

Construction and Validation of a Diagnostic Scoring System for Predicting Active Pulmonary Tuberculosis in Patients with Positive T-SPOT Based on Indicators Associated with Coagulation and Inflammation: A Retrospective Cross-Sectional Study

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Introduction: Tuberculosis (TB) is a life-threatening single infectious disease, which remains a major global public health concern. This study was to establish and validate a clinically practical diagnostic scoring system for predicting active pulmonary tuberculosis (APT) in patients with positive tuberculosis T cell spot test [T-SPOT] using indicators associated with coagulation and inflammation.

Methods: A single-center retrospective cross-sectional study was performed to include patients with positive T-SPOT registered and hospitalized at Wuhan Jinyintan Hospital between January 2017 and December 2019. All patients were separated into the active pulmonary tuberculosis (APT) group and the inactive pulmonary tuberculosis (IPT) group, according to the diagnostic criteria from China's Expert Consensus for APT and IPT. Subsequently, the patients were randomized into a training set and a validation set at a ratio of 2:1. Indicators associated with coagulation and inflammation, including prothrombin time activity (PTA), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen concentration (Fbg-C), C-reactive protein/albumin ratio (CAR), C-reactive protein/prealbumin ratio (CPR), neutrophils count/lymphocyte count ratio (NLR), platelet count/lymphocyte count ratio (PLR), monocyte count/lymphocyte count ratio (MLR), and erythrocyte sedimentation rate (ESR) were obtained from electronic medical record system (EMRS). Stepwise logistic regression was performed in the training set to build a diagnostic model for predicting APT, which was transformed into an easily applicable scoring system via nomogram. Receiver operating characteristic (ROC) analysis, calibration curve (CC), and decision curve analysis (DCA) were conducted to evaluate the predictive performance of the established diagnostic scoring system.

Results: A total of 508 patients [training set (211 cases of APT and 116 cases of IPT) and validation set (103 cases of APT and 78 cases of IPT)] with positive T-SPOT were recruited in the study. Stepwise logistic regression showed that CPR, MLR, ESR, APTT and Fbg-C were independent predictors for APT. The scoring system was subsequently formulated based on the abovementioned predictors, which correspond to scores of 10, 6, 7, 5, and 5, respectively. In addition, patients are more likely to be diagnosed as APT when the cut-off score was ≥ 16 scores, while patients with < 16 scores are more likely to be diagnosed as IPT. The scoring system showed good predictive efficacy in both the training set [area under the curve (AUC): 0.887] and the validation set (AUC: 0.898). Furthermore, both CC and DCA confirmed the clinical utility of the scoring system.

Conclusion: The data suggest that the combination of indicators associated with coagulation and inflammation could serve as biomarkers to identify APT in patients with positive T-SPOT. In addition, patients with positive T-SPOT were more prone to be diagnosed with APT when having a combined total of scores ≥ 16 in the scoring system.

Keywords: coagulation indices, inflammatory biomarkers, scoring system, active pulmonary tuberculosis

Introduction

Tuberculosis (TB) is a life-threatening single infectious disease, which remains a major global public health concern. According to the World Health Organization (WHO) Global TB 2022 Report, there were 1.6 million deaths of TB cases worldwide in 2021.¹ Over 80% of these clinical TB cases affect the lungs, which is known as pulmonary tuberculosis.² According to China's Expert Consensus of Inactive Pulmonary Tuberculosis³ and active Pulmonary Tuberculosis,⁴ IPTB was defined as asymptomatic TB patients with positive interferon-gamma release assay (IGRA) or tuberculin skin test (TST) results, lung imaging suggestive of stable tuberculosis lesions, and negative microbiological examination results (sputum smear microscopy, mycobacterial sputum culture, or nucleic acid amplification assays such as PCR and Xpert MTB/RIF), while APTB was defined as TB patients with positive mycobacterial tuberculosis cultures, or/and Xpert MTB/RIF. Numerous researches have shown that a certain proportion of IPTB may progress into APTB.^{5,6} Some developed countries have already included IPTB as part of the high-risk TB population for prevention and treatment.

In recent years, early determination of PTB activity has been a priority work in clinical practice. Existing diagnostic methods for APTB, including biomarker test, immunological test, histopathological test, laboratory microbiological test, and imaging test, have certain limitations.⁷ For example, histopathological examinations are usually invasive tests accompanied by trauma, Mycobacterium tuberculosis (MTB) cultures takes a long time before the results came out, and Xpert MTB/RIF are too expensive.⁷ Hence, these tests are not suitable for extension in underdeveloped or grass-roots hospitals. On the one hand, the failure to effectively and early identify APTB patients can lead to delays in treatment and thus disease progression. On the other hand, the misdiagnosis of IPTB as APTB may result in overtreatment, which may create more adverse events and drug-resistant TB, increasing the economic burden of PTB patients.⁸ Therefore, it is crucial to develop a method that can accurately and conveniently determine the activity of PTB, to better guide clinical diagnosis and treatment of tuberculosis.

Inflammation biomarkers, such as MLR, C-reactive protein (CRP), and high-sensitivity CRP (hs-CRP) were proven to be associated with the diagnosis of TB. Mayito et al found that MLR can be used for the early screening of HIV patients coinfecting with latent Mycobacterium tuberculosis.⁹ CRP may be a reliable indicator for the diagnosis of TB coinfecting with Pneumocystis jirovecii pneumonia,¹⁰ TB infection,¹¹ or APTB in HIV patients.¹² Also, the decreased CRP levels may suggest a significant reduction of the mycobacterium burden.¹³ In addition, Ciccacci et al found that hs-CRP was associated with the diagnosis and prognosis of TB.¹⁴ Changes in coagulation function of TB patients are also of great interest.^{15–17} Several studies have shown that the levels of coagulation indicators are altered after antituberculosis treatment in TB patients and that APTT and Fbg-C levels are also markedly higher in TB patients than in the healthy population, implicating the association between coagulation indicators and PTB activity.¹⁸ Furthermore, some scholars suggest that the interaction between coagulation and the inflammatory system in TB may be related to the increased replication of Mycobacterium tuberculosis.¹⁵ Therefore, the abovementioned markers related to inflammation and coagulation may play a role in differentiating PTB activity. In addition, indicators associated with coagulation and inflammation have the merits of easy availability, therefore the scoring system derived from these biomarkers could be effectively applied to clinical practice, especially in underdeveloped areas.

With the continuous advancement of research methods, methods of machine learning, such as nomogram, are widely applied for differential diagnosis and early identification of various diseases.¹⁹ The present study aimed to distinguish APTB from IPTB in patients with positive T-SPOT by constructing and validating a prediction model based on a combination of coagulation and inflammatory indicators. The prediction model was further transformed into a scoring system to facilitate clinical practice.

Materials and Methods

Study Design

A single-center retrospective cross-sectional study was performed to recruit participants with T-SPOT (+) who visited Wuhan Jinyintan Hospital from January 2017 to December 2019. All participants were classified as APTB and IPTB according to the diagnostic criteria from China's Expert Consensus for APTB³ and IPTB.⁴ The inclusion criteria are as follows: (1) APTB: patients positive for T-SPOT with positive mycobacterial tuberculosis cultures, or/and Xpert MTB/RIF. (2) IPTB: patients positive for T-SPOT with absence of symptomatic, bacteriologic (sputum smear microscopy,

mycobacterial sputum culture, or nucleic acid amplification assays such as PCR and Xpert MTB/RIF), or radiological evidence of APTB, and no history of TB. Patients with the following characteristics were excluded from this study: (1) Patients aged less than 18 years old; (2) Patients having received anti-tuberculosis treatment for more than 2 weeks before admission to our hospital; (3) Patients with other pulmonary diseases. Finally, 508 positive T-SPOT patients (314 cases of APTB and 194 cases of IPTB) were included in the study. All the eligible patients were randomized into two data sets at a ratio of 2:1, namely the training set (211 cases of APTB and 116 cases of IPTB) and the validation set (103 cases of APTB and 78 cases of IPTB) respectively, for model construction and validation. Chronic hepatitis B was confirmed by positive HbsAg and elevated plasma levels of alanine aminotransferase.

Data Processing

The baseline data including demographic characteristics (age and gender), history of diabetes mellitus, and chronic hepatitis B (positive for HbsAg), and laboratory parameters [prothrombin time activity (PTA), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen concentration (Fbg-C), C-reactive protein, albumin, pre-albumin, neutrophils count, platelet count, monocyte count, and erythrocyte sedimentation rate (ESR)] were retrospectively extracted from individual medical records. In addition, the computing method of CAR, CPR, NLR, PLR, and MLR are shown in [Supplementary Table 1](#). All participants' baseline data associated with coagulation and inflammation were retrospectively collected through the EMRS of our hospital.

Statistical Analyses

SPSS software (version 22.0, IBM Corp., Armonk, NY, USA) and RStudio software (version 4.20, PBC, Boston, USA) were used for data analysis and plotting. Missing values of the included variables associated with coagulation and inflammation were multiply imputed by the missForest method. Categorical variables were expressed as absolute values (n), and differences between groups were compared by chi-square test. The Shapiro–Wilk test was conducted to determine the normality of the continuous variables ([Supplementary Table 2](#)). The continuous variables with abnormal distribution were presented as median (interquartile range, IQR) and the Mann–Whitney *U*-test was used for the comparison of between-group differences.

The scoring system was constructed as follows: (1) variable screening: variables with significant between-group differences ($P < 0.05$) and an AUC greater than 0.6 in ROC analysis were selected for subsequent model construction; (2) variable transformation: the cut-off value for each variable was determined by the highest Youden index from ROC analysis, and the selected inflammatory biomarkers and coagulation indices were transformed into dichotomous variables based on their corresponding cut-off values. (3) model construction: stepwise logistic regression was conducted to determine the final parameters included in the model, and to establish a diagnostic model distinguishing APTB from IPTB. (4) construction of the scoring system: RStudio software was used to transform the diagnostic model into a nomogram and a scoring system. Detailed methods are as follows: The score of each variable (rounding to the nearest whole number) was determined by their corresponding regression coefficient in multivariable analysis by taking a score of 10 as reference (CPR with the highest regression coefficient in this study). The score of each variable was added up to get the total score of a patient. (5) assessment of the model and the scoring system: ROC curve, CC, and DCA were performed to assess the predictive performance of the model and the scoring system. (6) validation of the scoring system: internal validation of the model was performed in the validation set.

The main “R packages” used in this study included: “rms”, “mstate”, “ggDCA”, “ROCR”, “ggplot2” and “ggcorrplot”, etc. P -value < 0.05 was considered statistically significant. The description about statistical tools (“rms”, “mstate”, “ggDCA”, “ROCR”, “ggplot2”, and “ggcorrplot”) are shown in the [Supplementary Materials \(Additional Information 1\)](#).

Results

Patient Characteristics

There were 508 PTB patients with T-SPOT(+) in this study, including 314 APTB patients and 194 IPTB patients. The above patients were randomized into the training set (APTB: 211, IPTB: 129) and validation set (APTB: 103, IPTB: 65). Demographic, clinical, and laboratory characteristics of patients with positive T-SPOT are demonstrated in [Table 1](#).

Table 1 Demographic, Clinical, and Laboratory Characteristics of Patients with Positive T-SPOT in the Training Set and Validation Set

Variable	Training Set			P-value	Validation Set			P-value	P-value
	All (n=327)	APTB (n=211)	IPTB (n=116)		All (n=181)	APTB (n=103)	IPTB (n=78)		
Sex									
Male (%)	214 (65.44%)	140 (66.35%)	74 (63.79%)		117 (64.64%)	72 (69.90%)	45 (57.69%)		
Female (%)	113 (34.56)	71 (33.65%)	42 (36.21%)	0.642	64 (35.36%)	31 (30.10%)	33 (42.31%)	0.089	0.856
Age[median (25%, 75%)]	36 (26, 53)	37 (27, 56)	34 (25, 50)	0.082	37 (26, 56)	40 (27, 51)	32 (26, 58)	0.206	0.831
Microbiological test									
Positive mycobacterial smear (≥ 3 times)(%)	99 (30.28%)	99 (46.92%)	NA	NA	56 (30.94%)	56 (54.37%)	NA	NA	0.876
Positive mycobacterial culture (%)	164 (50.15%)	164 (77.73%)	NA	NA	81 (44.75%)	81 (78.64%)	NA	NA	0.243
Positive Xpert MTB/RIF (%)	102 (31.19%)	102 (48.34%)	NA	NA	59 (32.60%)	59 (57.28%)	NA	NA	0.745
Underlying condition or illness									
Diabetes mellitus (%)	33 (10.09%)	25 (11.85%)	8 (6.90%)	0.155	22 (12.15%)	16 (15.53%)	6 (7.69%)	0.11	0.474
Chronic hepatitis B (positive for HbsAg)(%)	38 (11.62%)	26 (12.32%)	12 (10.34%)	0.593	29 (16.02%)	20 (19.42%)	9 (11.54%)	0.152	0.160

Analysis of Coagulation and Inflammatory Indices of APTB and IPTB

In the training set, the levels of PT, PTA, INR, APTT, and Fbg-C were significantly different between APTB and IPTB patients, while the levels of TT were not statistically different ([Supplementary Table 3](#)). Fbg-C had the highest AUC of 0.835 (95% CI: 0.791–0.878, $P<0.001$) in ROC analysis, while AUCs for PT, PTA, INR, and APTT were 0.651 (95% CI: 0.589–0.712, $P<0.001$), 0.668 (95% CI: 0.609–0.727, $P<0.001$), 0.666 (95% CI: 0.605–0.728, $P<0.001$), 0.653 (95% CI: 0.59–0.714, $P<0.001$), respectively ([Table 2](#)). These results indicated that it is feasible to differentiate APTB from IPTB by indicators associated with coagulation function. Furthermore, the levels of all the inflammatory indicators, including CAR, CPR, MLR, NLR, PLR, and ESR, were markedly higher in the APTB group than in the IPTB group ([Supplementary Table 3](#)). The AUCs of CAR, CPR, ESR, NLR, MLR, and PLR were 0.847 (95% CI: 0.804–0.889, $P<0.001$), 0.850 (95% CI: 0.808–0.891, $P<0.001$), 0.831 (95% CI: 0.785–0.876, $P<0.001$), 0.788 (95% CI: 0.737–0.838, $P<0.001$), 0.793 (95% CI: 0.744–0.842, $P<0.001$), and 0.779 (95% CI: 0.729–0.829, $P<0.001$), respectively ([Table 2](#)).

Construction of a Diagnostic Scoring System Based on Indicators Associated with Coagulation and Inflammation

The cut-off values were determined according to the Youden index in ROC analysis. Statistically significant variables with an AUC > 0.6 were transformed into binary variables for subsequent analysis. As shown in [Table 3](#), CPR[OR(95% CI):4.95 (2.52, 9.85), $P<0.001$], MLR[OR(95% CI):2.59(1.29, 5.18), $P=0.007$], ESR[OR(95% CI):2.88(1.46, 5.69), $P=0.002$], APTT[OR(95% CI):2.32(1.26, 4.35), $P=0.008$], and Fbg-C[OR(95% CI):2.33 (1.12, 4.83), $P=0.023$] were independent risk factors for APTB. The results of step multivariable logistic regression analyses were subsequently transformed into a nomogram for distinguishing APTB from IPTB ([Figure 1A](#)). [Figure 1B](#) showed that the diagnostic nomogram had a high discriminatory capability with an AUC of 0.886 (95% CI: 0.851–0.921), sensitivity of 0.801, and specificity of 0.871. Both the calibration curve ([Figure 1C](#)) and

Table 2 The Performance of Parameters in ROC Analysis in the Training Set

Variables	AUC	95% CI		P value
		Lower	Upper	
CAR	0.847	0.804	0.889	<0.001
CPR	0.85	0.808	0.891	<0.001
NLR	0.788	0.737	0.838	<0.001
MLR	0.793	0.744	0.842	<0.001
PLR	0.779	0.729	0.829	<0.001
ESR	0.831	0.785	0.876	<0.001
PT	0.651	0.589	0.712	<0.001
PTA	0.668	0.609	0.727	<0.001
INR	0.666	0.605	0.728	<0.001
APTT	0.653	0.591	0.714	<0.001
Fbg-C	0.835	0.791	0.878	<0.001

Table 3 The Significant Indexes in the Step Multivariable Logistic Regression Analyses in the Training Set

Variables	OR (95% CI)	P value
CPR	4.95 [2.52, 9.85]	<0.001
MLR	2.59 [1.29, 5.18]	0.007
ESR	2.88 [1.46, 5.69]	0.002
APTT	2.32 [1.26, 4.35]	0.008
Fbg-C	2.33 [1.12, 4.83]	0.023

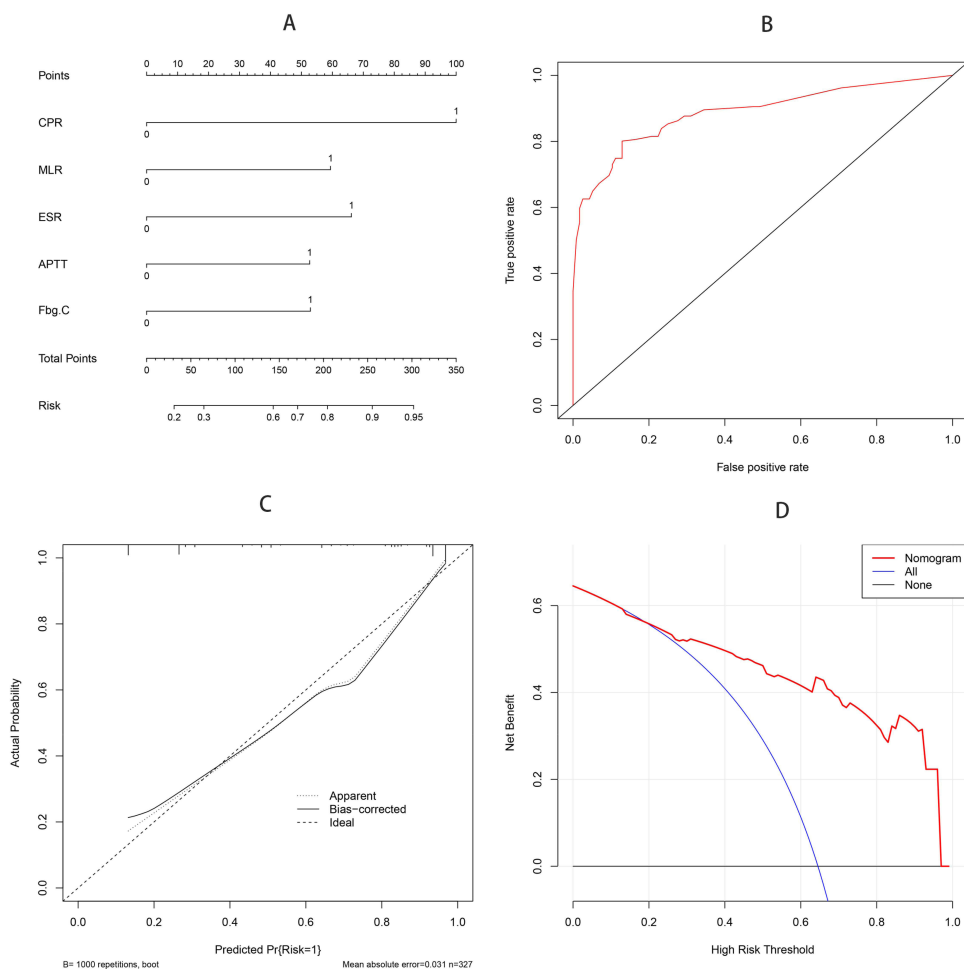


Figure 1 Calibration and clinical use of a diagnostic nomogram for discriminating APTB from IPTB. **Notes:** (A) Diagnostic nomogram for discriminating APTB from IPTB. (B) The ROC analysis of the diagnostic nomogram. (C) Calibration curve of the diagnostic nomogram. (D) Decision curve analysis of the diagnostic nomogram.

the DCA (Figure 1D) demonstrated the clinical utility of the diagnostic model. Finally, the nomogram was transformed into a scoring system, in which CPR was rated 10 points, MLR 6 points, ESR 7 points, APTT 5 points, and Fbg-C 5 points (Table 4).

Effectiveness Evaluation of the Scoring System in the Training Set

As shown in Table 5, the scoring system showed a maximum Youden index when the cut-off value of the total score was 16, and the scoring system presented the best diagnostic efficacy [AUC: 0.887 (95% CI: 0.852–0.922), sensitivity: 87.07%, specificity: 80.09%] at this point (Figure 2A). To be specific, PTB patients are more prone to be diagnosed with

Table 4 A Novel Scoring System Developed from a Nomogram in the Training Set

Parameters	Scores Generated from Nomogram/10 (Points)	Scores Modified from Nomogram/10 (Points)
CPR (≥ 1.7969)	10	10
MLR (≥ 0.2573)	5.94	6
ESR (≥ 24.2)	6.62	7
APTT (≥ 30.2)	5.27	5
Fbg-C (≥ 3.159)	5.29	5

Table 5 ROC Analysis of the Scoring System in the Training Set

Cutoff Score	Youden Index	Sensitivity%(95% CI)	Specificity%(95% CI)	Likelihood Ratio
≥14	0.591	77.59 (68.91% to 84.81%)	81.52 (75.61% to 86.51%)	4.198
≥15	0.608	79.31 (70.8% to 86.27%)	81.52 (75.61% to 86.51%)	4.291
≥16	0.672	87.07 (79.57% to 92.58%)	80.09 (74.06% to 85.26%)	4.374
≥17	0.648	87.07 (79.57% to 92.58%)	77.73 (71.5% to 83.15%)	3.909
≥18	0.62	87.07 (79.57% to 92.58%)	74.88 (68.47% to 80.58%)	3.466

APTb when the aggregate score was ≥ 16 scores. The CC presented a satisfactory fitting degree between the predicted and actual probabilities of the scoring system (Figure 2C).

Internal Validation of the Diagnostic Efficacy of the Scoring System

Similarly, when the aggregate score was ≥ 16 scores, a good diagnostic efficacy of the scoring system was demonstrated in the validation set, as evidenced by AUC of 0.898 (95% CI: 0.852–0.944) (Figure 2B) (Supplementary Table 4). In addition, the calibration curve also presented a good result (Figure 2D).

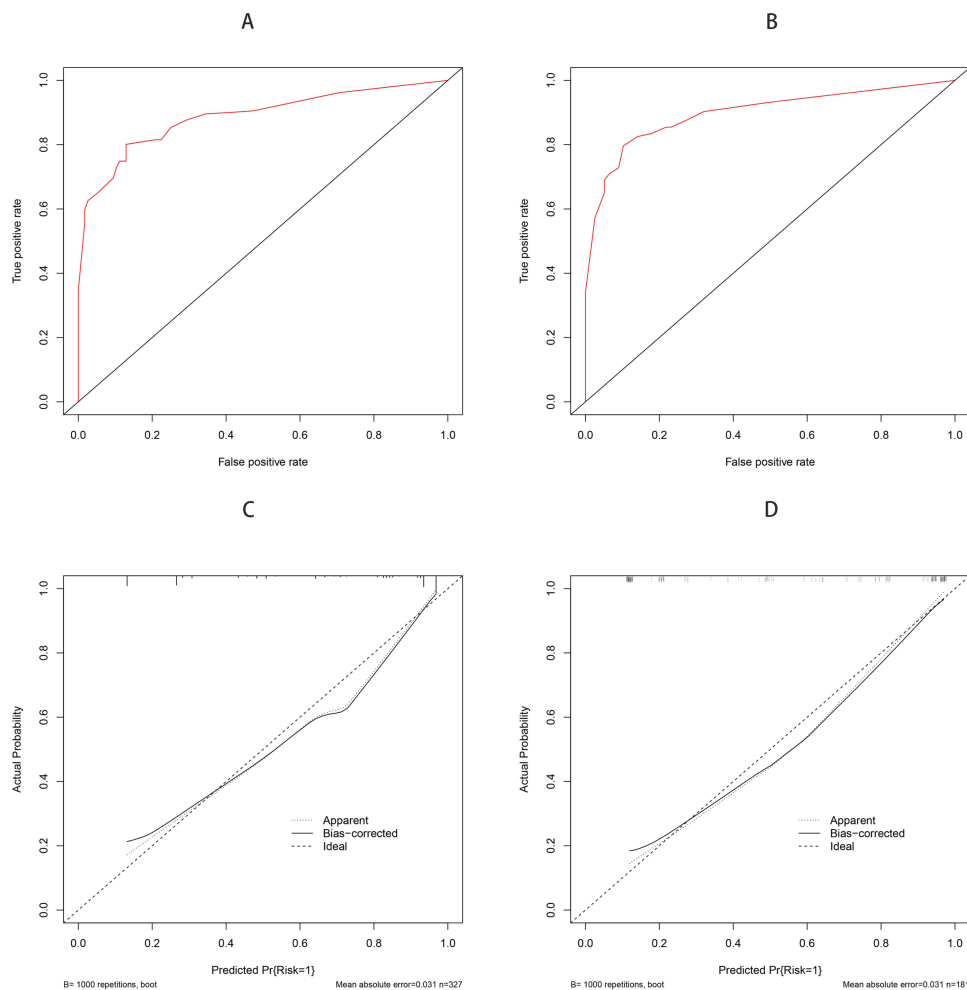


Figure 2 Discrimination and calibration of the scoring system for discriminating APTb from IPTb.

Notes: ROC curves of the scoring system in the training set (A) and validation set (B). Calibration curves of the scoring system in the training set (C) and validation set (D).

Discussion

APT_B and IPT_B represent two pathogenic states in TB patients, and current guideline recommendations vary widely for treatment regimens and treatment duration of APT_B and IPT_B. Therefore, early, timely, and accurate identification and diagnosis of APT_B or IPT_B is particularly important for clinical practice. However, the limitations of existing diagnostic methods hinder the diagnosis of PT_B activity from implementation and dissemination in remote and poor areas.

In this study, five parameters (CPR, MLR, ESR, APTT, and Fbg-C) were finally included in the scoring system through machine learning. To our best knowledge, this is the first scoring system for differentiating APT_B from IPT_B based on indicators associated with inflammation and coagulation. The scoring system has great advantages compared with traditional pathological or molecular biological methods in identification of PT_B activity. Firstly, the markers included in the scoring system are easily obtainable and widely applicable, and the scoring system can also be well used in economically less developed areas because of lower time and economic costs. Secondly, the scoring system is beneficial to clinical practice because it is simple to operate. Lastly, the indicators involved in the scoring system can also reflect the changes in inflammation levels and coagulation function of APT_B and IPT_B patients to a certain extent.

Combined indices such as CPR and MLR are relatively routinely tested indicators in clinical practice, hence they are easy to determine compared with single inflammation indicators like interleukins. Some studies have shown that levels of CPR and MLR relate to various diseases.^{19–23} CPR can stratify the risk degree for patients with acute heart failure.²⁰ It has also been shown that esophageal squamous carcinoma patients with higher preoperative MLR tend to have an unfavorable prognosis.²¹ Buttle et al reported the predictive value of MLR in patients with tuberculosis and found that higher MLR levels were liable to be associated with more severe disease and poorer prognosis.²² MLR can also be used to screen the coinfection of tuberculosis in HIV patients receiving antiretroviral therapy²³ and to predict treatment response in TB patients with pleurisy.²⁴ However, so far, no scholar has explored the diagnostic value of MLR and CPR to identify APT_B in TB patients with positive T-SPOT. The results of this study demonstrated that CPR (AUC: 0.850) and MLR (AUC: 0.793) in APT_B are higher than those in the IPT_B, and had a larger diagnostic value in differentiating APT_B from IPT_B, which indicating that APT_B had higher inflammation levels. Coagulation function in pulmonary tuberculosis attracted extensive attention in recent years. Wang et al reported that aspirin could improve the efficacy of anti-TB therapy in TB patients with type 2 diabetes mellitus comorbidity.²⁵ Another study showed that levels of APTT and Fbg-C were markedly lower in healthy population than in TB patients and Fbg-C value decreases after anti-TB treatment,¹⁷ which was roughly consistent with the results of the present study. In addition, Fbg-C were proven valuable in assessing early therapeutic reaction in patients with HIV/MDR-TB co-infection.²⁶

Currently, no domestic or foreign studies have reported on the determination of PT_B activity based on indicators associated with coagulation and inflammation. In this study, the first diagnostic scoring system for APT_B was established by combining coagulation and inflammation indicators. The scoring system was subsequently validated by data from the validation set, which further illustrated the stability and reliability of the scoring system. However, this study has some drawbacks. Firstly, the sample size used for the construction of the scoring system was small. Therefore, large multi-center researches are still required to validate the accuracy and reliability of the scoring system. Secondly, PT_B patients aged less than 18 were excluded from this study, hence the predictive performance of the model in minors remains unknown. Thirdly, we excluded patients with pulmonary diseases for a more determined diagnosis of IPT_B, but this will likely bias the results towards a more favorable conclusion regarding the value of the biomarkers. Lastly, there were no co-infected HIV patients included in this study, therefore the conclusion derived from our study can only be applied to patients without HIV infection.

Conclusion

In conclusion, CPR, MLR, ESR, APTT, and Fbg-C are valuable indicators in distinguishing APT_B from IPT_B. The diagnostic scoring system developed in this research has satisfactory predictive efficacy and could help clinicians make better clinical decisions. A patient with positive T-SPOT was more prone to be diagnosed with APT_B when having a combined total of scores ≥ 16 in the scoring system.

Abbreviations

APTb, active pulmonary tuberculosis; IPTb, inactive pulmonary tuberculosis; ROC, receiver operating characteristic curve; AUC, area under the curve; CI, confidence interval; CAR, C-reactive protein/prealbumin ratio; CPR, C-reactive protein/prealbumin ratio; NLR, Neutrophils count/lymphocyte count ratio; MLR, monocyte count/lymphocyte count ratio; PLR, Platelet count/lymphocyte count ratio; ESR, erythrocyte sedimentation rate; PT, prothrombin time; PTA, prothrombin time activity; INR, international normalized ratio; APTT, activated partial thromboplastin time; Fbg-C, fibrinogen concentration; OR, Odds Ratio; CI, confidence interval.

Data Sharing Statement

The datasets used in this study are obtainable from the corresponding author on request.

Ethics Statement

The study was conducted according to the good clinical practice guidelines and the Declaration of Helsinki. The Ethics Committee of Wuhan Jinyintan Hospital (KY-2022-06.01) reviewed and approved this study, and approved that informed consent was signed by patients or their guardians. Informed consent was signed by the guardians of the patients only if the patients are deemed incompetent for informed consent due to their physical conditions, such as psychiatric disorders, comatose state and so on.

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Author Contributions

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

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Disclosure

All authors have no competing interests to report.

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