# Time to sputum conversion in patients with pulmonary tuberculosis: A score to estimate the infectious period.

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**Research Article**

**Keywords:** Pulmonary tuberculosis (PTB), score, predictor factors, conversion, sputum conversion

**Posted Date:** February 14th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1349485/v1

## Abstract

# Purpose

Patients with pulmonary tuberculosis (PTB) disease and positive sputum cultures are the main source of infection. Culture conversion time is inconsistent and defining the length of respiratory isolation is challenging. The objective of this study is to develop a score to predict the length of isolation period.

# Methods

A retrospective study was carried out to evaluated risk factors associated with persistent positive sputum cultures after 4 weeks of treatment in 229 patients with PTB. A multivariable logistic regression model was used to determinate predictors for positive culture and a scoring system was created based on the coefficients of the final model.

# Results

Sputum culture was persistently positive in 40.6%. Fever at consultation (1.87, 95% CI:1.02–3.41), smoking (2.44, 95% CI:1.36–4.37), > 2 affected lung lobes (1.95, 95% CI:1.08–3.54), and neutrophil-to-lymphocyte ratio > 3.5 (2.22, 95% CI:1.24–3.99), were significantly associated with delayed culture conversion. Therefore, we assembled a severity score that achieved an area under the curve of 0.71 (95% CI:0.64–0.78).

# Conclusions

In patients with smear positive PTB, a score with clinical, radiological and analytical parameters can be used as a supplemental tool to assist clinical decisions in isolation period.

## Introduction

Pulmonary Tuberculosis (PTB) is an airborne disease considered a major global health problem. According to the World Health Organization 10 million people developed tuberculosis and 1.3 million people died from the disease in 2019 [1]. Despite the incidence rate and progressive decline in recent years (20% reduction between 2015 and 2020), eradication remains distant [1].

Patients with PTB discharge in infected droplet nuclei in the air that could infect healthy people. Once diagnosed, early respiratory isolation measures should be established to prevent transmission ideally until negative sputum culture samples are obtained. However, *Mycobacterium tuberculosis* has a slow growth in cultures and results are available 4-6 weeks after collection; nonetheless clinicians have to

decide whether to continue or remove isolation before knowing culture results and based on sputum smear results.

The objective of this study is to determine risk factors related to persistence of positive sputum cultures 4 weeks after treatment onset and to perform a score to predict respiratory isolation time for each patient individually.

# Methods

*Study design, setting and participants*

This multicentric, retrospective observational study was performed at Tuberculosis Units of 3 tertiary University Hospitals of Catalonia, Spain; namely Arnau de Vilanova (Lleida), Vall d'Hebron (Barcelona) and Bellvitge (L'Hospitalet de Llobregat). Patients with smear-positive PTB were recruited. Inclusion criteria were: (i) Age ≥ 18 years old; (ii) Positive acid-fast bacilli smear before treatment onset; (iii) Sputum culture sample at 4 weeks since treatment onset. Subjects with HIV, atypical mycobacteria infection and lost to follow-up were excluded. Participants at Arnau de Vilanova University hospital were evaluated from 1 January 2010 to 31 December 2017, whereas participants at Vall d'Hebron and Bellvitge Hospital were evaluated from 1 January 2010 to December 2014.

*Data collection*

All cases of sputum smear-positive PTB in the study period were identified from patient's medical records reviewed retrospectively. The following data were obtained by medical chart review: demographic data (age, sex, country of birth), alcohol abuse (alcohol intake exceeded 70 grams per day), drugs and tobacco use, comorbidities (cancer, immunosuppression, chronic liver disease, chronic renal failure, diabetes mellitus and chronic obstructive pulmonary disease (COPD)). Patients were also assessed for clinical symptoms (fever, cough, hemoptysis, chest pain, expectoration, weight loss) at diagnosis. Directly observed therapy (DOT), treatment tolerance and hepatic toxicity were also recorded.

The pre-treatment chest X-ray for each patient was reviewed and interpreted by an experienced radiologist. The presence or absence of cavities, pleural effusion, miliary pattern and number of affected lobes were noted and a radiological index that estimates the spread of the disease (proportion of total lung affected (%) + 40 if cavitation is present) was calculated [2].

In addition, laboratory data were collected including hemoglobin (g/dL), lymphocytes, leucocytes and neutrophil and neutrophil-to-lymphocyte ratio (NLR).

The results of the sputum smear obtained at diagnosis as well as the sputum culture sample collected 4 weeks after treatment onset were also recorded. The auramine stain was used during the study and bacillary load was measured by a semi-quantitative method as numerous (one or more bacilli/oil

immersion field), less numerous (10–99 bacilli/100 fields), and few bacilli (1–9 bacilli/100 fields)[3]. Cultures for *Mycobacterium tuberculosis* were carried out using the Lowenstein-Jensen technique or liquid culture and antimicrobial susceptibility testing was performed.

For the outcome analysis, persistent of infectivity was defined as positive culture at 4 weeks after treatment start.

### *Statistical methods*

Categorical variables were described as percentage and continuous variables, as they do not follow a normal distribution (Kolmogorov-Smirnov test), as median (interquartile range). For the comparison between the groups with positive (POSITIVE) or negative (NEGATIVE) culture, the Mann-Whitney test was used for continuous variables and the chi-square test for categorical variables. Significance level with $p < 0.05$.

Receiver operating characteristic (ROC) curve methodology was used to determine the optimal cut-off point for the NLR.

A multivariate logistic regression model was used to determinate independent predictors for positive culture. All variables with a p value lower than 0.20 in the univariate analysis were entered into the multivariate model with a forward stepwise selection of variables. Odds ratios (OR) with their 95% confidence interval were calculated.

A simple score was developed based on predictors that were independently associated with positive culture in the multivariate analysis. Score points were defined according to the β coefficients by rounding to the next positive integer value. The sum of the points is the value of the final score. The discriminating property of the score was assessed using the area under the ROC curve (AUC with 95% CI). The calculations were performed using SPSS software, version 23.0 (SPSS, Chicago, Ill).

### *Ethics statement*

The study protocol was approved by the Research Committee of each hospital.

## Results

From 1 January 2010 to 31 December 2017 619 patients were diagnosed of PTB in the 3 participant hospitals. Of these patients, 275 had one or more positive sputum smear tests (44.4%) and 229 fulfilled all the inclusion criteria.  46 subjects were excluded from the outcome analysis: 8 were HIV positive, 7 had an atypical mycobacteria and 31 lost follow-up.

The patients included in the study had a median age of 43 (31-55) years, were predominantly male (69%) and slightly more than half of them were active smokers (56%). The median interval between symptoms onset and treatment start was 8 weeks (4-12). Cough (93%), purulent sputum (72%) and weight loss (68%), were the most common symptoms. The median interval between treatment start and sputum culture collection was 31 days (26-41) and the prevalence of positive cultures after first month of treatment was 41%. All patients firstly received standard treatment and 7.9% were switched to alternative treatments due to resistance or intolerance. 6.7% of the positive culture samples had isoniazid resistance and 0.4% were multi-drug resistants. The baseline characteristics of the 229 patients studied are shown in Table 1, and clinical and microbiological characteristics are detailed in Table 2.

Factors associated with persistent positive culture after 4 weeks of treatment in univariate analysis were smoking, alcohol abuse, cough, fever at consultation, weight loss, DOT, pleural effusion, high bacillary load, more than 2 affected lung lobes, radiological index and NLR. The inclusion of the variable NLR higher than 3.5 was selected based on the most appropriate cut-off point on the ROC curve (Fig 1). Univariate analysis is detailed in Tables 1-3.

Multivariate analysis showed that smoking (OR, 2.44; 95% CI, 1.36-4.37), fever at consultation (OR, 1.87; 95% CI, 1.02-3.41), more than 2 affected lung lobes (OR, 1.95; 95% CI, 1.08-3.54) and NLR > 3.5 (OR, 2.22; 95% CI, 1.24-3.99) were significantly and independently associated with persistent positive culture at 4 weeks after treatment onset (Table 4).

Based on these results, and in order to facilitate clinical use, we elaborated a scoring model to predict culture positivity at 4 weeks, referred as PTBSCore, with scores ranging from 0 to 4 points (Fig 2). Patients who scored 4 points have a great probability (82%) of have a persistent positive culture after 4 weeks of treatment. On the other hand, patients with 0 or 1 point have a probability between 75 and 87% of having a negative culture. For remaining patients, with 2 or 3 points, the probabilities are intermediate (36 and 51%, respectively). A ROC curve analysis was performed and the novel PTBScore achieved an AUC of 0.71 (95% CI 0.64–0.78) indicating an appropriate discrimination for patients with higher risk (Fig 3).

# Discussion

In clinical practice it is very difficult to know when a patient with positive smear sputum stops spreading the disease and being contagious, therefore the end of isolation period may be difficult to determine. In one hand, a prolonged isolation period may be not necessary and could affect labor and family life. On the other hand, a short isolation period when patient is still contagious could facilitate community transmission threating the goal of achieving eradication. It is crucial to recognize the end of the period during which smear positive PTB patients are infectious, however *M. tuberculosis* has a slow growth in cultures and auramine stain could be negatively correlated with culture results.

To predict infectivity in patients with PTB, prior experiences have been reported without fully resolving the issue, Horita N et al. developed an “Infectivity Conversion Score” classifying each patient according to the

sputum smear grade and assessing the existence of cavitations in the lungs [4] and Bisognin F at al. found that older age, high Xpert MTB/RIF result category, high smear grading and severe involvement of the lung on radiography are risk factors for persistent sputum smear positivity [5]. Moreover, others have related age > 40 years, smoking, alcohol abuse and diabetes mellitus with delayed sputum smear or culture conversion [6][7][8][9][5][10]. However, these studies were restricted to a reduce number of potentially predictive parameters and do not analyze epidemiological, clinical and biological parameters altogether. In addition, most of them do not use sputum culture as a reference and they could be less reliable as it was described by some investigators that suggested that negative sputum smear due to low presence of bacilli, may remain contagious if culture is positive [11][12][13] and in the other hand, a smear sputum positive with negative culture may be due to the presence of nonviable organisms that are not able to grow in cultures and patient would be no contagious [14][15].

Because of this poor scientific evidence, clinical guidelines cannot provide a clear recommendation about the isolation period, although authors recognize that is usual a conversion period between 30 and 60 days [16][17]. Other guidelines suggest that respiratory isolation could be discontinued 2 to 3 weeks after initiation of treatment if there is clinical improvement, low risk of resistance and evidence of good therapeutic compliance [18][19] even though these recommendations differ in several studies that have determined that approximately 40-60% of patients could be contagious after one month of initiating treatment [20][5][21][16].

Immune response could be weakened by cigarette smoke, alcohol abuse and other diseases like diabetes mellitus and this could be a reason of a delayed conversion. According to our results, smoking and alcohol abuse were statically associated with persistence of infectivity, but no underlying disease was correlated with that finding including diabetes mellitus or immunosuppression.

Clinical variables have usually been omitted in the majority of the studies, in our cohort three clinical parameters at consultation, fever, cough and weight loss were related to a longer duration of infectiousness. We hypothesize that fever may be related with a higher inflammatory response due to the presence of high bacillary load at presentation. Hatsuda K et al found that nutritional markers predict the delay of conversion of sputum cultures to negativity and this could be due to altered immune system responses against TB caused by malnutrition[22]. The significance association with cough loses value because of the high percentage of patients that presented with this symptom.

Our cohort included patients from developed and developing countries, with varying sociodemographic backgrounds and living standards. This design suggests similar trends might be occurring in heterogeneous settings and clinical contexts. We decided to exclude HIV infected-patients from the study because the number of patients was small and may not be representative. Furthermore, Telzak E et al and Domínguez-Castellano A et al have demonstrated that HIV status does not prolong the time to culture conversion [23][24]. Therefore, PTBSCore cannot be used in HIV and needs further validation.

Our results also found that lymphopenia and NLR is strongly associated with delayed culture conversion. This pattern is similar to that described by Chedid C et al. who reported that lymphopenia had a significantly longer time to sputum culture conversion at two months of treatment and hypothesize that patients with high baseline blood white cell counts and low lymphocyte proportions had highly inflammatory clinical patterns [25]. Increased NLR was related with prognosis and mortality of PTB disease [26]. Based in our experience high NLR may also be useful in relation to a retard in culture conversion and this is the first study describing the association.

We evaluated several radiological findings detecting an association between radiological index and number of affected lung lobes with persistence in culture positivity in univariate analysis. In literature, radiographic features were associated with smear non-conversion, especially the extent of pulmonary involvement and the presence of cavitations [7][27][28][24]. Ralph et al developed a radiologic index concluding that the presence of cavities and percentage of affected lung area were related to severity of PTB disease [2]. These findings could be due to high bacillary load in necrotic material into consolidations or cavities that drain bacilli to central airways.

Finally, related to microbiological results, we found association between high bacillary load in sputum smear and time to sputum culture conversion as its widely described [6][7][27][23]. In addition, it is reasonable to believe that the presence of multidrug resistant strains of *M. tuberculosis* could be related to the persistence of positive cultures as reported by Fortun J et al [20]; however, resistance in our area is extremely low and we could not study this association in our sample.

Among these parameters statistically associated with the persistence of the infectivity in the univariate analysis, four were selected in the multivariate analysis: smoking habit, fever at the consultation, more than 2 affected lung lobes and NLR higher than 3.5. These variables allowed us to perform a score named PTBSCore, with 4 parameters that are commonly measured at consultation and can be easily tested in order to extend isolation period when a high risk of transmission is estimated. The ROC curve analysis showed an AUC of 0.71 indicating a useful discrimination for our model. If such potential risk factors are known at the start of treatment, subjects can be stratified before the commencement of therapy: Patients with 0-1 point have a low probability of being infectious at 4 weeks since treatment start, those who score 2-3 points have an intermediate risk and subjects with 4 points have a high risk of being contagious. This stratification may improve TB control and may offer greater efficiency in resource utilization. For example, patient with 4 points could be isolated 8 weeks instead of 4 weeks to prevent transmission, patients with 0-1 point could accomplish 4 weeks of isolation period and patients with intermediate risk (2-3 points) could wait to remove quarantine until negative cultures results are obtained.

In summary, we developed a score with 4 easy-to-use parameters that predicts persistent positive culture and therefore contagiousness, in patients with PTB 4 weeks after treatment onset. If validated, it could be very useful in clinical practice to determine isolation time and prevent further spreading.

# Declarations

ACKNOWLEDGEMENTS

The authors thank all of the medical staff and patients involved in the study. The authors declare that there is no conflict of interest.

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# Tables

**Table 1.** Baseline characteristics associated with positive culture after 4 weeks of treatment. (N=229)

| | ALL | NEGATIVE | POSITIVE | *p* |
|---|---|---|---|---|
| | N = 229 | N = 136 | N = 93 | |
| **Age (years)**[a] | 41 (31-55) | 39 (30-53) | 43 (33-56) | *0.174* |
| **Age groups** | | | | *0.251* |
| < 30 | 24.5 | 25.0 | 23.7 | |
| 30-40 | 24.5 | 28.7 | 18.3 | |
| 41-55 | 29.3 | 27.2 | 32.3 | |
| > 55 | 21.8 | 19.1 | 25.8 | |
| **Gender – (male)** | 68.6 | 64.0 | 75.3 | *0.071* |
| **Country of origin** | | | | *0.478* |
| Western Europe | 57.2 | 56.6 | 58.1 | |
| Eastern Europe | 12.2 | 11 | 14 | |
| Asia | 1.3 | 1.5 | 1.1 | |
| North Africa | 9.2 | 11.8 | 5.4 | |
| Rest of Africa | 7 | 5.1 | 9.7 | |
| South America | 10.5 | 11 | 9.7 | |
| Central America | 0.4 | 0 | 1.1 | |
| Arab countries | 1.3 | 1.5 | 1.1 | |
| **Comorbidities** | | | | |
| Immunosuppression | 3.1 | 2.2 | 4.3 | *0.366* |
| COPD | 8.5 | 5.9 | 12.9 | *0.065* |
| DM | 9.6 | 8.1 | 11.8 | *0.346* |
| Cancer | 7.0 | 8.8 | 4.3 | *0.187* |
| Renal failure | 2.6 | 2.9 | 2.2 | *0.713* |
| Smoking | 55.5 | 46.3 | 68.8 | *0.001* |
| Alcohol abuse | 20.5 | 15.4 | 28.0 | *0.021* |
| Drug abuse | 7.0 | 7.4 | 6.5 | *0.793* |

Values are presented as percentage. ([a]): mean ± standard deviation. ([b]): median (interquartile range). (p) calculated with chi-square test or Mann-Whitney test.

Abbreviations: COPD, Chronic obstructive pulmonary disease; DM, diabetes mellitus.

**Table 2.** Clinical characteristics at consultation and treatment tolerance associated with positive culture after 4 weeks of treatment (N=229)

| | ALL | NEGATIVE | POSITIVE | *p* |
|---|---|---|---|---|
| | N = 229 | N = 136 | N = 93 | |
| **CLINICAL SYMPTOMS** | | | | |
| **Cough** | 93.4 | 90.4 | 97.8 | *0.026* |
| **Fever** | 62.0 | 55.9 | 71.0 | *0.021* |
| **Expectoration** | 71.6 | 67.6 | 77.4 | *0.107* |
| **Chest pain** | 27.9 | 27.9 | 28.0 | *0.998* |
| **Haemoptysis** | 19.4 | 19.3 | 19.6 | *0.954* |
| **Weight loss** | 67.7 | 61.0 | 77.4 | *0.009* |
| **Weeks** *(a) | 8 (4-12) | 8 (4-14) | 8 (4-12) | *0.256* |
| **MICROBIOLOGY** | | | | *0.033* |
| **Pre-treatment smear grading** | | | | |
| Negative | 14.4 | 19.9 | 6.5 | |
| Few | 15.7 | 16.2 | 15.1 | |
| Less numerous | 43.2 | 40.4 | 47.3 | |
| Numerous | 26.6 | 23.5 | 31.2 | |
| **Resistance** | | | | *0.460* |
| Isoniazid | 6.7 | 6.7 | 6.7 | |
| Rifampicin | 1.3 | 1.5 | 1.1 | |
| Multidrug | 0.4 | 0.7 | 0 | |
| **TREATMENT** | | | | |
| **Anti-tuberculosis drug** | | | | *0.170* |
| Standard treatment | 92.1 | 90.4 | 94.6 | |
| Other | 7.9 | 9.6 | 5.4 | |
| **DOT** | 19.2 | 14.7 | 25.8 | *0.036* |
| **Vomits**** | 11.9 | 11.2 | 12.9 | *0.696* |

| | | | | |
|---|---|---|---|---|
| **Hepatic toxicity**** | 2.6 | 3.0 | 2.2 | *0.700* |

*weeks from onset of symptoms and initiation of treatment **Vomits and hepatotoxicity evaluated during first month of treatment.

Values are presented as percentage. ([a]) median (interquartile range (p) calculated with chi-square test or Mann-Whitney test.

Abbreviations: DOT, directed observed therapy.

**Table 3.** Radiological and analytical characteristics at consultation associated with positive culture after 4 weeks of treatment. (N=229)

| | ALL | NEGATIVE | POSITIVE | *p* |
|---|---|---|---|---|
| | N = 229 | N = 136 | N = 93 | |
| **RADIOLOGY** | | | | |
| **Cavitation** | 61.6 | 60.3 | 63.4 | *0.631* |
| **Alveolar pattern** | 84.1 | 81.3 | 87.9 | *0.191* |
| **Pleural effusion** | 16.6 | 12.5 | 22.6 | *0.044* |
| **Miliary pattern** | 18.8 | 16.9 | 21.5 | *0.382* |
| **Number of lobes** | | | | *0.005* |
| None | 4.4 | 5.1 | 3.2 | |
| 1 lobe | 34.5 | 41.2 | 24.7 | |
| 2 lobes | 24.0 | 25.7 | 21.5 | |
| > 2 lobes | 37.1 | 27.9 | 50.5 | |
| **Radiological index**[a] | 60 (40-100) | 60 (40-80) | 80 (40-100) | *0.005* |
| | | | | |
| **BLOOD TEST**[a] | | | | |
| **Haemoglobin** | 12.6 (11.3-13.7) | 12.9 (11.4-13.7) | 12.3 (11.1-13.7) | *0.185* |
| **Leukocytes** | 8.9 (7.1-11.3) | 8.5 (6.9-10.6) | 10.1 (7.6-11.9) | *0.008* |
| **Neutrophils** | 6.4 (4.7-8.4) | 5.9 (4.4-7.5) | 7.3 (5.0-9.4) | *0.001* |
| **Lymphocytes** | 1.7 (1.1-2.2) | 1.8 (1.3-2.3) | 1.5 (0.9-2.0) | *0.020* |
| **NLR** | 3.8 (2.6-5.9) | 3.3 (2.4-5.2) | 4.8 (3.1-7.3) | *<0.001* |
| **NLR > 3.5** | 54.1 | 44.9 | 67.7 | *0.001* |

Values are presented as percentage. ([a]): median (interquartile range). (p) calculated with chi-square test or Mann-Whitney test.

Abbreviations: NLR, Neutrophil-to-lymphocyte ratio.

**Table 4.** Multivariate logistic regression analysis for risk factors of positive culture after 4 weeks of treatment.

| Variable | B coefficient | OR (95 % CI) | p-value | Score points |
|---|---|---|---|---|
| Smoking | 0.892 | 2.44 (1.36-4.37) | 0.003 | 1 |
| Fever at consultation | 0.625 | 1.87 (1.02-3.41) | 0.042 | 1 |
| > 2 affected lobes | 0.670 | 1.95 (1.08-3.54) | 0.027 | 1 |
| NLR > 3.5 | 0.798 | 2.22 (1.24-3.99) | 0.008 | 1 |

Abbreviations: NLR, Neutrophil-to-Lymphocyte ratio; OR, Odds Ratio; CI, Confidence interval.

# Figures

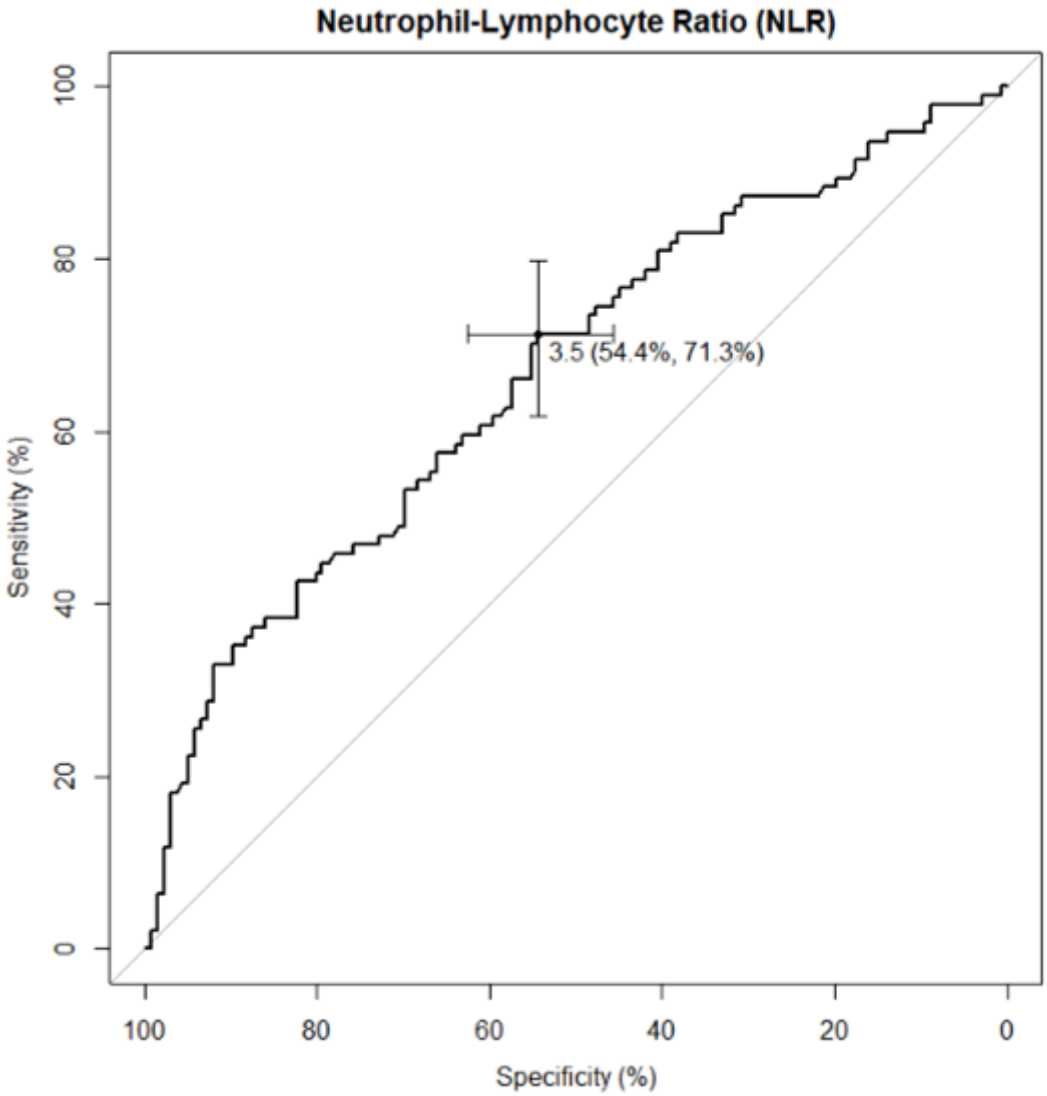
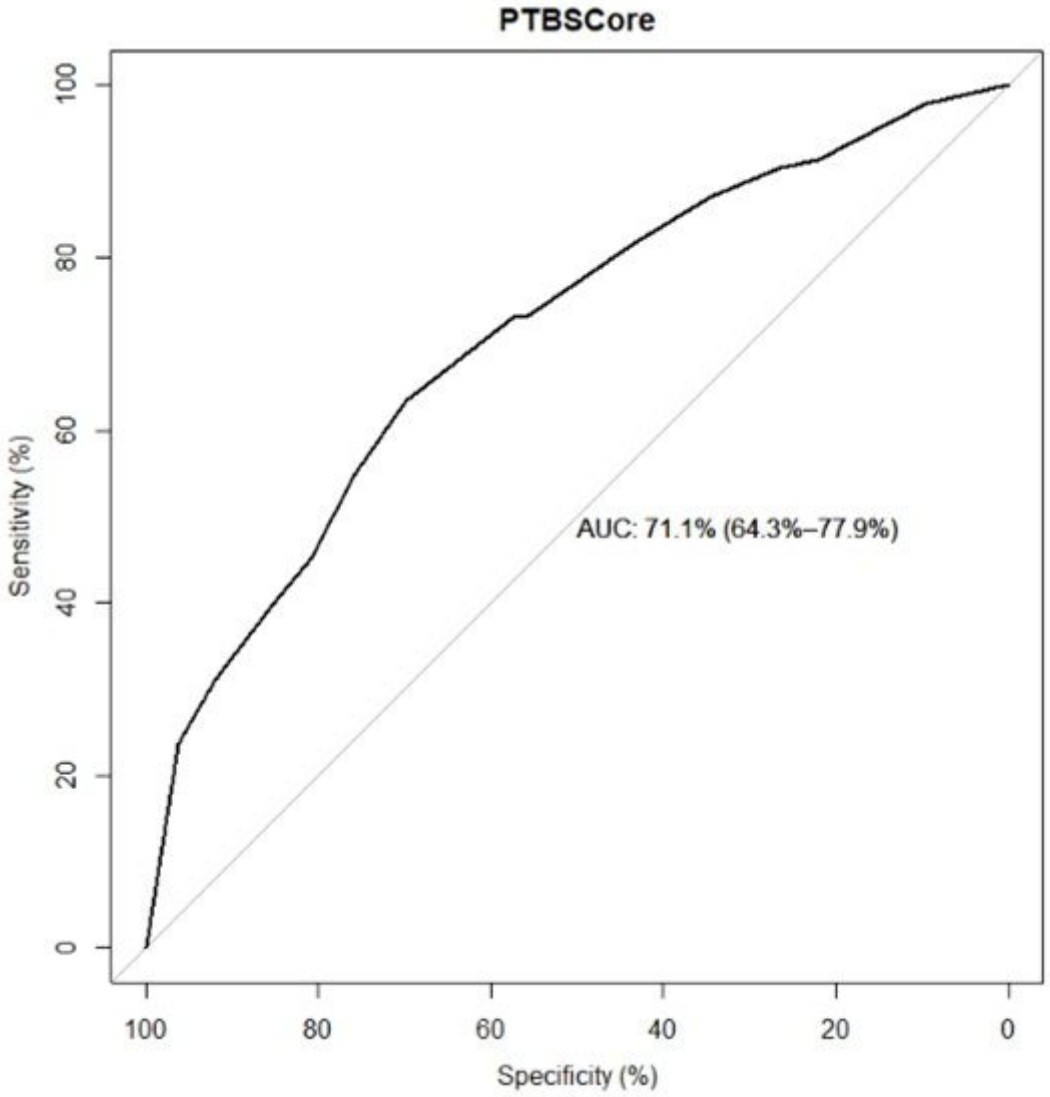


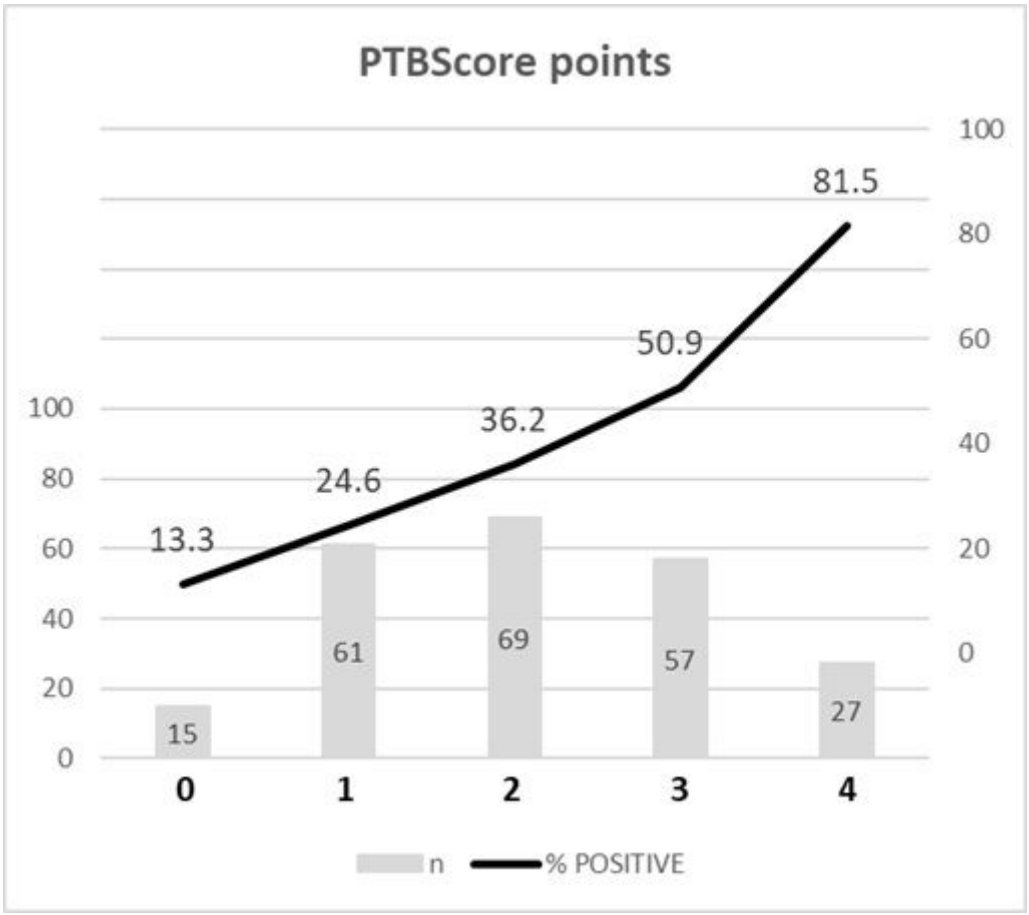

**Figure 1**

Cut-off point selection of neutrophil-to-lymphocyte ratio optimized value. ROC curve analysis.




## Figure 2

Percentage of positive cultures according to the number of risk factors. Abbreviations: PTBSCore, Pulmonary Tuberculosis Sputum-Conversion score




## Figure 3

Regression model ROC curve. Abbreviations: PTBSCore, Pulmonary Tuberculosis Sputum-Conversion score; AUC, area under the receiver operating characteristic curve.