Development of A Risk Score for Prediction of Poor Treatment Outcomes Among Tuberculosis Patients with Diagnosed Diabetes Mellitus from Eastern China

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Abstract

Background: Persons living with diabetes (PLWD) with newly diagnosed tuberculosis are known to have poor tuberculosis treatment outcomes. We investigated risk factors for poor treatment outcomes and developed a predictive risk score for tuberculosis control prioritization.

Methods: Among those PLWD diagnosed with tuberculosis, demographic, clinical, and tuberculosis treatment outcome data was collected. Poor treatment outcomes included treatment failure, death, default, and transfer. Multivariable logistic regression modeling was used to analyze risk factors of poor treatment outcomes. Risk scores were derived based on regression coefficients to classify participants at low-, intermediate-, and high-risk of poor treatment outcomes.

Results: Among 337 PLWD diagnosed with tuberculosis, 109 were cured and 172 completed treatment. Multivariable logistic regression demonstrated that risk factors of poor treatment outcomes includes bacteriologically-positivity, low body mass index <18.5, no physical activity, and pulmonary cavitation. Rates of poor treatment outcomes in low- (0–2), intermediate- (3–4), and high-risk (5–8) groups were 4.8%, 11.3%, and 55.4% (P_{trend} <0.0001), respectively. The risk score accurately discriminated poor and successful treatment outcomes (C-statistic, 0.83, 95% CI, 0.77–0.90).

Conclusions: PLWD diagnosed with tuberculosis have poor treatment outcomes if they present with culture or smear positivity, pulmonary cavitation, low BMI, and perform little physical activity. We derived a simple predictive risk score that accurately distinguished those at high- and low-risk of treatment failure, a potentially useful tool for tuberculosis control programs in settings with a high prevalence of both tuberculosis and diabetes.

Background

Tuberculosis has been identified as one of the top 10 causes of death globally [1]. Persons with an impaired immune system, such as those living with diabetes, are at a higher risk of tuberculosis and poor tuberculosis treatment outcomes once diagnosed. Globally, the burden of diabetes is increasing at alarming rates - in 2019, there were 463 million (9.3%) persons living with diabetes (PLWD), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045[2]. Currently, 80% of adults with diabetes reside in low- and middle-income countries where tuberculosis is also endemic.[3, 4] An estimated 11% of all global tuberculosis deaths are attributable to diabetes[5].

PLWD have been reported to have an increased risk of poor tuberculosis treatment outcomes including failure and death during treatment and subsequent relapse[6–9]. Characteristics that put PLWD at-risk for treatment default or death have been heterogeneous and how tuberculosis control programs can effectively and efficiently target PLWD newly diagnosed with tuberculosis for enhanced monitoring and investigation. Understanding subgroups of tuberculosis patients with diagnosed diabetes at highest risk of treatment failure is critical for tuberculosis control programs to prioritize enhanced management and resources for these patients. Few studies have been performed in Asia where diabetes and tuberculosis

are highly prevalent and the epidemiology of tuberculosis is distinct from Africa and other global regions. We aimed to investigate tuberculosis treatment outcomes among a cohort of all PLWD newly diagnosed with tuberculosis in Jiangsu province, China. We developed a risk classification model that may be clinically useful to identify and prioritize PLWD newly diagnosed with tuberculosis.

Methods

Study design and participants

National Basic Public Health Service Project is an important part of promoting the equalization of basic public health services and conducted from 2009 in China. It is the most basic public health service that Chinese government provides free of charge for all residents, focusing on children, pregnant women, elderly and patients with chronic diseases. It includes the management of patients with diabetes aged 35 and above, the physical examination were performed twice a year for them. Participants of this study was found based on it carried out in diabetic patients in Danyang, Rugao, Jiangyin and Nanjing city, China. All diagnosed diabetes patients in care participated in the diabetes physical examination from January to December 2017. Physical Examination for type 2 diabetes includes fasting blood glucose test, height, weight, waist circumference, body temperature, pulse, respiration and blood pressure. We compared the National Basic Public Health Service Diabetes Patients Physical Examination Project system and the Chinese Tuberculosis Information Management System to identified diabetes with tuberculosis patients. We collected the physical examination data and the treatment outcomes of diabetes with tuberculosis patients from Chinese Tuberculosis Information Management System.

Study definitions

All diagnosed diabetes patients were screened for tuberculosis by clinical symptoms, chest radiography findings, and bacteriological tests. Tuberculosis diagnosis was made in line with definitions provided by WHO[10]. New tuberculosis cases were defined as tuberculosis patients whose medical records indicated that the patient had denied having any prior anti-tuberculosis treatment or any history of more than 30 days of anti-tuberculosis treatment. Previously treated tuberculosis cases been receiving tuberculosis treatment for at least 30 days or who had documented evidence of prior treatment in the case report or surveillance database. The treatment regimen was used 3HRZE/6HR for diabetes-tuberculosis patients, which were based on recommend by WHO and the National Tuberculosis Control Program, China[10, 11].

Treatment outcomes

Treatment outcomes were defined as defined by WHO guidelines [12, 13]. A "cured" patient was defined as one who had completed treatment according to the program protocol and had been consistently culture-negative (with at least three results) for the final 6 months of treatment for tuberculosis. A patient who "Completed Treatment" was defined as a one who had completed treatment according to program protocol but did not meet the definition for cured because of lack of bacteriological results. Death was defined as any patient who died for any reason during the course of tuberculosis treatment. Treatment

failure was recorded if one or more of the three cultures recorded in the final 6 months of therapy were positive, or if any one of the final three cultures was positive. Default comprised of any patient whose tuberculosis treatment was interrupted for two or more consecutive months for any reason. Transfer comprised of any patient who transferred to another reporting and recording unit and for whom the treatment outcome was unknown. For analysis purposes, cured and completed treatment were combined as "treatment success", whereas others were combined as "poor treatment outcomes".

Statistical Analysis

The treatment outcome and factors of diabetes with tuberculosis patients were analyzed and compared. Descriptive analyses were performed to characterize the distributions of various variables in our study population with respect to the treatment outcomes. Logistic regression analysis was used to analyze the risk factors of the treatment outcomes for tuberculosis patients with diabetes and risk scores were estimated the rate of the poor treatment outcomes. Briefly, univariable logistic regression was used to determine the relationship of each independent variable for the poor treatment outcomes. For the multiple logistic regression model building, we selected variables with clinical significance and all the predictors with P<0.1 in the univariable level.[14] Sex and age were included in the multivariable logistic model regardless of P value. Then we identified variables with significant independent predictive value (P<0.1) in the multiple logistic regression model using Hosmer-Lemeshow model building criteria. We checked for linearity in the logit of continuous variables and for significant interaction terms[15], assessed goodness of fit and stability of the model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated and were used to describe the impact of related factors on treatment outcomes of diabetes patients with tuberculosis.

We then derived risk scores based on multivariable logistic regression models. We followed previously published recommendations for developing predictive risk scores[16, 17]. Briefly, we computed how far each subcategory of a risk factor was from the base category for each predictor variable in the multivariable analysis and derived a constant for the points system relating to the number of regression units corresponding to 1 point. The score risk model is derived to compute the required $\sum \beta X$ for a given risk factor profile. The risk estimate is then determined from a reference table which provides risk estimates for each point total. While the function itself can accommodate distinct values for the continuous risk factors (e.g. age, sex, BMI), the points system is organized around categories in order to mirror clinically meaningful risk factor states[14].

We then assigned a point score based on a transformation of corresponding β regression coefficients. The subsequent score was rounded to the nearest integer for clinical and programmatic practicality. We then calculated a risk score for each patient. The study population was grouped into 3 risk stratifications (low-, intermediate-, and high-risk) based on the probability of poor treatment outcomes in each group. Receiver operating characteristic curve analyses for the risk score was performed to assess the performance of the score. We internally validated the risk score using 10-fold cross-validation. All statistical analyses were conducted using SPSS software (version 23.0).

Ethics statement

This project was approved by Institutional Review Board of Jiangsu Provincial Center for Disease Control and Prevention. Written informed consent was obtained from all participants.

Results

Demographic Characteristics

The National Basic Public Health Service Diabetes Patients Physical Examination Project were conducted in four cities (Danyang, Rugao, Jiangyin and Nanjing). A total of 337 PLWD with tuberculosis were included in this study (Figure 1). Among them, the average age was 64.9 (±11.9) years old and 235 (69.7%) were male. Almost all patients were not drinking (79.5%) or smoked (71.8%). Chest radiographs and sputum smear were performed in all patients, 28.5% (96/337) patients have lung cavities; 57.3% (193/337) was smear-negative patients, 42.7% (N=144) was smear-positive patients; 85.2% (287/337) were new tuberculosis patients, 14.8% (N=50) were previously treated tuberculosis patients. Among smear-positive patients the sputum negative conversion rate was 77.1% (N=111) after intensive treatment. Of 337 patients, 109 were cured and 172 completed treatment. In all, 56 tuberculosis cases (17%) had poor treatment outcomes. Of these, 14 died (25%), 19 (33.9%) had treatment failure, 5 (8.9%) had adverse effects and default, and 18 (32.1%) were transferred (Table 1).

Risk Factors for Poor Tuberculosis Treatment Outcomes

In univariable logistic regression analyses, men were more likely to experience poor treatment outcomes (OR, 2.58, 95% CI, 1.21-5.50). Poor treatment outcomes were also more likely when patients were bacteriologically-positive (OR, 5.91, 95% CI, 2.87-12.18), had pulmonary cavitation (OR, 7.33, 95% CI, 3.93-13.67), had a previous tuberculosis episode (OR, 2.91, 95% CI, 1.47-5.75), no exercise (OR, 6.96, 95% CI: 2.45-19.82), and patients with a BMI<18.5 (OR, 4.06, 95% CI, 1.48-11.15 compared to participants with a BMI 18.5-23.9) (Table 2).

In a multivariable logistic regression analysis, similar characteristics were risk factors for poor treatment outcomes. These included a low BMI <18.5 (Adjusted Odds Ratio [AOR], 5.52, 95% CI, 1.55-19.65), no exercise (AOR, 6.77, 95% CI, 2.20-20.85), bacteriological positivity (AOR, 3.29, 95% CI, 1.45-7.45), and pulmonary cavitation (AOR, 5.28, 95% CI, 2.54-10.97) (Table 2).

Development of Predictive Risk Score

When assigning a point score, patients were assigned 1 point if they had a previous tuberculosis episode or were bacteriologically positive. Patients with lung cavitation, a BMI <18.5, or that did not do any physical activity were given a total of 2 points (Supplementary Table 1). The score ranged from 0 to 8 and treatment failure rates increased with higher score (P_{trend}<0.0001). The risk of poor treatment outcomes increased from 0.5% in patients with 0 points to 70.4% among patients with a score of 8 (Supplementary Table 2). After grouping patients into low- (0-2 points), intermediate- (3-4 points), and high-risk (5-8

points) classification groups, most treatment failures (64.3%, 36/56) occurred in the high-risk group and 85.7% (48/56) occurred in intermediate- and high-risk groups. Treatment failure rates were 4.8%, 11.3%, and 55.4% in low-, intermediate-, and high-risk groups, respectively (P_{trend}<0.0001). The absolute difference in probability of treatment failure between high- and low-risk groups was50.6% in the cohort (Table 3). The risk scores discriminated adverse and successful treatment outcomes well (AUC, 0.83, 95% CI, 0.77–0.90) (Figure 2). In an internal 10-fold cross-validation, the risk score had strong predictive ability with a C statistic of 0.82 (95% CI, 0.74–0.89) (Supplementary Figure 1).

Discussion

PLWD diagnosed with tuberculosis are at high-risk of treatment default and death. However, identifying PLWD that are at highest risk of treatment default is critical for tuberculosis control programs with a high diabetes prevalence, such as China. Effective and straightforward tools for public health professionals are urgently needed. We found that PLWD and tuberculosis that were bacteriologically-positive, with low BMI (< 18.5), no-exercise were more likely to experience poor treatment outcomes. We derived a prognostic score to predict treatment failure and death by ranging from 0–8 which predicted well with poor treatment outcomes and may be useful for implementation in tuberculosis control programs.

These results suggest that identifying tuberculosis patients at high- and low probability of poor outcome is feasible using a set of commonly collected patient-level factors. The risk score had a strong degree of accuracy to discriminate between adverse and successful treatment outcomes (C-statistic, 0.83). There may be unmeasured confounding and data quality might not be optimal. However, our study, which uses routinely collected data by National Basic Public Health Service Diabetes Patients Physical Examination Project and national tuberculosis programs, has an important ‘real-world’ context and may be easily applied to all PLWD without additional costs. Additional studies with additional risk factors may be useful to further improve the diagnostic accuracy of this prognostic model.

Patients that did not exercise had an increased risk of poor outcomes in PLWD diagnosed with tuberculosis, suggesting physical activity may significantly reduce risk of adverse outcomes. This may be related to case severity. If hospitalized patients, who are often the most severe, are unable to exercise this may explain this relationship. Low BMI (< 18.5) also increased the risk of adverse treatment outcomes. This has been shown in previous studies[18]·[19]. Having a low BMI or nutritional disequilibrium alters the host immune response leading to severe form of tuberculosis disease and subsequent poor treatment outcomes [20].

We found that patients with culture or smear positivity were also more likely to experience poor outcome. In this study, 82.1% of patients with poor treatment outcomes were bacteriologically positive, of which 39 were sputum smear positive. Our study did not demonstrate an association of alcohol consumption and smoking with poor treatment outcomes. Other determinants of poor treatment outcomes among tuberculosis patients include lifestyle factors such as smoking, alcohol consumption and drug abuse [19]. There are various mechanisms through which smoking may adversely impact tuberculosis treatment

outcome, for example through altering immunological host defense mechanisms, impacting lung structure and function, and modifying mechanisms of pathogen clearance [21]. This lack of association may be attributed to small numbers of self–reported alcohol consumption and smoking, likely an underestimate considering the social, cultural and religious norms that exist in China[22].

There are limitations to this study. First, we were unable to study the effect of glucose control on tuberculosis treatment outcome. Poor treatment outcomes are likely mediated through hyperglycemia and, due to this, our results may be impacted. However, two and six-month FBG levels among tuberculosis patients did not have statistically significant association with adverse outcomes in prior studies[23]. We consecutively enrolled tuberculosis patients living with diabetes registered for treatment within a program setting. The diagnosis of diabetes was not based on blood glucose levels alone; we enrolled subjects who were known to have diabetes to rule out bias associated with transient hyperglycemia attributed to tuberculosis[24]. All patients were treated with the same regimen with outcomes monitored according to standardized treatment outcome definitions provided by WHO. Lastly, we were not able to externally validate our prognostic model in another setting which is necessary prior to implementation of such a score in a public health program.

Conclusions

Our study shows that PLWD with tuberculosis experienced treatment failure more commonly when bacteriologically positive, previous tuberculosis treatment, low BMI, limited physical activity, or lung cavitation. Integrated models of care with early screening and management for diabetes and tuberculosis should be initiated. The detection of diabetes in tuberculosis patients and linking these persons to care may improve tuberculosis treatment outcomes. Strengthening early diagnosis and identifying tuberculosis patients with diabetes that are at high-risk of poor treatment outcomes is needed in areas with a high burden of both diabetes and tuberculosis.

Abbreviations

PLWD: persons living with diabetes; CI: confidence intervals; OR: odds ratios; AOR: adjusted odds ratio.

Declarations

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Author contributions

Qiao Liu, Nannan You, Hongqiu Pan conceived the study, analyzed the data and drafted the manuscript; Wei Lu, Limei Zhu, Peng Lu participated in the study design; Yi Zeng, Feng Lu, Hengfu Cao, Tao Zhu

implemented the field investigation; Leonardo Martinez participated in the study design and helped draft the manuscript. All authors contributed to the study and have read and approved the final manuscript.

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Availability of data and materials

Please contact the first author for data requests.

Ethics approval and consent to participate

Mentioned in manuscript.

Consent for publication

All co-authors consent to this submission

Competing interests

The authors declare no conflict of interest.

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Tables

Table 1
Characteristics of 337 Persons Living with Diabetes Diagnosed with Tuberculosis in Eastern China

Variable	Total, N (%)	Treatment success, N (%)	Poor outcomes, N (%)
All	337 (100)	281 (83.4)	56 (16.6)
Age (mean ± SD),years	64.90 ± 11.86	64.96 ± 11.40	64.59 ± 14.06
Sex			
Male	235 (69.7)	188 (66.9)	47 (83.9)
Female	102 (30.3)	93 (33.1)	9 (16.1)
City			
Jiangyin	115 (34.1)	106 (37.7)	9 (16.1)
Danyang	50 (14.8)	41 (14.6)	9 (16.1)
Rugao	89 (24.3)	80 (28.5)	9 (16.1)
Nanjing	83 (24.6)	54 (19.2)	29 (51.8)
Body Mass Index, kg/m^2			
<18.5	18 (5.3)	10 (3.6)	8 (14.3)
18.5–23.9	174 (51.6)	145 (51.6)	29 (51.8)
24.0–26.9	96 (28.5)	82 (29.2)	14 (25.0)
≥27.0	47 (13.9)	42 (14.9)	5 (8.9)
Smoking History*			
Yes	95 (28.2)	75 (26.8)	19 (33.9)
No	242 (71.8)	205 (73.2)	37 (66.1)
Drinking History*			
Yes	70 (20.5)	58 (20.7)	11 (19.6)
No	267 (79.5)	222 (79.3)	45 (80.4)
Physical Activity, Exercise*			
No	235 (69.7)	183 (65.1)	52 (92.9)
Yes	102 (30.3)	98 (34.9)	4 (7.1)
Lung Cavitation			

* Physical Activity, Smoking History and Drinking History were self-reported, including currently or past. Bacteriological#, including the result of sputum culture or smear examination.

Variable	Total, N (%)	Treatment success, N (%)	Poor outcomes, N (%)
Yes	96 (28.5)	59 (21.0)	37 (66.1)
No	241 (71.5)	222 (79.0)	19 (33.9)
Sputum Smear			
Positive	144 (42.7)	105 (37.4)	39 (69.6)
Negative	193 (57.3)	176 (62.6)	17 (30.4)
Bacteriological#			
Positive	169 (50.1)	123 (43.8)	46 (82.1)
Negative	168 (49.9)	158 (56.2)	10 (17.9)
Treatment history			
New	287 (85.2)	247 (87.9)	40 (71.4)
Retreated	50 (14.8)	34 (12.1)	16 (28.6)

* Physical Activity, Smoking History and Drinking History were self-reported, including currently or past. Bacteriological#, including the result of sputum culture or smear examination.

Table 2
Multivariable logistic regression analysis to identify risk factors for poor treatment outcomes in persons living with diabetes diagnosed with tuberculosis in eastern China

Variable	Univariable analysis			Multivariable analysis			
	P-value	Odds Ratio	95%CI	P-value	Odds Ratio	95%CI	
Age (continuous), years	0.832	1.00	0.97–1.02	0.839	0.997		0.97–1.03
Sex							
Female		1(Referent)			1(Referent)		
Male	0.014	2.58	1.21–5.50	0.141	1.93		0.81–4.62
Treatment history							
New		1(Referent)			1 (Referent)		
Retreated	0.002	2.91	1.47–5.75	0.084	2.05		0.91–4.61
Bacteriological#							
Negative		1(Referent)			1(Referent)		
Positive	0.000	5.91	2.87–12.18	0.004	3.29		1.45–7.45
Lung Cavitation							
No		1(Referent)			1(Referent)		
Yes	0.000	7.33	3.93–13.67	0.000	5.28		2.54–10.97
Physical Activity Exercise							
Yes		1(Referent)			1(Referent)		
No	0.000	6.96	2.45–19.82	0.001	6.77		2.20-20.85
BMI*, kg/ m^2							

*BMI, Body mass index, taking into account factors such as differences in the diet and physique of Chinese and foreigners, BMI of this study is classified by Chinese standards, including < 18.5 was thin, 18.5–23.9 was normal level, 24.0-26.9 was overweight and ≥ 27.0 was obesity. Physical Activity, Exercise, including walking, running or other forms of exercise. Bacteriological#, including the result of sputum culture or smear examination.

Variable	Univariable analysis				Multivariable analysis			
	P-value	Odds Ratio	95%CI		P-value	Odds Ratio	95%CI	
18.5–23.9			1(Referent)				1(Referent)	
< 18.5		0.007	4.06	1.48–11.15		0.008	5.52	1.55–19.65
24.0-26.9		0.683	0.87	0.43–1.73		0.824	0.91	0.40–2.07
≥ 27.0		0.327	0.60	0.22–1.66		0.947	1.04	0.32–3.35

*BMI, Body mass index, taking into account factors such as differences in the diet and physique of Chinese and foreigners, BMI of this study is classified by Chinese standards, including < 18.5 was thin, 18.5–23.9 was normal level, 24.0-26.9 was overweight and ≥ 27.0 was obesity. Physical Activity, Exercise, including walking, running or other forms of exercise. Bacteriological#, including the result of sputum culture or smear examination.

Table 3. Risk of poor outcomes among persons living with diabetes diagnosed with tuberculosis according to risk category.

	Risk Category			All Participants
	Low (<3 points)	Intermediate (3–4 points)	High (≥5 points)	
No., %	166 (49.3)	106 (31.4)	65 (19.3)	337
Poor Outcomes, % (95% CI)	4.8 (1.5–8.1)	11.3 (5.2–17.5)	55.4 (43.0–67.8)	16.6 (12.6–20.6)
Odds Ratio (95% CI), *P*-value	1 (Referent)	2.5 (1.0-6.4), 0.051	24.5 (10.4-58.1), 0.000	…
Risk Difference, % (95% CI)	1 (Referent)	6.5 (3.7-9.4)	50.6 (41.5-59.7)	…
C–statistic (95% CI)‡	…	…	…	0.86 (0.78–0.93)
10–fold Cross-Validation				
Optimism-adjusted C–statistic (95% CI)‡*	…	…	…	0.85 (0.65–0.91)
All Poor Outcomes in High, %	…	…	…	64.3
All Poor Outcomes in High and Intermediate, %	…	…	…	85.7

Risk Difference, this is the percent difference between the intermediate- and high-risk group versus the low-risk group.

Figures

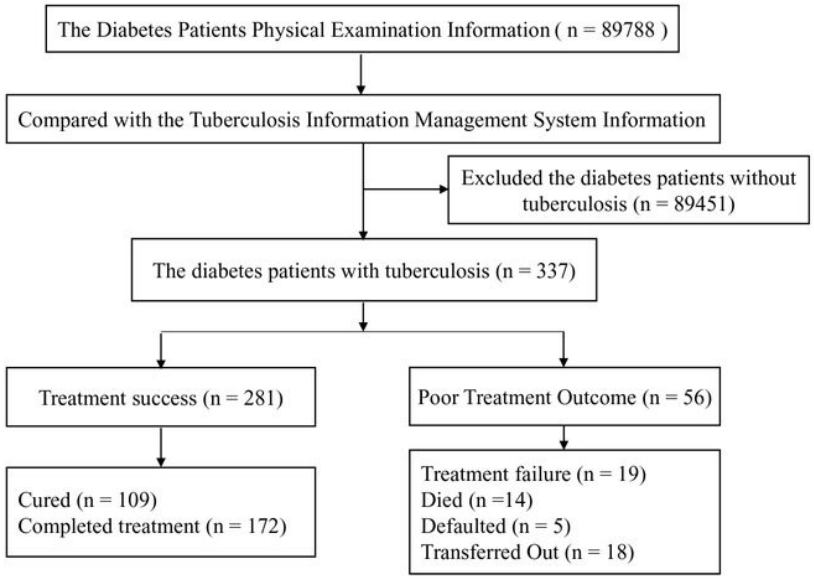

Figure 1

Flowchart for the treatment outcomes of tuberculosis patients with diabetes after treatment completed in Jiangsu province, China

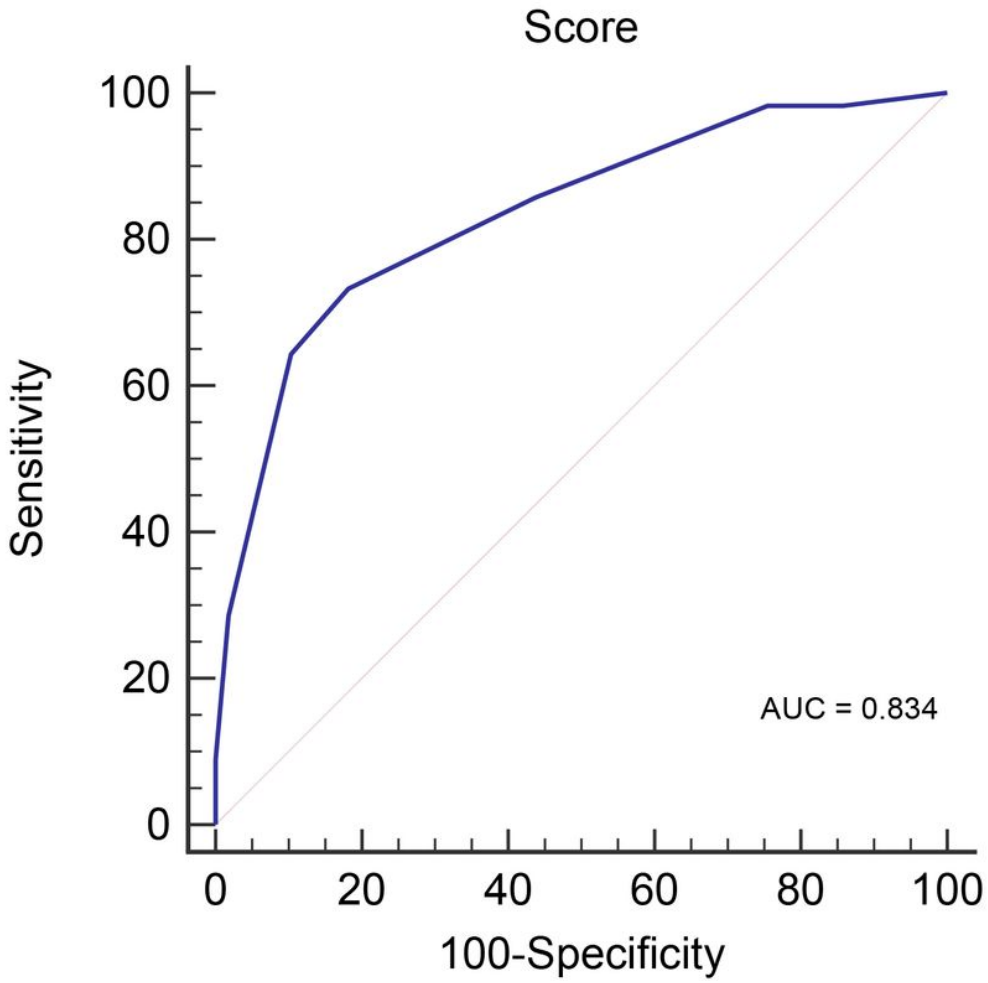

Figure 2

Receiver operating characteristic curve analysis for the risk scores in tuberculosis patients with diabetes.

Supplementary Files

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