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The Validity of Medical History, Classic Symptoms, and Chest Radiographs in Predicting Pulmonary Tuberculosis*

Derivation of a Pulmonary Tuberculosis Prediction Model

Pierre Tattevin, MD; Enrique Casalino, MD; Laurent Fleury, MD; Gérald Egmann, MD; Michel Ruel, MD; and Elisabeth Bouvet, MD

Study objective: To improve the respiratory isolation policy for patients with suspected pulmonary tuberculosis (TB).

Design: Prospective, descriptive, French multicenter study.

Setting: Emergence of nosocomial outbreaks of TB.

Patients: All consecutive patients admitted with suspicion of pulmonary TB.

Measurements and results: Medical history, social factors, symptoms, and chest radiograph (CXR) pattern (symptoms and CXR both scored as typical of pulmonary TB, compatible, negative, or atypical) were obtained on admission. Serial morning sputa were collected. Of the 211 patients, 47 (22.3%) had culture-proven pulmonary TB, including 31 (14.7%) with a positive smear. Mean age was 46.2 years; 52 patients were HIV positive (24.6%). The sensitivity of the respiratory isolation policy was 71.4%, specificity was 51.7%, negative predictive value (NPV) was 88.2%, and positive predictive value (PPV) was 26.3%. On univariate analysis, predictive factors of culture-proven pulmonary TB were CXR (p < 0.00001), symptoms (p = 0.0004), age (mean, 40.8 years for TB patients vs 47.5 years for non-TB patients; p = 0.04), absence of HIV infection (89.4% vs 71.3%; p = 0.01), immigrant status (72% vs 55%; p = 0.03), and bacillus Calmette-Guérin status (p = 0.025). On multivariate analysis, CXR pattern (p < 0.00001), HIV infection (p = 0.002), and symptoms (p = 0.009) remained independently predictive. Based on these data, a model was proposed using a receiver operating characteristics curve. In the derivation cohort, the sensitivity and NPV of the model in detecting smear-positive pulmonary TB would have been 100%. The specificity and PPV would have been 48.4% and 25%, respectively. The model performed less well when evaluated on two retrospective groups, but its sensitivity remained above that of the current respiratory isolation policy (91.1% and 82.4% for the retrospective groups vs 71.1% for the current policy).

Conclusions: Improved interpretation of clinical and radiologic data available on patient admission could improve adequacy of respiratory isolation. A prediction model is proposed.

Key words: diagnosis; isolation; predictive model; tuberculosis

Abbreviations: BCG = bacillus Calmette-Guérin; CXR = chest radiograph; NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristics; TB = tuberculosis

*From the Clinique de Réanimation des Maladies Infectieuses (Drs. Tattevin, Casalino, and Bouvet), Hôpital Bichat-Claude Bernard, Paris, France; Assistance Publique-Hôpitaux de Paris (Dr. Fleury Paris, France; Service des Urgences (Dr. Egmann), Hôpital La Madeleine, Cayenne, French Guyana; and Service de Médecine A (Dr. Ruel), Hôpital Max Courestier, Nanterre, France.

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Correspondence to: Elisabeth Bouvet, MD, Clinique de Réanimation des Maladies Infectieuses, Hôpital Bichat-Claude Bernard, 46 rue Henri-Huchard, 75877 Paris Cedex 18, France

The recent resurgence of tuberculosis (TB) has been associated with numerous outbreaks caused by nosocomial exposure, involving both patients and health-care workers.1–7 The rapid rate of progression to active disease among the growing number of susceptible patients (HIV-infected patients, those treated with immunosuppressive agents) was probably determinant in the amplified detection of nosocomial TB.7–9 However, some outbreaks occurred
among immunocompetent patients. One of the most commonly cited explanations for these outbreaks is the delayed recognition and isolation of patients with active pulmonary TB that has been well documented and may play an important part in the occurrence of nosocomial transmission of TB.

Many experts are convinced that prompt recognition and effective isolation of patients with active pulmonary TB should be a high priority in TB control policies. This may be a challenging task, as clinicians differ in their experience and ability to recognize pulmonary TB. Because the shortcomings in the clinical diagnosis of TB result in delay in isolating patients, an automatic isolation policy was proposed in some institutions, stating that all patients for whom sputum is ordered for acid-fast bacillus smear and culture must be placed in isolation until three sputum smears return negative. This policy allowed the appropriate isolation of 95% of those subsequently diagnosed with TB. In a low endemic area with such a policy, however, it has been estimated that for one patient with pulmonary TB, as many as 92 patients would have to be isolated (positive predictive value [PPV], < 1.1%). Even in institutions dealing with great numbers of TB patients, such as in New York City hospitals, TB is confirmed in only about one in seven patients isolated because of such a policy. Systematic isolation would place a high financial burden on hospitals, as effective respiratory isolation requires a single-bed room with negative pressure ventilation and respiratory precautions.

This article describes a French, multicenter, prospective study, the objective of which was to develop a predictive model allowing prompt recognition and isolation of smear-positive patients among those suspected of having pulmonary TB. This study included three steps: (1) an evaluation of the adequacy of current respiratory isolation of suspected pulmonary TB patients; (2) the identification of predictive factors for pulmonary TB among these patients; and (3) the derivation of a pulmonary TB prediction model based on data available on patient admission, to be used by admitting physicians as a guide for respiratory isolation.

**Materials and Methods**

**Setting**

This study was conducted in three hospitals. Hôpital Bichat-Claude Bernard is a 1,200-bed, university-affiliated teaching hospital that serves as a referral center and a primary-care facility in the Paris metropolitan area. Hôpital La Madeleine is a 300-bed hospital serving as a referral center and a primary-care facility in Cayenne, French Guyana. Hôpital Max Fourastier is a 300-bed hospital that serves as a referral center for homeless persons in the Paris suburban area and as a primary-care facility in Nanterre, France.

**Subjects**

From January 1 to April 30, 1997, 211 consecutive patients admitted to our institutions with suspicion of pulmonary TB were prospectively studied.

**Methods**

Past medical history (TB, TB contact, bacillus Calmette-Guérin [BCG] immunization, HIV infection, alcoholism, IV drug use), social factors (homeless, immigrant), and symptoms were obtained in face-to-face interviews. Symptoms were scored as typical of TB (cough, fever, or drenching night sweats for ≥ 3 weeks; hemoptysis), compatible with TB (cough, unexplained fever, nonpurulent sputum production, anorexia, weight loss), atypical, or negative. Admission chest radiographs (CXRs) were scored as typical of TB (the presence of nodular, alveolar, or interstitial infiltrates predominantly affecting the zones above the clavicles or upper zones; the presence of cavitation affecting the upper zones or the apical segment of the lower lobe), compatible with TB (enlarged hilar nodes, pneumatic lesion, atelectasis, mass lesion, miliary, pleural exudate), or atypical (any other pattern, including normal CXR). Patients were classified as HIV seropositive if they had a positive enzyme-linked immunosorbent assay and Western blot test at any time prior to or during this admission. Initial evaluation was performed by the on-call resident or fellow, who decided on the need for respiratory isolation.

Spontaneously expectorated sputa were collected every morning for at least 3 days. Inspection of conventional auramine-rhodamine fluorochrome smear and standard mycobacterial cultures was performed on Lowenstein-Jensen slants and Middlebrook 7H10 media. A χ² test with a two-tailed Fisher’s exact test for categorical variables was used for statistical analysis of between-group comparisons of frequency. The variables found significant in univariate analysis were included in a logistic regression model and were eliminated one by one in a backwards fashion, based on the adjusted odds ratios, in order to develop a model with the strongest relationships. Based on these results, a prediction model was proposed. Clinical and radiologic data easily available to the admitting physician were assigned weights on the basis of the multivariate analysis results in order to quantify the risk of the most contagious form of TB (smear-positive pulmonary TB) in an individual patient. The sensitivity and specificity of the model for predicting smear-positive pulmonary TB in the population studied was determined for each score value. Following stratification, performance of the TB prediction model in the derivation cohort was assessed using the receiver operating characteristics (ROC) curve. Analysis was done using computer software (EPI-INFO 6.0; World Health Organization; Geneva, Switzerland; and STATISTICA; StatSoft; Maisons-Alfort, France).

The TB prediction model was then retrospectively assessed using medical charts of patients previously admitted to a 45-bed infectious diseases department at the Hôpital Bichat-Claude Bernard, including 66 consecutive patients admitted in 1994 for suspicion of pulmonary TB (unpublished data) and all the patients with smear-positive TB admitted between 1990 and 1998.
RESULTS

Of the 211 patients, 47 were found to have culture-proven pulmonary TB (22.3%). Of these, 30 were smear positive (14.7%). Mean age was 46.2 years; 151 patients (71.6%) were male. Fifty-two patients were HIV positive (24.6%). Clinical symptoms and radiologic patterns in TB and non-TB patients are described in Tables 1 and 2. The distribution of TB and non-TB patients among the different centers is given in Table 3.

Data pertaining to respiratory isolation on admission were available in 180 patients. Among these, 35 patients had confirmed TB, 25 of whom were appropriately isolated on admission (sensitivity of respiratory isolation, 71.4%). Of the 95 patients isolated on admission, 25 had confirmed TB (PPV, 26.3%; specificity, 51.7%; negative predictive value [NPV], 88.2%).

In univariate analysis, the factors predictive of pulmonary TB were CXR pattern (p < 0.00001), clinical symptoms (p = 0.0004), age (mean, 40.8 years for pulmonary TB vs 47.5 years for other diagnoses; p = 0.04), absence of HIV infection (80.4% vs 71.3%; p = 0.01), immigrant status (72% vs 55%; p = 0.03), and BCG status (p = 0.025). Homeless status (38.3% vs 23.8%; p = 0.06) was close to significance (Table 4). In multivariate analysis, CXR (p < 0.00001), absence of HIV infection (p = 0.002), and clinical symptoms (p = 0.009) remained independently significant (Table 5).

Each of the three significant multivariate predictors (CXR, HIV infection, and clinical symptoms) was given a point score based on the value of the odds ratio. The variable typical CXR had the highest independent predictive value and was assigned a point score of 14; typical clinical symptoms were assigned 12 points; compatible CXR, 7 points; absence of HIV infection, 6 points; and compatible clinical symptoms, 5 points (Table 6). Because the limited sample size of our study may have precluded the identification of some independent predictors, we included three additional variables found as predictive in univariate analysis: homeless status (assigned a point score of 2), BCG immunization (assigned a point score of 2 if never performed, and 1 if performed > 10 years before admission), and immigrant status (2 points if the patient was born in sub-Saharan Africa, Southeast Asia, or Haiti, and 1 point if the patient was born in North Africa, South or Central America, or Southern or Eastern Europe).

Using the scoring system described above, each patient from this study was evaluated for the presence of each predictor and given a point total. Results of the application of the model to the derivation cohort are shown in Table 6. As the risk score increased, the probability of smear-positive pulmonary TB increased. The ROC curve derived from this model identified 18 as the ideal threshold, with a sensitivity of 100% and a specificity of 48.4% in adequately isolating smear-positive TB in the derivation cohort (Fig 1). The PPV would have been 25%. In extenso, if all the patients in the derivation cohort whose score was > 18 with this model would have been isolated, no smear-positive TB patient

### Table 1—Clinical Symptoms*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Culture-Proven Pulmonary TB</th>
<th>Other Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative or atypical</td>
<td>2 (4.2)</td>
<td>56 (34)</td>
</tr>
<tr>
<td>Compatible</td>
<td>12 (25.5)</td>
<td>40 (24.4)</td>
</tr>
<tr>
<td>Typical</td>
<td>33 (70.2)</td>
<td>68 (41.4)</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>164</td>
</tr>
</tbody>
</table>

*Values are given as No. (%).

### Table 2—Radiologic Signs*

<table>
<thead>
<tr>
<th>Signs</th>
<th>Culture-Proven Pulmonary TB</th>
<th>Other Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative or atypical</td>
<td>6 (12.8)</td>
<td>76 (46.4)</td>
</tr>
<tr>
<td>Compatible</td>
<td>9 (19.1)</td>
<td>45 (25.4)</td>
</tr>
<tr>
<td>Typical</td>
<td>32 (68.1)</td>
<td>43 (26.3)</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>164</td>
</tr>
</tbody>
</table>

*Values are given as No. (%).

### Table 3—Distribution of Culture-Proven Pulmonary TB and Other Diagnoses (Non-TB) in the Three Participating Centers*

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>Paris</th>
<th>Nanterre</th>
<th>Suburban Cayenne</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>26 (20.6)</td>
<td>17 (39.5)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Non-TB</td>
<td>100 (79.4)</td>
<td>26 (60.5)</td>
<td>38 (90.5)</td>
</tr>
<tr>
<td>Total</td>
<td>126</td>
<td>43</td>
<td>42</td>
</tr>
</tbody>
</table>

*Values are given as No. (%).
would have been missed (not isolated), and 25% of the patients isolated would have been later confirmed as smear-positive TB cases.

The TB predictive model was then assessed in another population of 66 patients from a previous study (unpublished data). This population differed from the 211 patients of our study in three main respects. First, the pulmonary TB prevalence was much higher: 36 of the 66 patients (54.5%) suspected of having pulmonary TB had this diagnosis confirmed during their hospital stay. Second, more than half of the patients were HIV seropositive (34 of 66, or 51.5%). Last, this study was performed during 1994, when highly active antiretroviral treatment was not routinely available. Using the threshold determined in our cohort of 211 patients, the score value obtained with the TB predictive model would have indicated the need for isolation in 14 of the 17 patients who were later found to have smear-positive pulmonary TB (sensitivity, 82.4%). Among the 44 patients who would have been isolated using the TB predictive model, 14 had smear-positive pulmonary TB (PPV, 31.8%). In this population, the NPV of the model would have been 86.4%, with a specificity of 38.8%. The three patients with smear-positive pulmonary TB who were not identified with the model were all HIV seropositive.

Eventually, we retrospectively reviewed the charts of 56 consecutive patients with smear-positive TB admitted to our Department of Infectious Diseases at Hôpital Bichat-Claude Bernard between January 1990 and September 1998. Using the TB predictive model, 51 patients (91.1%) would have been isolated on admission. The five patients who were not identified with the model were HIV seropositive.

### Table 5—Results of the Multivariate Analysis To Define Independent Predictive Factors of Culture-Proven Pulmonary TB

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Parameter Estimate ((\beta))</th>
<th>Odds Ratio</th>
<th>SE of (\beta)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>-1.01</td>
<td>0.36</td>
<td>0.56</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>0.78</td>
<td>2.18</td>
<td>0.28</td>
</tr>
<tr>
<td>CXR</td>
<td>1.05</td>
<td>2.85</td>
<td>0.26</td>
</tr>
</tbody>
</table>

### Table 6—Smear-Positive TB Prediction Model

<table>
<thead>
<tr>
<th>Immigrant From Eastern or Southern Europe, South America, French Guyana (1 Point)</th>
<th>Immigrant From sub-Saharan Africa, North Africa, Haiti, Southeast Asia (2 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC immunization (&gt;10) yr earlier (1 Point)</td>
<td>No RBC immunization (2 Points)</td>
</tr>
<tr>
<td>No HIV infection (5 Points)</td>
<td>No HIV infection (5 Points)</td>
</tr>
<tr>
<td>Homeless (1 Point)</td>
<td>Homeless (1 Point)</td>
</tr>
<tr>
<td>Compatible clinical symptoms (6 Points)</td>
<td>Typical clinical symptoms (12 Points)</td>
</tr>
<tr>
<td>Compatible CXRs (7 Points)</td>
<td>Typical CXR (14 Points)</td>
</tr>
</tbody>
</table>

### Discussion

The lack of easily applicable recommendations in cases of suspected pulmonary TB may explain both the low specificity (51.7%) and the suboptimal sensitivity (71.4%) of the current respiratory isolation policy in France. This may be improved with the identification of relatively simple and useful predictors available at the time of admission, which could be used to help predict who will have confirmed pulmonary TB. Few studies have compared the clinical and CXR manifestations of confirmed pulmonary TB patients with those of patients in whom pulmonary TB is suspected but later ruled out. In a prospective study, Cohen et al.\(^{19}\) identified the absence of the sentinel symptoms of 2 weeks of cough, sputum, weight loss, and the absence of a typical CXR as strong negative predictors for pulmonary TB. The population studied had a high TB prevalence rate (44%), and these indicators may not be applicable to populations with a lower prevalence of TB as was the case in our study (22.3%). In a recent prospective study, Bock et al.\(^{20}\) identified typical CXR (upper lobar infiltrate or cavity), recent contact with TB, a positive tuberculin skin test, and lack of isoniazid preventive therapy as independent predictive variables. A retrospective study showed that patients with pulmonary TB were more likely than control subjects to be foreign born and to have a CXR with cavitary or apical infiltrates, positive tuberculin skin test, diabetes, recent contact with TB, and weight loss.\(^{18}\)

Based on our study, the independent predictive variables are CXR score, clinical score, and HIV infection. The independent PPV of CXR or clinical score is consistent with the results of previous studies.\(^{18–20}\) The NPV of HIV infection could be explained by the many differential diagnoses for typical symptoms of TB in HIV-infected patients (e.g., the occurrence of fever, weight loss, and persistent cough is much more suspicious of pulmonary TB in non–HIV-infected patients than in HIV-infected patients, for whom the array of diagnoses is much broader). Clinical symptoms and CXR pattern cannot always be used to distinguish between TB and
other multiple pulmonary pathogens, especially among HIV-infected patients with advanced immunodeficiency. These factors, therefore, lose their predictive value.

Based on these results, we built a predictive model using clinical and CXR data readily available on admission, which would help admitting physicians to evaluate the probability of smear-positive pulmonary TB in order to guide their decision about respiratory isolation. The aim of this model was to allow adequate respiratory isolation on admission of all contagious patients, with an acceptable degree of overisolation. The hypothetical accuracy which this model would have had in predicting smear-positive pulmonary TB in the derivation cohort (100% sensitivity and 48.4% specificity) is encouraging, and supports the usefulness of such a model in improving the current respiratory isolation policy. However, models such as the one we developed often do not perform as accurately when used in populations other than the one in which they were established.

Even when applied to patients from a similar population, models tend to perform less well when tested prospectively.

Indeed, this TB predictive model was somewhat disappointing when retrospectively tested in a population of patients admitted for suspected pulmonary TB: 3 of 17 smear-positive TB patients (17.6%) would have been missed by the model. However, some points attenuate these disappointing results. Although suboptimal, the sensitivity of the model in this population remains higher than that of the current isolation policy in France (82.4% vs 71.4%).

Also, the rate of pulmonary TB among this population (54.5%) is rather unusual, indicative of patients highly suspected of having pulmonary TB. In such a population admitted to rule out pulmonary TB, systematic respiratory isolation should be the rule, pending the results of three consecutive acid-fast bacillus smears; furthermore, the model would have isolated on admission 51 of the 56 consecutive patients (91.1%) with smear-positive TB admitted to
our Department of Infectious Diseases at Hôpital Bichat-Claude Bernard from 1990 to 1998. It is worth pointing out that when tested on two different groups of subjects, the only patients that the model could not identify were HIV-infected patients. The model may perform less well in this population, since it does not take into account the different stages of HIV infection and the great variability of susceptibility to infection in this group of patients. Furthermore, many reports have documented the alterations in HIV-related disorders brought about by highly active antiretroviral therapy, including the clinical presentation of atypical mycobacteria. TB patterns may also be modified in this population.

Despite these restrictions, this model could be a cost-efficient means to control nosocomial acquisition of TB. By improving the accuracy of respiratory isolation policy, it may allow correct isolation of more TB patients and spare hospital resources by limiting the number of unnecessarily isolated patients. It should be validated prospectively in various populations of patients with suspected pulmonary TB in order to determine if and how it may be routinely used by admitting physicians to improve the adequacy of current respiratory isolation.

**CONCLUSION**

Among patients with suspected pulmonary TB, CXR pattern, clinical symptoms, and HIV status are independent predictive factors that indicate who will have confirmed pulmonary TB. A predictive model based on data readily available on patient admission is proposed. The model should improve current respiratory isolation of patients suspected of having TB.

**REFERENCES**

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