

## Original Article

**Predictive nomogram of high-risk patients with active tuberculosis in latent tuberculosis infection**Kui Li<sup>1,2</sup>, Siyi Liu<sup>2</sup>, Yingli He<sup>2</sup>, Renyu Ran<sup>1</sup><sup>1</sup> Department of Infectious Diseases, Ankang Central Hospital, Ankang, Shaanxi, China<sup>2</sup> Department of Infectious Diseases, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China**Abstract**

**Introduction:** The absence of predictive models for early latent tuberculosis infection (LTBI) progression persists. This study aimed to create a screening model to identify high-risk LTBI patients prone to active tuberculosis (ATB) reactivation.

**Methodology:** Patients with confirmed ATB were enrolled alongside LTBI individuals as a reference, with relevant clinical data gathered. LASSO regression cross-validation reduced data dimensionality. A nomogram was developed using multiple logistic regression, internally validated with Bootstrap resampling. Evaluation included C-index, receiver operating characteristic (ROC) curve, and calibration curves, with clinical utility assessed through decision curve analysis.

**Results:** The final nomogram incorporated serum albumin (OR = 1.337,  $p = 0.046$ ), CD4<sup>+</sup> (OR = 1.010,  $p = 0.004$ ), and CD64 index (OR = 0.009,  $p = 0.020$ ). The model achieved a C-index of 0.964, an area under the ROC curve of 0.962 (95% CI: 0.926–0.997), sensitivity of 0.971, and specificity of 0.910. Internal validation showed a mean absolute error of 0.013 and 86.4% identification accuracy. The decision curve indicated substantial net benefit at a risk threshold exceeding 10% (1: 9).

**Conclusions:** This study established a biologically-rooted nomogram for high-risk LTBI patients prone to ATB reactivation, offering strong predictability, concordance, and clinical value. It serves as a personalized risk assessment tool, accurately identifying patients necessitating priority prophylactic treatment, complementing existing host risk factors effectively.

**Key words:** Tuberculosis; albumins; T-lymphocyte subsets; neutrophil CD64 index; nomogram.

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**Introduction**

Preventing progression from latent tuberculosis infection (LTBI) to active tuberculosis (ATB) is a major personal and public health goal. It is estimated that 23% (approximately 1.7 billion) of the global population are infected with *Mycobacterium tuberculosis* (Mtb) and have progressed to LTBI, with high-burden countries accounting for approximately 80% [1] and China accounting for a quarter of the high-burden countries (approximately 350 million) [2]. LTBI is viewed as a reservoir of pathogens for new-onset tuberculosis, and will progress to ATB in 5–10% of patients during their lifetime [3]; however, it is difficult to distinguish such a population from the LTBI population before the onset of clinical symptoms and imaging changes (i.e., those at high risk of progression or who have already progressed [4], whom we refer to as patients at high risk of ATB). Prophylactic treatment for the entire LTBI population would target a population that is too broad and face issues of cost, drug resistance, and drug side effects. Such confusion has led to delays in

interventions and is possibly a reason for the slow decline in TB incidence (approximately 2% per year).

The target populations for LTBI prophylaxis have recently been recommended based on the epidemiology of TB exposure and host risk factors [4]; however, this is simply a recommendation based on medical history. Also, differences in TB-specific antigen (TBAg) to phytohaemagglutinin (PHA) ratio (TBAg/PHA) in T-SPOT.TB [5], immune cytokines [6-8], iron homeostasis indicators [9], vitamin D2 [10], and neutrophil CD64 [11] have been reported between ATB and LTBI. These blood-based biomarker risk factors are primarily subjected to univariate analyses, some results are inconsistent, and individual risk probabilities are unknown; notably, these studies are independent of medical history. Risk scoring models for assessing ATB in multidrug-resistant TB and HIV (Human immunodeficiency virus) positive patients have also been reported [12,13]; nevertheless, these models are still based on medical history and individual biomarkers. To our knowledge, there are no medical

history-independent risk scoring models for patients at high risk of ATB in HIV-negative LTBI.

This study aimed to develop a risk prediction model for patients at a high risk of ATB using data from countries with a high burden of TB, based on risk factors in blood biomarkers, and to assess its efficacy, to provide clinicians with a more accurate and personalised assessment tool to identify the target populations for priority prophylactic treatment, which may contribute to sustained reductions in TB incidence.

## Methodology

### *Study design and sampling*

In this prospective study, we enrolled inpatients with confirmed ATB and recruited LTBI patients from 1 January 2021 to 30 June 2021 at the Ankang Central Hospital, a general hospital with an infectious disease specialty, where patients with confirmed ATB were further managed and treated in the infectious disease department. The study sample size was calculated following the method used to develop the clinical prediction model [14]. The parameter for the C-index was set to 0.8; the incidence of ATB in LTBI was estimated at 0.1; the number of predictors was 13; and the minimum sample size calculated was 251.

### *Inclusion criteria*

**ATB group:** The diagnosis of ATB complied with the health industry standard of the People's Republic of China (WS 288-2017) [15]; T-SPOT.TB examination and chest CT examination were completed; and one of the following items was met: (1) positive Mtb-DNA/RNA test in sputum or body fluid; (2) positive acid-fast bacilli staining on sputum smear; (3) positive sputum *Mycobacterium* culture and the strain identified as Mtb. **LTBI group:** Recruited from healthy individuals with positive T-SPOT.TB, no obvious lesions on chest CT, and no recent respiratory-related manifestations.

### *Exclusion criteria and number of cases*

(1) Non-tuberculous mycobacterial lung disease (1 patient); (2) current use of immunosuppressants (1 patient); (3) HIV antibody positive (2 patients); (4) rifampicin resistant (5 patients); (5) complicated with cirrhosis or tumour (2 patients); (6) complicated with diabetes mellitus (13 patients); and (7) complicated with silicosis (1 patient).

### *Methods*

The following data were collected: (1) Demographic data: age, sex, height, and weight; (2)

Immunological indexes and serum cytokines tested: 25-hydroxyvitamin D [25-OH-VD, chemiluminescence immunoassay analyser (iFlash 3000-C) and supporting reagents from Shenzhen YHLO Biotechnology Co., Ltd]; Interleukin-6 (chemiluminescence instrument and supporting reagents from Hangzhou Precision Biotechnology Co., Ltd.); CD4<sup>+</sup>, CD8<sup>+</sup>, and CD64 [Myriad Flow Cytometer (BriCyte E6) assay platform, lymphocyte assay kits from BD, and CD64 assay kit from Beijing Tongsheng Shidai Biotech Co., Ltd.]; and T-SPOT.TB (TB infection T cell spot diagnostic kit from Shanghai Fosun Long March Medical Science Co., Ltd.). The kit instructions were strictly followed and the results were interpreted according to the manufacturer's recommendations. The ratio of the maximum value of ESAT-6 or CFP-10 to PHA was defined as TBAg/PHA. The ATB group collects samples on the second working day after meeting the inclusion criteria, and the LTBI group collects and submits samples uniformly after recruitment. These tests were performed and reported by professionally trained laboratory technicians.

### *Ethical approval*

The study complied with the Declaration of Helsinki, and ethical approval was obtained from the Ethics Committee of the Ankang Central Hospital (approval number ECACH-2020005). All participants who agreed to take part in the study gave written consent after figuring out the objectives, meaning, and advantages of the research, and that participation used to be voluntary.

### *Statistical analysis*

Normally distributed measures were expressed as  $\bar{x} \pm s$  and non-normally distributed measures were expressed as M (IQR); the missing values were replaced with means. R software 4.1.3 (<http://www.r-project.org>) was adopted; the sample size was calculated using Calculates the Minimum Sample Size Required for Developing a Multivariable Prediction Model package; LASSO regression glmnet package 5-fold cross-validation was applied to screen variables, and the screened variables were subjected to multivariate logistic regression. The nomogram was developed using Regression Modeling Strategies and pROC packages, and the receiver operating characteristic (ROC) curve was employed to reflect the nomogram's recognition ability. Bootstrap was applied to resample 1000 times for internal validation of the model, calibration curves were adopted to judge its concordance, and the goodness of fit of the model was

subjected to the Hosmer–Lemeshow Test (HL test). Clinical decision curves were plotted using Risk Model Decision Analysis package. The model development and validation codes are shown in Supplementary Table 1, and differences reached statistical significance at  $p < 0.05$ .

**Results**

*Patients' characteristics*

A total of 258 study subjects were included in the analysis (194 men and 64 women; mean age: 56.00 years [range: 44.00–67.25 years]; mean body mass index:  $19.76 \pm 2.64 \text{ kg/m}^2$ ), were divided by inclusion criteria into the ATB group (223 patients, 86.43%) and the LTBI group (35 patients, 13.57%). Table 1 presents all data for both groups, including demographics and blood biomarkers.

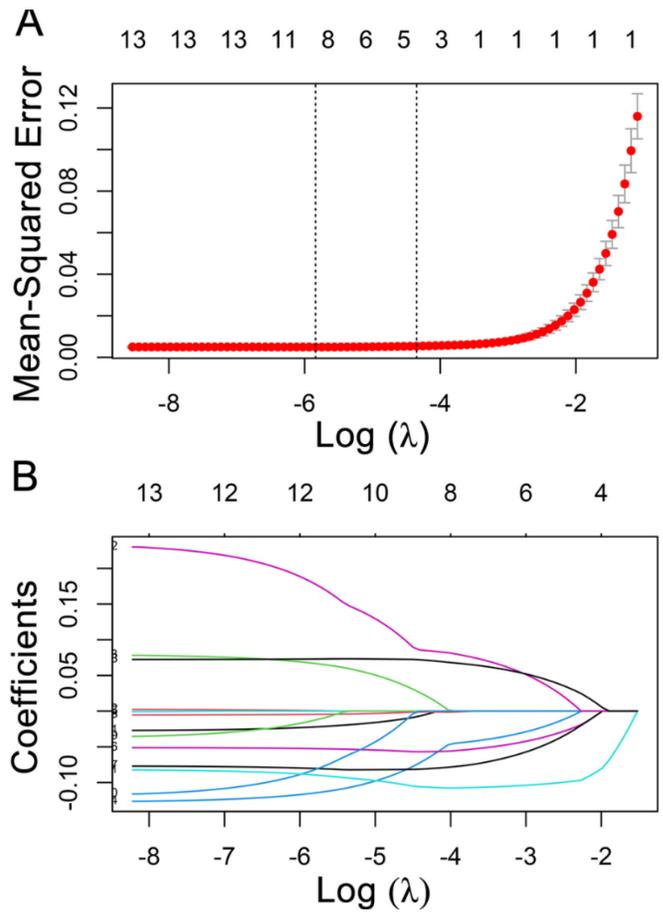
*Feature selection*

In the cohort of 258 study subjects, 13 demographic and blood biomarker features were reduced to four potential predictors (Figure 1A and 1B) that had non-zero coefficients in the LASSO regression model for further model development, namely serum albumin,  $\text{CD4}^+$ , TBAg/PHA, and  $\text{CD64}$ . The nine excluded features were sex, age, body mass index, Interleukin-6, 25-hydroxy vitamin D,  $\text{CD8}^+$ , ESAT-6, CFP-10, and PHA.

*Development of a prediction model*

ATB and LTBI as dependent variables (assignment:  $\text{LTBI} = 0$ ,  $\text{ATB} = 1$ ), and serum albumin,  $\text{CD4}^+$ , TBAg/PHA, and  $\text{CD64}$  as independent variables, were included in the logistic regression. The analysis indicated that serum albumin,  $\text{CD4}^+$ , and  $\text{CD64}$  were independent risk factors, TBAg/PHA was introduced

**Figure 1.** Demographic and clinical feature selection using the LASSO binary logistic regression model.



**A.** The selection of the moderating parameter ( $\lambda$ ) in the LASSO model was performed by minimum standard using 5-fold cross-validation, plotting the mean squared error versus  $\log(\lambda)$  with vertical dashed lines at the minimum  $\lambda$  value (0.0029) versus the minimum  $\lambda$  value + 1 standard deviation (0.0129). **B.** Plot of LASSO coefficient profiles for 13 clinical features, with each variable transformed to Rankit normal integration over the raw data, and coefficient profiles plotted against  $\log(\lambda)$  series, where the best  $\lambda$  yields four non-zero coefficients for the features. LASSO, least absolute shrinkage and selection operator; SE, standard error.

**Table 1.** Demographic and clinical characteristics of LTBI patient reactivated to ATB.

Characteristics	LTBI (N = 35)	ATB (N = 223)
Gender, male, N (%)	26 (74.28)	168 (75.34)
Age, years, M (IQR)	50.00 (39.00-59.00)	57.00 (44.00-68.00)
Body mass index, $\text{kg/m}^2$ , $\bar{x} \pm s$	$19.88 \pm 2.54$	$19.61 \pm 2.63$
Serum albumin, g/L, $\bar{x} \pm s$	$38.01 \pm 3.68$	$30.33 \pm 6.17$
Interleukin-6, pg/L, M (IQR)	0.043 (0.021-0.090)	0.045 (0.023-0.077) <sup>a</sup>
25-hydroxy vitamin D, $\mu\text{g/L}$ , M (IQR)	17.32 (13.39-21.48)	27.36 (25.53-31.00)
$\text{CD4}^+$ , cells/uL, M (IQR)	682.00 (548.00-771.00)	300.00 (197.00-446.00)
$\text{CD8}^+$ , cells/uL, M (IQR)	544.00 (432.00-615.00)	268.00 (184.00-372.00)
<b>T-SPOT.TB, SFCs, M (IQR)</b>		
ESAT-6	28.00 (16.00-31.00)	67.00 (24.00-150.00) <sup>b</sup>
CFP-10	39.00 (33.00-48.00)	76.00 (17.25-219.00) <sup>b</sup>
PHA	321.00 (307.00-3.00)	154.50 (147.25-160.00) <sup>b</sup>
TBAg/PHA	0.125 (0.102-0.158)	0.642 (0.299-1.692) <sup>b</sup>
$\text{CD64}$ index, MFI, $\bar{x} \pm s$	$0.67 \pm 0.34$	$1.26 \pm 0.33^c$

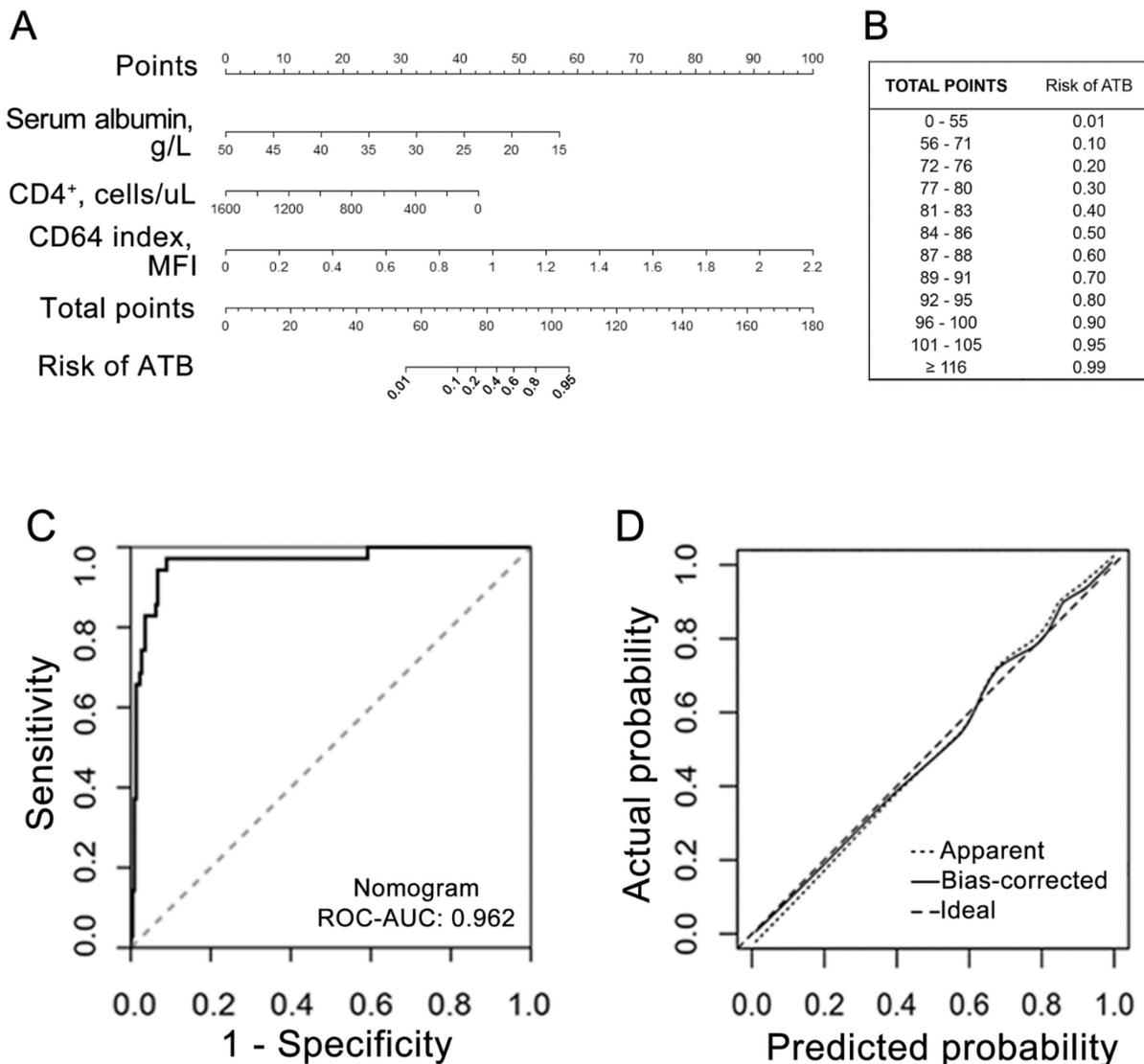
<sup>a</sup> 2 cases were missing; <sup>b</sup> 3 cases were missing; <sup>c</sup> 2 cases were missing. LTBI: latent tuberculosis infection; ATB: active tuberculosis; N: number of cases; M: median; MFI: ratio of mean fluorescence intensity; IQR: interquartile range; T-SPOT.TB: T cell spot test for tuberculosis infection; SFCs: spot-forming cells; ESAT-6: early secreted antigenic target 6 kDa; CFP-10: culture filtrate protein 10 kDa; PHA: phytohemagglutinin; TBAg: CFP-10 and ESAT-6 had a larger number of SFCs.

**Table 2.** Logistic regression analysis of active tuberculosis.

Intercept and variable	$\beta$ - coefficient	S $\bar{z}$ value	Wald $\chi^2$ value	p value	Odds ratio	95% CI
(Intercept)	- 7.784	5.618	1.920	0.166	0.000	
Serum albumin, g/L	0.291	0.145	3.988	0.046	1.337	1.005 - 1.778
CD4 <sup>+</sup> , cells/uL	0.010	0.003	8.371	0.004	1.010	1.003 - 1.017
TBAg/PHA, SFCs	- 18.928	10.187	3.452	0.063	0.000	0.000 - 2.825
CD64 index, MFI	- 4.697	2.021	5.400	0.020	0.009	0.000 - 0.479

$\beta$  is the regression coefficient. CI: confidence interval; MFI: ratio of mean fluorescence intensity; SFCs: spot-forming cells; TBAg: CFP-10 and ESAT-6 had a larger number of SFCs; PHA: phytohemagglutinin.

**Figure 2.** Nomogram, risk calculator, ROC-AUC and calibration curves of ATB.



**A.** Column plots of ATB risk were constructed using serum albumin, CD4<sup>+</sup>, and CD64 levels in the cohort. In our line graph, the CD64 index was the largest risk factor for patients at high risk of ATB (100 points), followed by the serum albumin level (57 points), and CD4<sup>+</sup> level showed the least effect on the probability of patients at high risk of ATB (43 points). **B.** Calculate the probability of ATB. **C.** ROC curve for nomogram, X-axis is 1-specificity, Y-axis is sensitivity. The ROC-AUC quantifies the performance of a classifier and falls between 0.1 and 1. The higher the value, the better the classifier’s performance, making it a straightforward measure for evaluation. **D.** The X-axis represents the predicted ATB risk, and the Y-axis represents the actual ATB risk. The diagonal dashed line indicates the perfect prediction of the ideal model. The solid line indicates the performance of the column plot, where closer to the diagonal dashed line indicates a better prediction. ATB, active tuberculosis; MFI, ratio of mean fluorescence intensity; ROC-AUC, area under the curve of receiver operating characteristic.

into the model but had no statistical significance, and the logistic regression model was statistically significant ( $\chi^2 = 136.54, p < 0.0001$ ) with  $R^2 = 0.750$  (Table 2). A nomogram was developed with serum albumin, CD4<sup>+</sup>, and CD64 (Figure 2A and Supplementary Table 2). The risk probabilities for patients at a high risk of ATB at the total scores of 95 and 105 were 80% and 95%, respectively (Figure 2B).

*Apparent performance and validation of a prediction model*

The area under the ROC curve for the nomogram model was 0.962 (95% CI: 0.926–0.997), sensitivity of 0.971, and specificity of 0.910, as shown in Figure 2C. The area under the ROC curve for the nomogram model differed from a single hazard and had a better diagnostic performance (Supplementary Table 3 and 4).

Internal validation using Bootstrap resampling 1000 times showed good concordance with a mean absolute error of 0.013 (C-index = 0.964); the HL test showed no statistical significance ( $\chi^2 = 13.798, p = 0.087$ ), which suggested that the performance of the nomogram did not deviate from the ideal goodness-of-fit; the calibration curves showed a good overlap with

the diagonal, with a prediction accuracy of 86.4% (Figure 2D). This demonstrates that the model has good predictive power for predicting LTBI progression to ATB in high-risk patients.

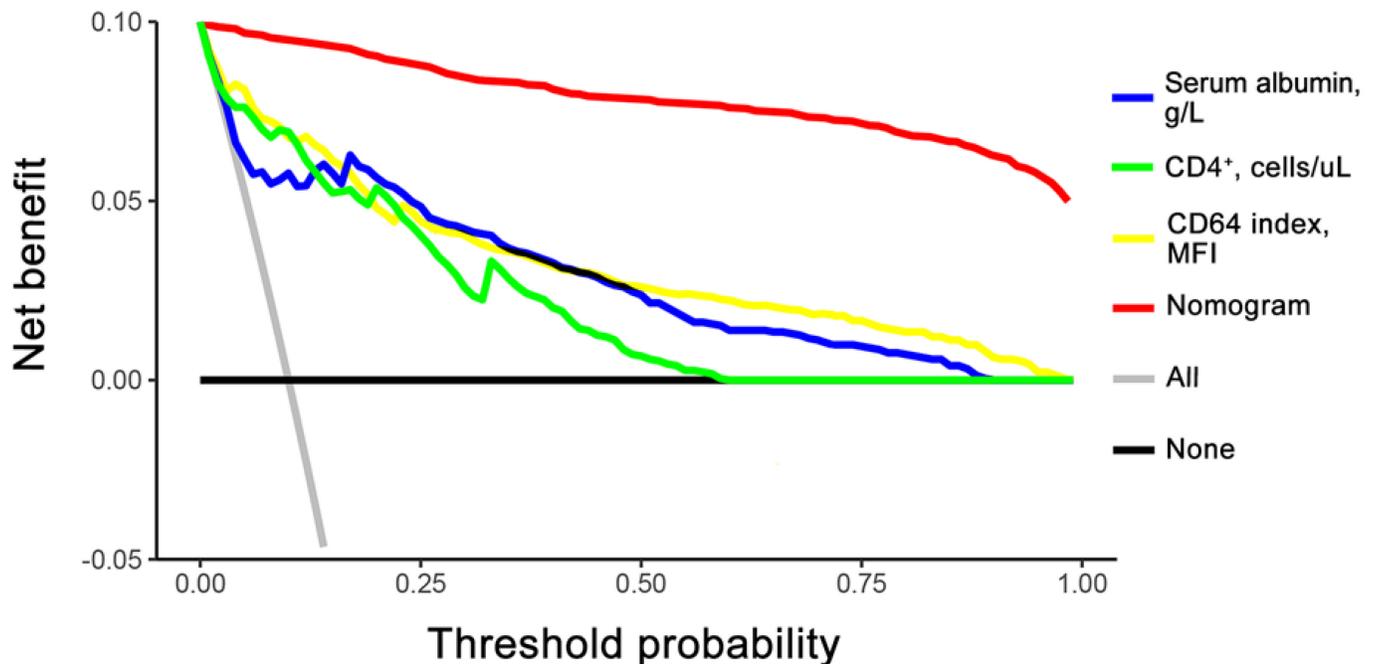
*Clinical use*

The incidence of LTBI progressing to high-risk ATB was set at 0.1 and the decision curve analysis for the nomogram is shown in Figure 3. The curve shows that the nomogram provides the highest net benefit within a risk threshold of > 10% compared to patients predicted to be at high risk of ATB or not. The cost-effectiveness ratio is 1:9 within this threshold, which is better than other single risk factors.

**Discussion**

The biological risk factors for the progression of LTBI to tuberculosis are clinically difficult and topical. In this study, we developed and validated a simple and intuitive statistical prediction model that improves the detection of patients at a high risk of ATB, and its high sensitivity is regarded as the start of prophylactic treatment. The detection of the predictors CD4<sup>+</sup> and CD64 is possible in most cases.

**Figure 3.** Decision curve analysis for the nomogram and risk factors.



The X-axis represents the high-risk threshold and the Y-axis represents the net benefit. The black straight line represents the hypothesis that patients are all not predicted to be high risk for ATB after nomogram assessment, with a net benefit rate of 0. The grey sloping line represents the hypothesis that LTBI patients are all predicted to be high risk for ATB after model assessment. The red curve indicates the decision curve for the nomogram model for patients at high risk of ATB. The decision curves show that when the threshold probability of LTBI and ATB high risk patients is >10%, the column line graph was used in the current study to predict a greater increase in benefit for ATB high risk patients than for all patients at risk or not at risk. ATB, active tuberculosis; LTBI, latent tuberculosis infection; MFI, ratio of mean fluorescence intensity.

The findings revealed that patients with ATB had lower serum albumin levels and that serum albumin was the final independent variable included in the model, which was more contributory. The mechanism for serum albumin decrease could be: (1) decreased anabolism due to a reduced nutrient intake caused by gastrointestinal disorders and loss of appetite, as some studies [16] reported a 44.2% reduction in the baseline albumin secretion rate in patients complicated with tuberculosis, and (2) increased catabolism due to *Mtb* using body protein for its metabolism [17]. Because of its half-life of 15–20 days [18] and good robustness, albumin may be more valuable in the differentiation from LTBI. In the present study, patients had a 1.337-fold increased risk of ATB per unit decrease in albumin, which could be a major factor in TB progression. Column 1 of the index variable in the nomogram model was serum albumin, with a maximum score of 57, and the score was higher when the patient's albumin was lower, suggesting that clinical caregivers should adopt nutritional support measures. The predictive value of albumin in ATB has recently gained more attention, similar to the report of related studies [19-21].

As an essential anti-inflammatory and pro-inflammatory factor, interleukin-6 affects the occurrence and development of various diseases by regulating the body's response to infection, injury, and immune reactions. Studies have demonstrated that interleukin-6 is associated with poor prognosis and early treatment response in tuberculosis [22,23]. However, these studies have targeted people with diabetes and HIV-tuberculosis co-infection, with no such difference observed in our study. This may be related to the body's different immune responses and the severity of tuberculosis.

25-OH-VD may induce the formation of phagosomes via phosphatidylinositol-3-kinase products, thus limiting the intracellular growth of *Mtb* in macrophages [24]. On the one hand, vitamin D can inhibit the response of pro-inflammatory cytokines and enhance the anti-inflammatory response. Contradictory results are reported in the clinical trials assessing the correlation between vitamin D and the incidence of tuberculosis [25,26]. The results of this study showed that in patients with ATB, serum levels of 25-OH-VD were significantly higher than those in LTBI, but this effect is not statistically significant and was not taken into consideration in the final model. The potential role of vitamin D supplementation in reducing the risk of tuberculosis still requires further evaluation through randomized controlled trials.

CD4<sup>+</sup> T lymphocytes are the major cells in the immune response to tuberculosis infection, and there is a basic consensus that *Mtb* infection may induce low CD4<sup>+</sup> expression [27,28] by interfering with the proximal and downstream signals of T cells to downregulate CD4<sup>+</sup> cell activation through secreted proteins, which results in Th1/Th2 imbalance [29,30]. In the present study, a simultaneous decrease in CD4<sup>+</sup> and CD8<sup>+</sup> was observed, showing a strong positive correlation ( $r = 0.706$ ,  $p < 0.0001$ ; Supplementary Figure 1); however, ultimately only CD4<sup>+</sup> had a significant effect in the model, possibly because CD8<sup>+</sup> function partly relied on CD4<sup>+</sup> [31]. CD4<sup>+</sup> is related to tuberculosis activity, which agrees with the findings of Orlando *et al.* [32]. The maximum score in the nomogram model was 43 (Column 2 of the index variable), suggesting that decreased cellular immunity is crucial to TB activity. Previous studies have demonstrated that the T-SPOT.TB results are influenced by T lymphocytes [33,34] which have a limited value in distinguishing LTBI from ATB, with a significantly higher specificity when the TBAg/PHA ratio is used. QuantiFERON-TB Gold Plus and T-SPOT.TB demonstrated similar diagnostic performance [35]. Zhang *et al.* reported a higher sensitivity in the diagnosis of recent infections [36], while Wang *et al.* indicated a certain correlation between bacterial load and disease severity [37]. These studies provide evidence for the theory that tuberculosis immunity falls under the category of infection immunity, also known as “infection-induced immunity”. The predictive efficacy for ATB may rely more on quantitative differences, but comprehensive large-sample, long-term follow-up studies are still lacking. The data in the present study found similar differences between the two: TBAg/PHA was included in the final model at multivariate analysis; however, the effect was not significant ( $p > 0.05$ ), indicating that CD4<sup>+</sup> T lymphocytes performed better than CD8<sup>+</sup> and TBAg/PHA in the diagnosis of ATB. A more detailed study of the function and specificity of the *Mtb*-reactive CD4<sup>+</sup> T cell phenotype at the single cell level may uncover more valuable potential indexes.

CD64 is a receptor that recognises the IgG Fc segment (i.e., FcγRI) and is expressed on the surface of monocytes and macrophages, whereas in neutrophils its expression is significantly upregulated with inflammatory cytokine stimulation [38], inducing reactive oxygen species production and triggering antibody-dependent cell-mediated cytotoxicity for phagocytosis and bactericidal action [39,40]; moreover, CD64 can over-stimulate the monocyte respiratory

burst in mononuclear phagocytes to promote Mtb control. The increase usually starts 4–6 hours after inflammatory factor stimulation and peaks at 22 hours [41,42], which has been described as the "whistleblower" of the inflammatory factor storm. The CD64 index considers the differences in cellular expression between individuals and has good stability and accuracy. Our results demonstrated that the CD64 index in patients with ATB had increased expression and a score of 100 in the nomogram model, which should be taken more seriously in TB activity and could be a new index for identifying patients at a high risk of progression from LTBI to ATB, similar to what has been reported in related studies [11,43-45]. Future research needs to validate the use of neutrophil CD64 in clinical practice as a complementary diagnostic tool for managing Mtb infection.

The nomogram combined the above three factors to visualise the risk probability in patients at high risk of ATB. The nomogram allowed us to interpret individual needs for interventions according to the risk level, and both doctors and patients could easily use the scoring system to make personalised predictions of TB activity risk, which accords with the current trend towards personalised medicine and helps doctors make informed clinical decisions. Furthermore, the study defined risk thresholds, and the nomogram performed better and had higher yields compared to single risk factors. Thus, the model can be used for screening high-risk groups and periodic re-assessment of TB risk, which contributes to the primary prevention of pulmonary TB.

Limitations of this study: (1) This study was an analysis of inpatients, and the lack of subjects with early progression of TB may have affected the sensitivity of the model. (2) The serum albumin and CD4<sup>+</sup> values may vary with different regions and delays in attendance, and specific application is required for practice. (3) The data were obtained from a single hospital, the population may not be well represented, and multicentre, large sample studies are needed for internal and external validation. The study optimised the biomarker risk factors for patients at high risk of progression from LTBI to ATB, and for the first time developed a nomogram identification model with a superior net benefit, filling the gap of no validated screening assessment between those at high risk of progression after Mtb infection and those under effective control. Several promising diagnostic biomarkers warrant further study, including recombinant methylated Mtb heparin-binding hemagglutinin interferon- $\gamma$  release assay (rmsHBHA

IFN- $\gamma$ ) [46], a transcriptomic signature of tuberculosis (RISK11) [47], iron-related biomarkers (including serum iron, ferritin and transferrin) [48], a 5-protein panel (complement factor H related 5, leucine rich alpha-2-glycoprotein 1, C-reactive protein, lipopolysaccharide binding protein and serum amyloid A1) [49], and gamma-glutamylthreonine and hsa-miR-215-5p [50].

## Conclusions

Low levels of serum albumin and CD4<sup>+</sup> as well as high CD64 levels are independent risk factors for patients at high risk of progression from LTBI to ATB, and such patients should be alert to the possibility of developing ATB. The nomogram identification model we developed demonstrated good prediction, concordance, and possible clinical utility. This study provides a potential personalised assessment tool for identifying patients at high risk of LTBI progressing to ATB, and in addition to identifying high-risk patients who require prophylactic treatment, it serves as a prominent addition to host risk factors. Future efforts could be made to reduce ATB incidence by prioritising more aggressive prophylactic/treatment measures in high-risk patients.

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## Annex – Supplementary Items

**Supplementary Table 1.** Related Computer Programs for Nomogram With R.

### **For LASSO**

```

Library (glmnet)
Set current working directory and parameters
data=read.csv("atbmodel.csv")
head(data)
x <- as.matrix(data[, 2:14])
y <- as.matrix(data[, 1])
lasso <- glmnet(x, y, family = "binomial",alpha = 1)
print(lasso)
lasso.coef
plot(lasso, xvar = "lambda", label = TRUE)
set.seed(317)
lasso.cv = cv.glmnet(x, y, nfolds = 5)
plot(lasso.cv)
lasso.cv$lambda.min
lasso.cv$lambda.1se
lasso.coef <- predict(lasso,s = 0.0129, type = "coefficients")

```

### **For Nomogram**

```

Library (rms)
attach(data)
dd<-datadist(data)
options(datadist='dd')
fit1<-lrm(y~serum_albumin+CD4+CD64_index,data=data,x=T,y=T)
fit1
summary(fit1)
nom1<-nomogram(fit1,fun=logis,fun.at=c(.01,0.1,seq(.2,.8,by=.2),.95),lp=F,funlabel="y")
plot(nom1)
cal1<-calibrate(fit1,method='boot',B=1000)
plot(cal1,xlim=c(0,1.0),ylim=c(0,1.0))

```

### **For Decision Curve Analysis**

```

library(rmda)
library(ggplot2)
data<-read.csv('atbmodel.csv',sep = ',')
res_blue<- decision_curve(y~serum_albumin, data=data,family=binomial(link='logit'),thresholds=seq(0,1,
by=0.01),confidence.intervals=0.95,study.design='case-control',population.prevalence= 0.1)

res_green<- decision_curve(y~CD4, data=data,family=binomial(link='logit'),thresholds=seq(0,1,
by=0.01),confidence.intervals=0.95,study.design='case-control',population.prevalence= 0.1)
res_yellow<- decision_curve(y~CD64_index, data=data,family=binomial(link='logit'),thresholds=seq(0,1,
by=0.01),confidence.intervals=0.95,study.design='case-control',population.prevalence= 0.1)

res_red<- decision_curve(y~serum_albumin+CD4+CD64_index, data = data,family = binomial(link =
'logit'),thresholds = seq(0,1, by = 0.01),confidence.intervals = 0.95,study.design = 'case-
control',population.prevalence = 0.1)
list<- list(res_blue, res_green, res_yellow, res_red)
plot_decision_curve(list,curve.names=c('res_blue ','res_green',
res_yellow','res_red'),cost.benefit.axis=FALSE,col=c('blue','green','yellow','res_red'),confidence.interv
als=FALSE,standardize=FALSE)
summary(complex,measure = 'NB')

```

**Supplementary Table 2.** Calculate the point of ATB.

Predictors	Category	Nomogram score
Current serum albumin levels (g/l)	≤ 15	57
	20	49
	25	41
	30	33
	35	24
	40	16
	45	8
	≥ 50	0
Current CD4 <sup>+</sup> cell count (cells/ul)	0	43
	200	38
	400	32
	600	27
	800	22
	1000	16
	1200	11
	≥ 1600	5
Current CD64 index	≥ 2.2	100
	2.0	91
	1.8	82
	1.6	73
	1.4	64
	1.2	55
	1.0	45
	0.8	36
	0.6	27
	0.4	18
	0.2	9
0	0	

**Supplementary Table 3.** Results of comparison with the area under the curve between nomogram model and a single risk factor.

	Difference between two areas	<i>S</i> $\bar{z}$ value	95% CI for difference	Z value	<i>p</i> value
Nomogram Vs. Serum albumin	0.107	0.026	0.056 – 0.158	4.116	< <b>0.0001</b>
Nomogram Vs. CD4 <sup>+</sup>	0.068	0.016	0.036 – 0.100	4.179	< <b>0.0001</b>
Nomogram Vs. CD64 index	0.063	0.027	0.011 – 0.115	2.374	<b>0.018</b>
Serum albumin Vs. CD4 <sup>+</sup>	0.038	0.030	(-0.020) – 0.096	1.301	0.193
Serum albumin Vs. CD64 index	0.044	0.041	(-0.037) – 0.124	1.067	0.286
CD4 <sup>+</sup> Vs. CD64 index	0.005	0.035	(-0.064) – 0.075	0.152	0.879

CI: Confidence interval.

**Supplementary Table 4.** Performance of risk factors and model for predicting ATB high-risk patients.

Risk factors	Youden index (%)	Cutoff value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Serum albumin	64.25	33.26	94.29	69.96	67.00	98.73
CD4 <sup>+</sup>	70.18	498.50	88.57	81.61	43.06	97.85
CD64 index	72.38	0.815	80.00	92.38	62.22	96.71
Nomogram	88.17	2.804	97.14	91.03	62.96	99.51

ATB: active tuberculosis.

**Supplementary Figure 1.** The correlation between CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocyte counts.

