Evaluation of Clinical Parameters to Predict *Mycobacterium tuberculosis* in Inpatients

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Background: Respiratory isolation has been recommended for all patients with suspected tuberculosis (TB) to avoid transmission to other patients and health care personnel. In implementing these guidelines, patients with and without TB are frequently isolated, significantly increasing hospital costs. The objective of this study was to derive a clinical rule to predict the need for respiratory isolation of patients with suspected TB.

Methods: To identify potential predictors of the need for isolation, 56 inpatients with sputum cultures positive for TB were retrospectively compared with 56 controls who were isolated on admission to the hospital based on clinically suspected TB but whose sputum cultures tested negative for TB. Variables analyzed included TB risk factors, clinical symptoms, and findings from physical examination and chest radiography.

Results: Multivariate analysis revealed that the following factors were significantly associated with a culture positive for TB: presence of TB risk factors or symptoms (odds ratio [OR], 7.9 [95% confidence interval (CI), 4.4-24.2]), a positive purified protein derivative tuberculin test result (OR, 13.2 [95% CI, 4.4-40.7]), high temperature (OR, 2.8 [95% CI, 1.1-8.3]), and upper-lobe disease on chest radiograph (OR, 14.6 [95% CI, 3.7-57.5]). Shortness of breath (OR, 0.2 [95% CI, 0.12-0.53]) and crackles noted during the physical examination (OR, 0.29 [95% CI, 0.15-0.57]) were negative predictors of TB. A scoring system was developed using these variables. A patient's total score of 1 or higher indicated the need for respiratory isolation, accurately predicting a culture positive for TB (98% sensitivity [95% CI, 95%-100%]; 46% specificity [95% CI, 33%-59%]).

Conclusion: Among inpatients with suspected active pulmonary TB, a prediction rule based on clinical and chest radiographic findings accurately identified patients requiring respiratory isolation.

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PREVENTING THE spread of tuberculosis (TB) within hospitals is a major concern, particularly since the resurgence of TB in the mid-1980s[1-5] and recent reports[6-8] of nosocomial outbreaks of multidrug-resistant TB. The current guidelines[9] for controlling the transmission of TB within institutions emphasize early identification of patients considered at high risk for the disease. The conventional strategy to deal with this problem is to isolate potentially contagious patients until 2 to 3 smears of sputum are negative for acid-fast bacilli (AFB). The sensitivity of the AFB smear, however, is not high,[10-14] and transmission of TB from patients with smears negative for AFB has been reported.[15] Delayed recognition and isolation of patients with TB is a well-documented problem. For example, 3 studies[16-18] reported that in as many as 50% of the patients with a final diagnosis of TB the risk of the disease was not suspected and the appropriate infection control measures were not instituted on admission to the hospital. Conversely, Scott et al[19] reported that in their institution, 92 patients without TB were isolated for every patient with TB, leading to a significant increase in hospital costs.

Both the underdiagnosis and overdiagnosis of patients at risk for TB make present isolation guidelines difficult to implement and not fully effective.[19,20] In this context, it would be useful to develop predictive guidelines to more precisely identify patients at high risk for TB who require respiratory isolation on admission to the hospital. To identify early predictors of the need for respiratory isolation, the present study was designed to compare the clinical parameters of patients whose sputum cultures were positive for TB with individuals who were isolated on admission because of suspected disease but whose sputum cultures tested negative for TB.

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PATIENTS AND METHODS

STUDY DESIGN

The study was conducted at the Weill Medical College of Cornell University, New York–Presbyterian Hospital, a 786-bed tertiary care teaching institution located in the Upper East Side of New York, NY. The objective of the study was to identify clinical and chest radiographic findings to accurately predict which patients admitted to the hospital had active pulmonary TB. The study was carried out retrospectively by identifying 2 groups of patients who had been isolated because of suspected pulmonary TB. In one group of patients, active pulmonary infection with TB was proved by sputum cultures positive for TB (cases), and in the other group, the sputum cultures tested negative for TB (controls). At admission, the admitting physician thought that both groups of patients were at significant risk for pulmonary TB and required respiratory isolation. Once the groups had been identified, the data available to the physician at admission were collected and analyzed to determine a set of variables that correlated with the diagnosis of TB. These variables were used to construct a clinical prediction rule. Power calculation estimated that a minimum of 52 pairs of patients were needed to have a β level less than .10 to detect clinical predictors with at least a relative risk of 3.5, based on clinically relevant risk factors gathered from a review of the TB literature.[21]

PATIENT SELECTION

Cases were selected from a TB registry maintained by the hospital that contains the names of all the patients diagnosed as having TB and is used to notify the New York City Department of Health. The registry was reviewed to identify 56 consecutive patients with a sputum culture positive for TB who were isolated on admission to the hospital because of suspected disease. The initial group of cases comprised 73 patients with cultures positive for TB identified from December 1, 1991, to January 31, 1997. From this group of 73, 17 were excluded because of 1 of the following reasons: 4 were receiving antituberculous medications at the time of admission; 3 were younger than 18 years; 8 were never isolated; and 2 were admitted to the hospital with the knowledge of a smear positive for AFB.

Controls were selected from a log of all the patients who had a sputum sample submitted to the hospital microbiology laboratory for TB testing (AFB smear and culture). Although potential controls were randomly selected, a control was selected only if the age (±3 years), sex, and year of presentation matched a particular case. Patients were included as controls if further chart review revealed that they had been isolated on admission to the hospital and had at least 3 smears negative for AFB and cultures negative for TB.

SPUTUM SAMPLE ASSESSMENT

Sputum samples were concentrated and stained with auramine O fluorescent stain to screen for TB; the results were recorded in the log and the TB register. The samples were prepared in Lowestein-Jensen culture medium, Middlebrook 7H11 selective agar, and Mycobacteria Growth Indicator Tube and maintained for at least 6 weeks to detect the presence of growing organisms.

CHART REVIEW

Charts were reviewed to identify potential risk factors for active pulmonary TB. Only data available to the admitting physician at the time of making the decision of the need for respiratory isolation were collected for analysis. Data sources included reports and/or notes from the emergency medical services, emergency department, house staff, nurse, and attending physician during admission. These notes were photocopied and given for review to investigators who had not participated in the patient selection

RESULTS

The mean ± SEM ages for the cases and controls were 40 ± 1.7 years and 40 ± 1.6 years, respectively (**Table 1**). Of 112 patients, 41 (36.6%) were black; 31 (27.7%), Hispanic; 30 (26.8%), white; and 9 (8.0%), Asian. There were 62 patients (55.3%) with human immunodeficiency virus. Of 56 cases, 30 (54%) had at least 1 smear positive for AFB. Among the 73 patients eventually diagnosed as having TB, 23 (32%) either were not initially isolated or were removed from isolation after 3 smears tested negative for AFB. Thus, only 50 (68%) of the 73 inpatients with TB between December 1, 1991, and January 31, 1997, were appropriately treated according to the current Centers for Disease Control and Prevention guidelines[9] for avoiding exposure of hospital personnel to TB.

The presence of chronic symptoms, 1 or more TB risk factors, the temperature at admission, and history of a positive PPD tuberculin test result were associated with the presence of TB using univariate analysis (Table 1). History of shortness of breath and crackles noted during the physical examination were associated with the absence of TB. There was no significant difference between the cases and controls in the number of days of fever before presenting to the hospital, the presence or amount of hemoptysis, the white blood cell count at admission, the serum lactate dehydrogenase level, CD4 cell count, or the alveolar-arterial oxygen gradient. Antituberculous medications were given immediately after admission to 24 cases (43%) compared with 5 controls (9%) ($P = .001$).

The final impression of the investigator reviewing the charts regarding the presence of TB and a working diagnosis of TB by the admitting team were statistically associated with the presence of TB ($P = .001$). *Upper-lobe consolidation*, which was defined as the presence of any consolidation above the third rib posteriorly, excluding diffuse consolidation consistent with congestive heart failure, was associated with the presence of TB; this finding was present in 19 cases (34%) compared with 3 controls (5%) ($P = .001$; **Table 2**). The proportion of patients with unilateral or bilateral pleural effusions, cavities, lymphadenopathy, and reticular, nodular, or reticulonodular infiltrates was not significantly different beprocess and were unaware of the status (case vs control) of the patients.

Demographic information collected included age, sex, race, and immigration status. Risk factors for TB included history of exposure to an individual with TB, institutionalization (prison, shelter, or nursing home) in the last 3 years, and homelessness.

Potential clinical predictors included significant weight loss (at least 10% of the body weight), night sweats for a minimum of 3 weeks, symptoms of malaise or weakness for more than 3 months, persistent fever, presence of cough, history of shortness of breath, hemoptysis, and a positive purified protein derivative (PPD) tuberculin test result. Data from the physical examination included temperature on admission (<38.5°C, 38.5°C-39.0°C, or >39.0°C) and the presence of crackles during the chest examination.

The following laboratory data were recorded: the total white blood cell count, serum lactate dehydrogenase level, CD4 cell count, and arterial blood gas values. The alveolar-arterial oxygen gradient was calculated using the alveolar equation, assuming a barometric pressure of 760 mm Hg and a respiratory quotient of 0.8.

Original chest radiographs were reviewed by 2 radiologists (C.H. and J.K.) unaware of the patients' clinical data or tuberculous status. The presence of the following findings were recorded: infiltrates (reticular, nodular, reticulonodular, or miliary patterns), consolidation, cavities, pleural effusion, lymphadenopathy (hilar and mediastinal or paratracheal disease), and fibrotic changes. The chest radiographs were divided into 3 zones: upper (above the third rib posteriorly), middle (between the third and seventh rib posteriorly), and lower (below the seventh rib posteriorly). The extent and location of disease and a final impression of the probability (low, intermediate, or high) of TB were noted.

Finally, we recorded the initial working diagnosis and treatment of the admitting team and the impression of the investigator (blinded to the TB status) collecting the clinical data.

The study design required that each case was matched to a control, creating a 1:1 ratio of patients with and without TB, equivalent to a 50% prevalence of TB. In actuality, a significantly larger number of patients without TB were isolated for each patient with TB. To estimate the actual ratio of patients with TB to the total number of patients isolated during the same period (actual prevalence of the disease), we reviewed the log of all the patients who had a sputum sample submitted to the microbiology laboratory for TB testing (the same log used to identify controls included in the study). All the patients with at least 3 AFB smears and cultures during a 4-month period (January 1, 1997, to April 30, 1997) were identified. The charts of these patients were reviewed to verify the result of the AFB smears and cultures and to determine if they were isolated on admission to the hospital. The actual prevalence of the disease was then calculated as the ratio of patients with TB divided by the total number of patients who were isolated for possible TB but whose results were negative for the disease during the 4-month period.

STATISTICAL ANALYSIS

The mean ± SEM was calculated for each variable. Univariate analysis was performed using the χ^2 test for proportions and the pooled *t* test or Wilcoxon rank sum test (when appropriate) for continuous variables. All variables were used in the stepwise logistic regression analysis (the intercept of the logistic regression analysis was adjusted for the prevalence of TB) to develop a subset of variables that were significant predictors of TB. Sensitivities and specificities were calculated according to standard methods.[22] Likelihood ratios were calculated as the ratio of patients with a given score and disease divided by the number of patients with the same score but without disease,[23,24] together with the 95% confidence intervals (CIs). All analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

tween cases and controls. Five cases had a miliary pattern on chest radiograph, whereas no controls had this pattern ($P = .002$). Three cases (5%) had a normal chest radiograph compared with 6 controls (10%) ($P > .10$). Overall, the findings on the chest radiograph were interpreted as being consistent with TB more often in cases than in controls ($P = .001$).

Multivariate analysis revealed that the presence of chronic symptoms for more than 3 months (significant weight loss, malaise, weakness, and night sweats), TB risk factors (recent immigrant, institutionalization, and history of exposure to TB), shortness of breath, crackles noted during the physical examination, the temperature at admission, history of a positive PPD tuberculin test result, and the finding of upper-zone disease (defined as the presence of any upper-lobe consolidation or diffuse reticulonodular or miliary infiltrates) on the chest radiograph were independent predictors of the presence of TB (**Table 3**).

These clinical and radiographic variables were used to construct a prediction rule for the need for respiratory isolation. A scoring system was developed by assigning points to each predictor according to the magnitude of the association between each of these factors and a culture positive for TB.

Variable	Points
TB risk factors or chronic symptoms	4
Positive PPD tuberculin test result	5
Shortness of breath	−3
Temperature, °C	
<38.5	0
38.5-39.0	3
>39.0	6
Crackles noted during examination	−3
Upper-lobe consolidation	6

A history of chronic symptoms, presence of TB risk factors, history of a positive PPD tuberculin test result, high temperature at admission, and upper-zone disease on chest radiograph were associated with an increased risk of TB. Crackles noted during the examination and shortness of breath were negative predictors of TB and probably represented signs and symptoms of other infectious pneumonias or congestive heart failure. The patients' score was calculated by adding the corresponding points for each

Table 1. Comparison of Clinical and Laboratory Data of Patients With and Without Tuberculosis (TB)

Variable	Patients: With TB (n = 56)	Without TB (n = 56)	P
Demographics			
Age, y, mean ± SEM	40 ± 2	40 ± 2	>.90
Sex, M/F	41/15	41/15	>.90
History and Physical Examination			
TB risk factors, No. (%)	22 (40)	6 (11)	.001
Chronic symptoms, No. (%)	23 (41)	7 (13)	.001
Fever, days before admission, mean ± SEM	18 ± 4	8 ± 3	>.06
Cough, days before admission, mean ± SEM	22 ± 4	9 ± 2	.005
Hemoptysis, No. (%)	8 (14)	5 (10)	>.50
Positive purified protein derivative tuberculin test result, No. (%)	15 (27)	3 (5)	.006
Shortness of breath, No. (%)	19 (35)	39 (70)	.001
Body temperature, °C, mean ± SEM	39 ± 0.1	38.5 ± 0.1	.005
Crackles noted during examination, No. (%)	20 (34)	31 (55)	.02
Laboratory Data			
White blood cell count, $\times 10^3/\mu L$, mean ± SEM	9.2 ± 1.1	7.3 ± 0.7	>.20
Serum lactate dehydrogenase, U/mL, mean ± SEM	364 ± 30	308 ± 19	>.10
Alveolar-arterial oxygen gradient, mm Hg, mean ± SEM	29 ± 3.6	92 ± 30	.03
CD4 cell count/µL, mean ± SEM	150 ± 39	76 ± 21	>.10
Clinical Impression and Treatment			
Admitting diagnosis of TB, No. (%)	36 (65)	21 (38)	.02
Treatment for TB, No. (%)	24 (43)	5 (9)	.001
Reviewer's final diagnosis was TB, No. (%)	27 (48)	4 (7)	.001

Table 2. Assessment of Chest Radiographs*

Finding	No. (%) of Patients: With Tuberculosis (n = 56)	Without Tuberculosis (n = 56)	P
Upper-lobe consolidation	19 (34)	3 (5)	.001
Miliary infiltrate	5 (9)	0 (0)	.02
Reticulonodular infiltrate	8 (15)	3 (5)	>.10
Unilateral pleural effusion	10 (18)	7 (13)	>.40
Adenopathy	15 (26)	11 (20)	>.40
Cavity	11 (20)	6 (10)	>.10
Normal	3 (5)	6 (10)	>.10

Some patients had more than 1 finding.

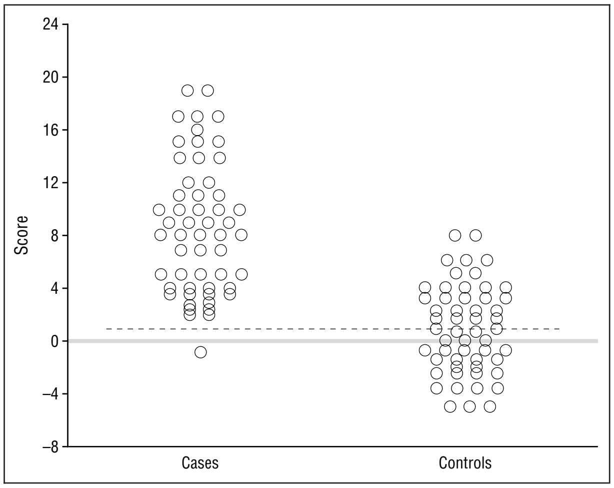
Table 3. Logistic Regression of Predictors of Tuberculosis (TB)*

Variable	Logistic Coefficient	Odds Ratio (95% Confidence Interval)
TB risk factors or chronic symptoms	2.07	7.9 (4.4-24.2)
Positive purified protein derivative tuberculin test result	2.58	13.2 (4.4-40.7)
Shortness of breath	−1.38	0.2 (0.1-0.5)
High temperature	1.05	2.8 (1.1-8.3)
Crackles noted during examination	−1.23	0.3 (0.1-0.5)
Abnormalities on chest radiograph	2.68	14.6 (3.7-57.5)

The TB risk factors and abnormalities on chest radiographs are listed in the "Patients and Methods" section.

of the variables present at admission. The patients' total score ranged from −6 to 21, with higher values associated with a higher risk of TB.

Based on the distribution of the final scores in cases and controls, a score of 1 or higher was chosen to indicate the need for respiratory isolation (98% sensitivity [95% CI, 95%-100%]; 46% specificity [95% CI, 33%-59%]; **Figure**). Using the estimated prevalence of the disease in the hospital (2%), the positive predictive value was 3.3% and the negative predictive value was 99.9%. In this context, only 1 patient with a culture positive for TB would not be isolated if the prediction rule were applied to the group of patients included in the study. All patients with a score of 10 or higher had TB. Likelihood ratios were calculated for scores of 1, 2, 4, and 8 (**Table 4**). A score less than 1 suggested a very low probability that a patient had TB. In contrast, in patients with scores of 2, 4, and 8, the estimated probabilities of the disease were .69, .85, and .93, respectively, given a .50 pretest probability of active TB.



Distribution of final score for patients with tuberculosis (TB) (cases) and without TB (controls). Each patient's score was obtained by adding the points assigned to each of the predictive variables present at admission to the hospital as described in the "Patients and Methods" section. The dashed line indicates the minimum score (1) chosen as a cutoff for the decision to isolate a patient.

COMMENT

The results of this study show that among adult patients with suspected active pulmonary TB, those with very low risk of the disease could be discriminated from those with a higher risk of TB based on data immediately available from the medical history, physical examination, and chest radiograph obtained in the emergency department. Because effective respiratory isolation has been shown to reduce nosocomial transmission of TB,[25-27] this measure should be used to protect other patients and heath care personnel. All patients admitted to the hospital could be isolated until a defined number of smears are negative for AFB; however, such a policy is impractical and expensive. Although current Centers for Disease Control and Prevention guidelines recommend the isolation of all patients with suspected pulmonary TB, this group of patients is difficult to identify.[1,9,26,28] Furthermore, the low prevalence of TB among patients isolated for suspected TB supports the concept that the present guidelines create a pattern of overisolation that could be at least partially corrected if patients requiring isolation could be more easily identified.[10,19] In this context, the use of the prediction rule derived in this study could allow for an effective identification of patients with TB, thereby decreasing the frequency of unnecessary isolation and significantly reducing the costs of hospitalization.

Given that approximately 54 patients without TB were isolated for each patient with TB in our institution, there were approximately 3000 episodes of isolation from December 1, 1991, to January 31, 1997. Because it is routine hospital practice to isolate and test (using the criterion standard, sputum culture) every patient considered at risk for TB, verification bias did not significantly affect the mix of patients included in the present study.[29] If the prediction rule had been applied in these patients, 1400 patients would not have been unnecessarily isolated. Although 1 of the 56 patients with TB would have been misclassified, 32% of all patients with TB between December 1, 1991, and January 31, 1997, were not isolated at some point during their stay in the hospital. Among these, in 15 patients with TB, respiratory isolation was discontinued because of smears negative for AFB (1 patient was sent home without treatment). Of these 15 patients, 3 had a score higher than 10 (associated with a very high risk of TB); therefore, by knowing the patient's score, further diagnostic tests could have been performed before isolation was discontinued.

One of the advantages of this prediction rule is that the information required to determine each patient's score is readily available from the information obtained at admission (eg, medical history and physical examination and chest radiographic findings), so it can be applied with no additional cost. The rule can also be used in patients with human immunodeficiency virus and/or acquired immunodeficiency syndrome. Some of the factors found to be predictors of a culture positive for TB, including a history of a positive PPD tuberculin test result, the presence of TB risk factors, the temperature at admission, and upper-lobe infiltrates on the chest radiograph, have been shown to be associated with TB in other studies,[12,30-32] which were undertaken to determine the risk factors for the disease.

This rule was designed to be applied in patients already considered to be at risk of pulmonary TB by the admitting physician. This distinction may explain why some of the classic symptoms (chronic cough or hemoptysis) or chest radiographic findings (upper-lobe cavities) of TB were not found more frequently in cases than in controls. They were probably considered initially at the time it was determined if a patient was at risk of the disease, and therefore, they were equally present in cases and controls.

Table 4. Posttest Probabilities of Tuberculosis for Varying Pretest Probabilities and Prediction Rule Scores

Score	Likelihood Ratio	Pretest Probability*				
		.20	.40	.50	.60	.80
1	0.03	.10	.03	.03	.06	.13
2	2.30	.37	.61	.69	.78	.90
4	5.70	.59	.79	.85	.90	.96
8	15.50	.79	.91	.93	.96	.98

*The prevalence of tuberculosis in the study population was estimated to be 0.02 (see the "Patients and Methods" section).

Race is also known to affect the susceptibility of infection with TB. As shown by Stead et al,[33] black individuals were almost twice as likely as white individuals to become infected with TB as a result of an exposure to an infectious source. In addition, in black patients, the smears were more often positive for AFB; thus, black patients were potentially more infectious than their white counterparts. Although race did not appear to be a predictor of TB in multivariate analysis, the effect of race in the prediction rule should be explored further in the future.

As an alternative strategy to the prediction rule in the present study, a decision tree can be used for the prediction of active pulmonary TB.[31] The reported sensitivity, specificity, and positive predictive value of this strategy are similar to the presently derived rule. However, a tree design, because of its dichotomous nature, has less discriminative power than a prediction rule with multiple likelihood ratios.[24] In this context, the availability of a final probability of disease may provide the admitting physician with a better instrument than a simple answer of isolate or do not isolate.

Our study has some methodological limitations. Because cases and controls were matched for age and sex, potential differences in these 2 important variables could not be assessed. The information was obtained retrospectively from chart review and probably was not as complete and accurate as when data collection is done prospectively. However, blinded assessment of the predictors and outcomes should have avoided significant review bias.[34,35] Furthermore, we reviewed the original chest radiographs, and the temperature obtained at admission was most likely accurately recorded in the charts.

Before clinical implementation, the rule has to be prospectively validated in a different group of patients in a different setting to assess the reproducibility of the rule's predictive capability. The impact of clinical use of the rule should also be measured by comparing outcomes of patients treated according to the rule with outcomes of patients isolated according to the current guidelines. If validated by other studies in a prospective fashion, the current prediction rule could be used to identify patients at high risk for TB who require respiratory isolation, thus decreasing hospital costs without increasing the risk of nosocomial transmission of TB.

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