role of standardized TB treatment against incident MDR-TB and provide a strong evidence for the treatment of re-treatment TB patients. From the discussion, one may conclude that the DST should be performed to inform the choice of re-treatment TB patients' TRs. Most notably, this study also observed that re-treatment TB patients were treated by using the TRs of 9-month, which were dramatically increased the risk of incident MDR-TB. This association may be attributed to the longer the time of exposure to anti-TB drugs, the greater the chance of occurrence of DR-TB [29]. To decrease the risk of MDR-TB, it is vital that standardized TRs are implemented by re-treatment TB patients. Some researchers found a highly significant association between the contact with MDR-TB patient and incident MDR-TB [6, 14, 30]. Our study also suggested that a history of direct contact was one of the strongest independent predictors for incident MDR-TB in individuals with PTBH. However, a prospective cohort study in Peru [31] found that MDR-TB patients were less able to cause secondary disease in contacts, which might appear to conflict with the result of our study. After considering possible explanations of this discrepancy, our tentative suggestion is that the ethnic characteristic is associated with the risk estimate of MDR-TB [32]. This result implies that potential intervention measures like early detection of the high-risk population, early isolation and treatment of MDR-TB patient, and personal protective measures of susceptible persons, are urgently needed to curb the epidemic of MDR-TB among individuals with PTBH. In addition, considering the advantages of nomogram, our government should energetically support and cultivate the development of this tool.

Besides the novel identified predictors of incident MDR-TB, what the predominant finding in the present study was that we first integrated these existing predictors into an excellent risk prediction tool called nomogram [33]. According to this practical tool, we can comprehensively predict a personalized risk of incident MDR-TB among individuals with PTBH.

Most importantly, the best way to interpret and apply these findings is not in terms of how the individual factors contribute to risk but how these parameters can be modified or improved to potentially decrease the incidence of MDR-TB [34]. Since the pathogenic mechanism of MDR-TB is still unclear, our findings and algorithm should be used to modify identified risk factors of MDR-TB in an effort to minimize morbidity. In terms of our findings, identifying the risk of incident MDR-TB for individuals with PTBH may have an impact on the treatment, healthcare, surveillance, and management options of TB cases. In addition, the selection of TB patients who need additional treatment, or intensive surveillance and management remains controversial after completing treatment [35]. This clinic tool may be able to help physicians to solve such problems. Moreover, this nomogram can provide information in the design of clinical intervention, and guiding clinicians' decision-making regarding the most effective intervention strategies among individuals with PTBH. For example, according to this algorithm, an individual with PTBH is found to be high-risk for incident MDR-TB. This finding has an important implication for developing the strategy of early intervention and management in the high-risk population of DR-TB. Overall, our results suggest that this nomogram may display the advanced public health concept of predictive, preventive, and personalized medicine [36]. This tool deserves to be further explored in future researches of clinic and public health.

Our study does have some limitations. First, our study is limited by the retrospective nature the data, which could suffer from recall bias and failure to incorporate some recognized prognostic parameters (e.g., the frequency or intensity of exposure). Second, potential confounders such as the mental health status of TB patients, TB drug quality and drug malabsorption could not be controlled. Third, further efforts regarding prospective data collection and patient follow-up, wider geographic recruitment, and the incorporation of additional factors are encouraged to improve this tool. Despite these limitations, as we know, there are limited numbers of published data on the risk of incident MDR-TB in individuals with PTBH. Therefore, this study could contribute information about the novel concept of predictive, preventive, and personalized medicine for incident MDR-TB.

Conclusions

In conclusion, we developed and validated a novel nomogram for predicting and preventing the risk of incident MDR-TB among individuals with PTBH. Through this clinic tool, TB control executives could more precisely monitor, estimate and intervene the risk of incident MDR-TB for individuals with PTBH.

Abbreviations

MDR-TB: multidrug-resistant tuberculosis; TB: tuberculosis, DR-TB: drug-resistant tuberculosis; PTBH: previous tuberculosis history; NDTH: newly diagnosed TB history; RTH: re-treated TB history; NDTPs: newly diagnosed TB patients; RTPs: re-treated TB patients; DST: drug susceptibility testing; TRs: treatment regimens; NTSS: national TB surveillance system; ROC: receiver operating characteristic; AUC: area under curve; HIV: human immunodeficiency virus; TO: treatment outcome; FDC: fixed-dose combination; TIOFMV: time interval from illness onset to the first medical visit; TIOLC: time interval from

illness onset to laboratory confirmation; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin; WHO: World Health Organization; MTB: mycobacterium tuberculosis; OR: odds ratio; HR: hazard ratio; CI: confidence interval; DPC: duration of pulmonary cavities; DPSC: duration of positive sputum culture

Declarations

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Authors' contributions

QLC contributed to the study conception and design, data analysis, interpretation of the data, and drafting the manuscript. GZ and LX contributed to the interpretation of the data and critical revision of the manuscript. GZ, LX, LW, QCL, ML, YFW, YYH, and QJJ contributed to the collection of the data. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Availability of data and materials

According to Chinese law, the public health data are not publicly available, but are available on reasonable requests from the corresponding author.

Ethics approval and consent to participate

This study has been approved by the Hangzhou Center for Disease Control and Prevention Ethics Committee. Written informed consent was obtained from all participants, or from guardians or parents on behalf of participants under the age of 18 years. In addition, all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

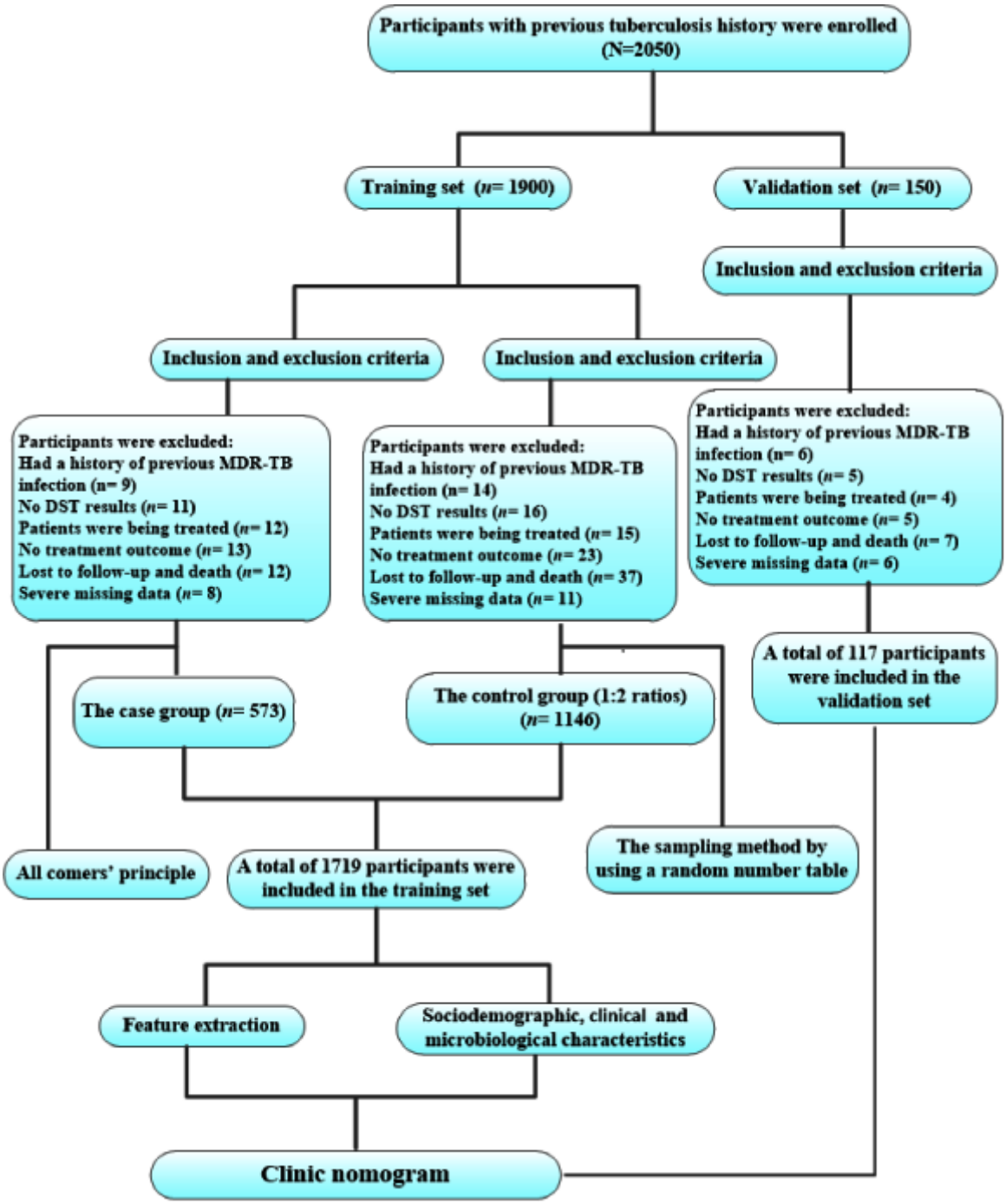

Figure 1

Workflow in this study. Abbreviations: MDR-TB multidrug-resistant tuberculosis, TB tuberculosis, DST drug susceptibility

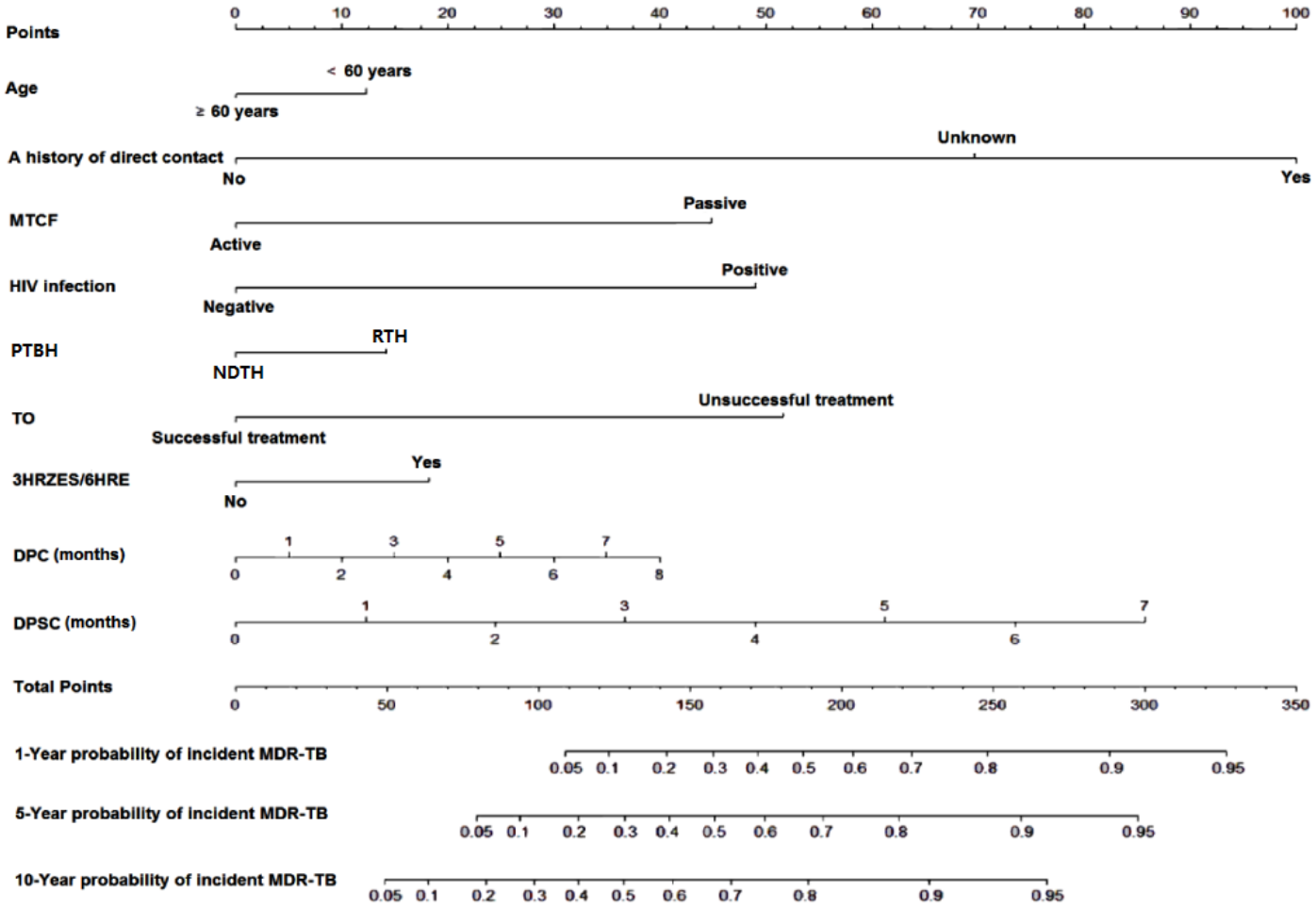

Figure 2

The nomogram for individualized predicting the risk of incident MDR-TB from individuals with previous tuberculosis history. Abbreviations: MDR-TB multidrug-resistant tuberculosis, MTCF mode of TB case finding, HIV human immunodeficiency virus, PRTH previous re-treated TB history, NDTH newly diagnosed TB history, RTH re-treated TB history, TO treatment outcome, H isoniazid, R rifampicin, Z pyrazinamide, E ethambutol, S streptomycin, DPC duration of pulmonary cavities, DPSC duration of positive sputum culture

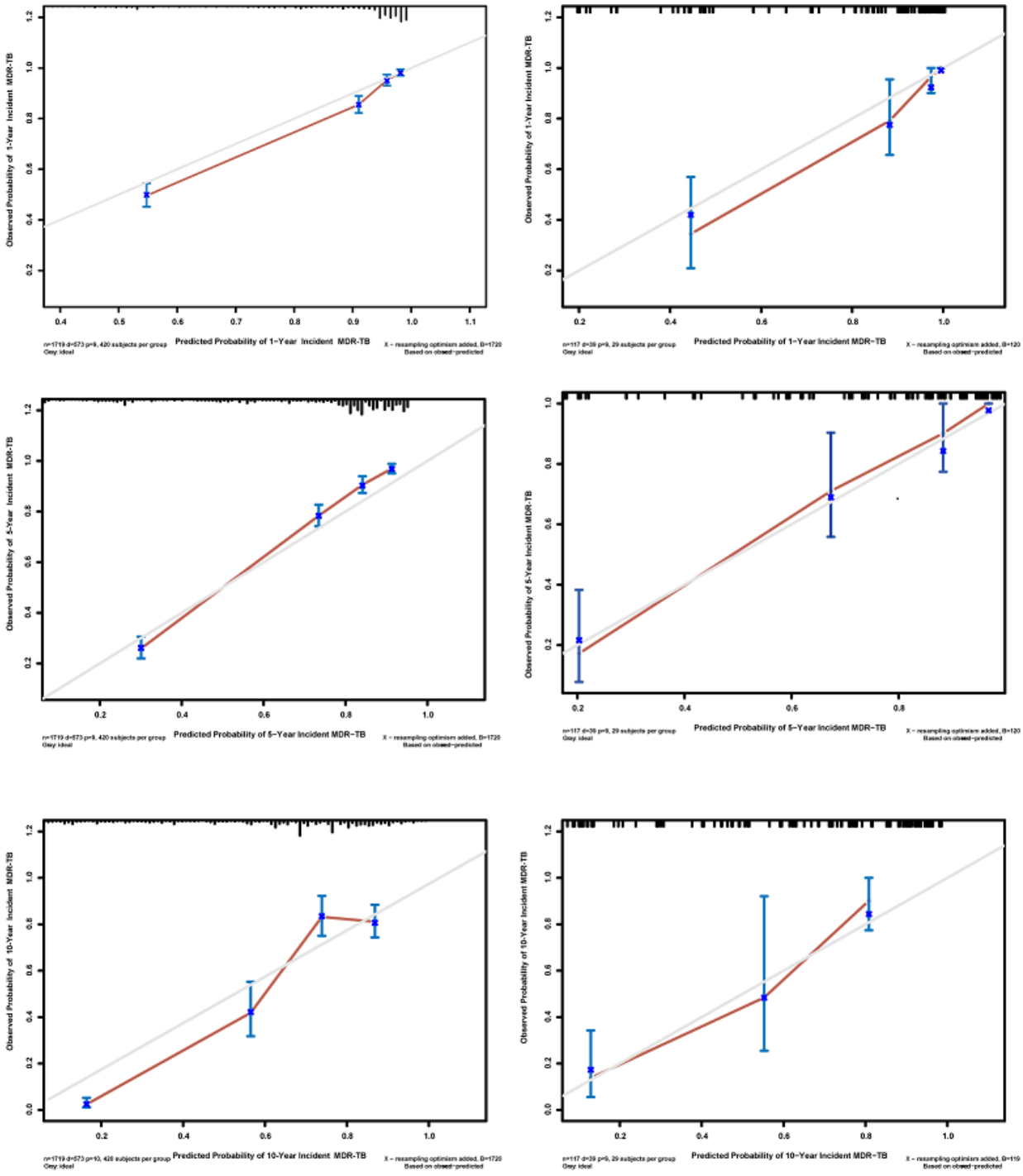

Figure 3

The calibration curves for predicting the risk of incident MDR-TB from individuals with PTBH at each time point in the training set (A) and the external validation set (B), respectively. Nomogram predicted the probability of incident MDR-TB from individuals with PTBH which is plotted on the X-axis and observed the probability of incident MDR-TB from individuals with PTBH which is plotted on the Y-axis. Abbreviations: PTBH previous tuberculosis history, MDR-TB multidrug-resistant tuberculosis

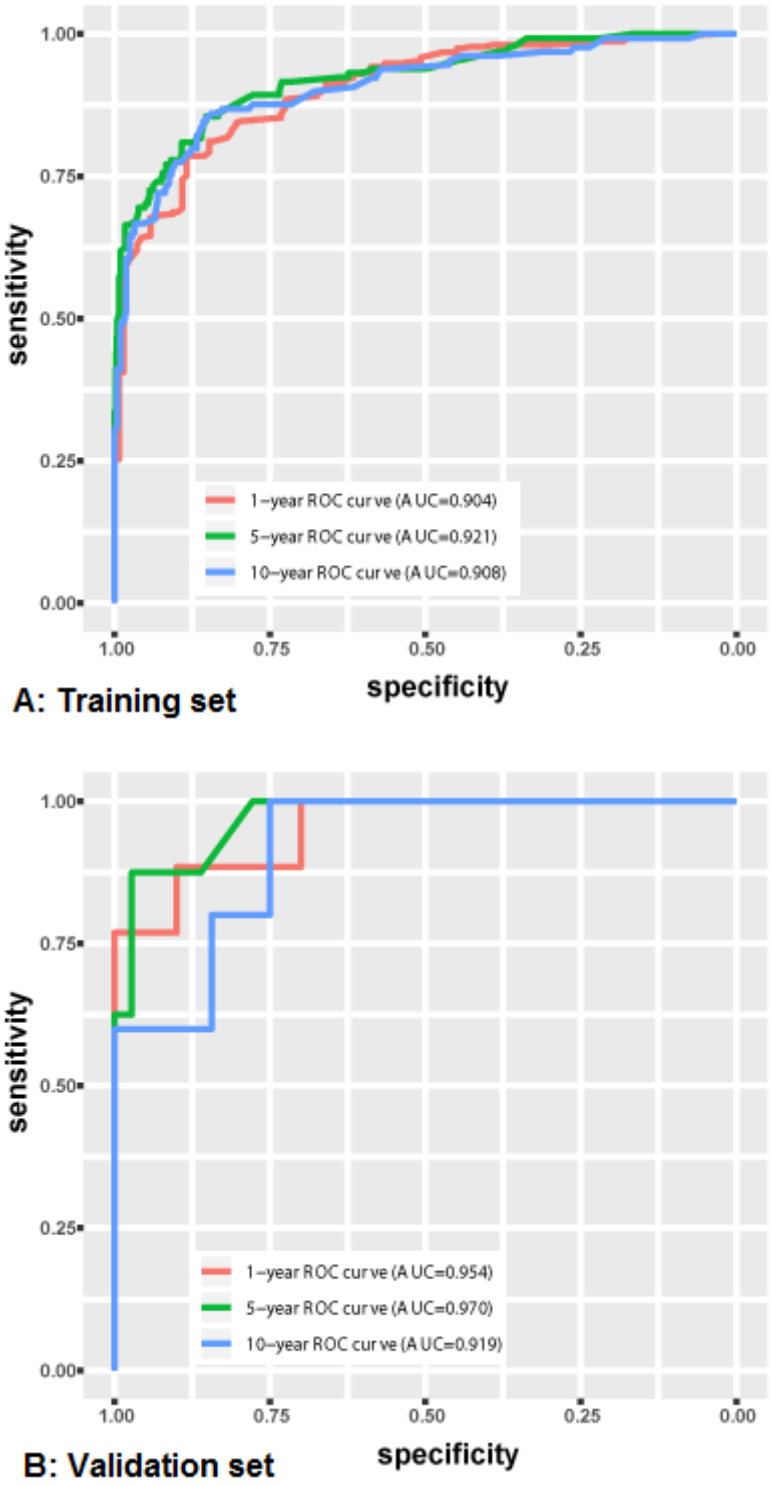

Figure 4

Area under receiver operating characteristic (ROC) curves (AUCs) of the nomogram. The AUCs of the nomogram to predict overall incidence at 1-, 5-, and 10-year (A) using the training set as well as at 1-, 5-, and 10-year (B) using the external validation set.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Formulas.pdf
- SampleSizeCalculation.pdf