MAJOR ARTICLE

Evaluation of Clinical Prediction Rules for Respiratory Isolation of Inpatients with Suspected Pulmonary Tuberculosis

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Background. In the framework of hospital infection control, various clinical prediction rules (CPRs) for respiratory isolation of patients with suspected pulmonary tuberculosis (PTB) have been developed. Our aim was to evaluate their performance in an emergency department setting with a high prevalence of PTB.

Methods. We searched the MEDLINE and OVID databases to identify CPRs to predict PTB. We used a previously collected database containing clinical, radiographical, and microbiological information on patients attending an emergency department with respiratory complaints, and we applied each CPR to every patient and compared the result with culture for *Mycobacterium tuberculosis* as the reference standard. We also simulated the proportion of isolated suspects and missed cases for PTB prevalences of 5% and 30%.

Results. We withheld 13 CPRs for evaluation. We had complete data on 345 patients. Most CPRs achieved a high sensitivity but very low specificity and very low positive predictive value. Mylotte's score, which includes results of sputum smear as a predictive finding, was the best-performing CPR. It attained a sensitivity of 88.9% and a specificity of 63.9%. However, at a 30% PTB prevalence, 498 of 1000 individuals with suspected PTB would have to be isolated; 267 of these cases would be true PTB cases, and 33 cases would be missed. Two consecutive sputum smears had a sensitivity of 75.6% and a specificity of 99.7%.

Conclusions. In a setting with a high prevalence of PTB, only 1 of the 13 assessed CPRs demonstrated high sensitivity combined with satisfactory specificity. Our results highlight the need for local validation of CPRs before their application.

BACKGROUND

Various nosocomial outbreaks of drug-susceptible and drug-resistant tuberculosis have been described in personnel and patients in health care settings that were attributable to the failure to correctly identify and isolate subjects with active pulmonary tuberculosis (PTB) [1,2]. Prompt identification and accurate isolation of patients with potentially infectious tuberculosis (TB) is a key component of nosocomial infection control measures [3]. Unfortunately, this is not always adhered to in emergency departments, particularly in low-income countries, because of the high inflow of patients, lack of diagnostic awareness, laboratory limitations, shortage of isolation rooms, and, most of all, the nonexistence of feasible, cost-effective isolation policies [4, 5].

According to recommendations from the Centers for Disease Control and Prevention, a patient presenting to a health facility who has clinical symptoms that are compatible with PTB should be isolated until 3 consecutive sputum smears have negative results [3]. However, the "clinical symptoms" are not well defined and leave room for interpretation. Additionally, in most resource-constrained settings with moderate to high PTB prevalence, the application of this recommendation would lead to overcrowding of isolation rooms. The decision to isolate a patient with clinically suspected PTB is thus frequently based on clinicians' widely

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variable criteria or, in the best scenario, on the result of 1 or 2 sputum smear examinations. Both alternatives have serious limitations [6, 7].

Prognostic models provide objective estimates of outcome probabilities to complement clinical intuition and guidelines and can be used in many ways, in particular as Clinical Prediction Rules (CPRs) [8]. The validity of signs and symptoms to predict PTB has been widely addressed, and several CPRs have been developed to assist clinicians in the decision to isolate patients suspected of having PTB. They could possibly be applied in emergency department settings, but formal external validation is required as a previous step to the assessment of their potential impact [9]. The objective of this study was to evaluate the performance of the existing clinical prediction rules for PTB in patients attending hospital emergency departments in Lima, Peru.

METHODS

Identification of CPRs

To identify the existing CPRs for PTB prediction, we searched the MEDLINE and OVID databases using the key word "tuberculosis" combined with each of the following: "emergency room," "emergency department," "prediction," "isolation," "decision," "score," and "clinical prediction rule." The search was limited to material published in English, French, Spanish, and Portuguese from January 1980 through September 2009. We screened the abstracts of the retrieved papers and withheld all publications that dealt with CPRs in adults. Additionally, we retrieved the abstracts of their "related articles" in MEDLINE and of the references that they cited, and we screened those in the same way. Subsequently, we studied the full text of all selected articles and excluded papers that were not CPRs for PTB, were not based on original data, or which presented CPRs designed for a specific subpopulation, such as smear-negative individuals with suspected PTB, people living with human immunodeficiency virus (HIV) infection or AIDS, or prison inmates. Finally, we excluded CPRs in complex formats (eg, computer-dependent systems).

Dataset for the Assessment of CPRs

We used the dataset from a study designed to derive a local CPR for PTB [10]. It contains data on 345 adult patients who were recruited from August 2002 through August 2003 in the Emergency Department of Cayetano Heredia Hospital. This university-affiliated, tertiary level hospital is situated in Lima, Peru, which is a city with an incidence of tuberculosis of 150 cases per 100,000 population and a low prevalence of HIV infection (<1%). Patients were included on the basis of having symptoms suggestive of PTB, as follows: productive cough for 1 week or more; or hemoptysis; or constitutional symptoms (temperature >38°C for 3 days or more, weight loss of 3 kg or more, or night sweats for at least 3 days) or suspicion of PTB by the attending physician. Patients younger than 18 years of age or already receiving PTB treatment were excluded from the study. Full demographic, clinical, and radiographic data are available, as well as microbiological results, including 2 sputum smears for acid-fast bacilli (AFB) and culture in Ogawa medium, which was taken as a reference standard for diagnosis of tuberculosis [11]. The tuberculin test (purified protein derivative [PPD]; Mantoux test), which is a predictive finding used by some CPRs was not performed at hospital admission because of the amount of time needed for obtaining the result (48–72 h), but the history of a previous result (also used in some CPRs) was taken. The protocol of the study that generated the dataset was revised and approved by the Ethics Committee of Hospital Cayetano Heredia (Lima, Peru).

Data Analysis

Analysis was done with SPSS software, version 11 (SPSS, Chicago, IL, USA). We applied each of the identified CPRs to every PTB suspect included in the dataset to obtain a prediction of PTB (Yes/No) in that subject. In the CPRs that included the result of a PPD performed at hospital admission as a predictive finding, we recorded the value as "missing." We then compared the results obtained using each CPR with our reference standard (the sputum culture) and calculated the respective sensitivities and specificities. The CPRs in the format of a score were evaluated at the cutoff point proposed in the original publication, but we also calculated their area under the receiver-operating characteristic (ROC) curve. To calculate simulate the potential effect of the use of the various CPRs in different settings, we simulated 2 scenarios (a prevalence of PTB among suspects of 5% and of 30%) and determined the positive and negative predictive values for the CPRs as well as the total number of subjects to be isolated per 1000 individuals with suspected PTB and the number of patients with PTB who would be missed.

RESULTS

Initially, our research retrieved 1072 articles. Of these, 28 articles dealt with CPRs that were related to TB in adults. We excluded 3 articles that analyzed predictive findings for PTB but that, in the end, did not derive a prediction/decision tool [12–14]; 1 study that was a score for the prediction of clinical evolution during treatment [15]; 1 score that presented the same data as that presented in an earlier study [16]; and a review article [17]. We further excluded 1 article that presented the validation of a previously published CPR [18], 6 articles that dealt with specific subpopulations (people living with HIV/AIDS [19, 20]; individuals with smear-negative PTB [21–23]; and prison inmates [24, 25]), 1 article that reported a neural network [26],

Table 1. Predictive Findings Included in CPR for PTB

Clinical prediction rule	Country, year	Age/ institution alization	Previous contact/ previous history of PTB	Immigration/ race	Homeless/ intravenous drug use/ MSM	Incarceration/ history of incarceration	Prophylaxis with H/BCG immunization	History of positive PPD	HIV status/ immunosuppression	Weight loss	Fever	Cough	Night sweats/ abnormal sweating	Hemoptysis	Sputum production
Aguilar et al [28][a]	US, 2009	●	●	●				●	●	●			●		●
Moran et al [29]	US, 2009		●	●	●	●		●		●					
Wang et al [30]	Taiwan, 2008	●									●				
Rakoczy et al [31]	US, 2008			●					●	●	●		●		
Tessema et al [32]	Ethiopia, 2001									●	●	●	●	●	
Wisnivesky et al [33]	US, 2000	●	●	●				●		●	●		●		
Tattevin et al [34]	France, 1999			●	●		●		●	●	●	●	●	●	●
Gaeta et al [35]	US, 1997		●		●			●	●					●	
Mylotte et al [36]	US, 1997	●								●					
El-Solh et al [37]	US, 1997									●	●				
Pegues et al [38]	US, 1998		●	●	●	●			●	●	●	●		●	●
Redd et al [39]	US, 1996		●		●			●			●				
Bock et al [40]	US, 1996		●				●	●							
No. of CPRs using the variable		4	7	6	5	2	2	7	5	9	8	3	5	4	3

Clinical prediction rule	Country, year	Chest pain	Dyspnea	Crackles	Hyporexia, weakness, malaise	Upper lobe infiltrate	Cavity	Miliary pattern	Athelectasis/ Pleural effusion	Consolidation, other abnormality	Sputum smear for Acid Fast Bacilli	ppd result	CD4+ CELL count/ Anergy panel	White Blood Cell count	Number of predictive findings in CPR
Aguilar et al [28][a]	US, 2009				●	●						●		●	12
Moran et al [29]	US, 2009					●	●								8
Wang et al [30]	Taiwan, 2008					●	●			●					5
Rakoczy et al [31]	US, 2008		●		●	●									8

Table 1. (*Continued*)

Clinical prediction rule	Country, year	Age/ institution alization	Previous contact/ previous history of PTB	Immigration/ race	Homeless/ intravenous drug use/ MSM	Incarceration/ history of incarceration	Prophylaxis with H/BCG immunization	History of positive PPD	HIV status/ immunosuppression	Weight loss	Fever	Cough	Night sweats/ abnormal sweating	Hemoptysis	Sputum production
Tessema et al [32]	Ethiopia, 2001	●	●		●	●	●	●							11
Wisnivesky et al [33]	US, 2000		●	●	●	●		●							12
Tattevin et al [34]	France, 1999				●	●	●	●	●	●					16
Gaeta et al [35]	US, 1997					●	●					●			8
Mylotte et al [36]	US, 1997								●	●	●				5
El-Solh et al [37]	US, 1997					●							●		4
Pegues et al [38]	US, 1998		●				●			●	●				14
Redd et al [39]	US, 1996					●	●	●	●	●					9
Bock et al [40]	US, 1996					●	●								5
No.of CPRs using the variable		1	4	1	5	11	8	4	3	5	2	2	1	1	

NOTE. BCG, bacillus Calmette-Guérin; CPR, clinical prediction rule; HIV, human immunodeficiency virus; MSM, men who have sex with men; PPD, purified protein derivative; PPV, positive predictive value; PTB, pulmonary tuberculosis.

[a] Only the subanalysis without computed tomography.

and an automated clinical decision support system [27]. Thus, we retained 13 CPRs for evaluation [28–40].

The predictive variables of these CPRs are shown in Table 1. All CPRs are composed of radiographic as well as clinical parameters, and all but 1 CPR included sociodemographic risk factors. Mylotte's and Pegue's scores are the only 2 CPRs that take into account the result of sputum smear examination. The number of predictor variables used ranges from 4 through 16, and variables such as weight loss, upper lobe infiltrate visible on a chest radiograph, cavity visible on a chest radiograph, and fever are the most common ones. All of the CPRs but one were derived for the purpose of isolation of individuals with suspected TB. Only Tessema's score [32] was constructed as a diagnostic tool for treatment initiation, and it was the only one derived in a high-prevalence setting.

Of the 345 subjects in our dataset, 112 (32.4%) had PTB. Age <35 years, no PTB history, weight loss, miliary pattern, cavity and upper lobe infiltrate visible on a chest radiograph were associated with PTB [10]. The sensitivity and specificity of 2 consecutive sputum smears was 75.7% and 99.7%, respectively. The sensitivity, specificity, and likelihood ratios of each CPR for identifying PTB among our suspects are shown in Table 2. For the CPRs that are scores, the ROC curves and areas under the curves of the 4 CPRs that performed the best are presented in Figure 1. Most CPRs achieved a high sensitivity, but all had low to very low specificity, except for Tessema's score, which had a high specificity at the expense of a low sensitivity. It is also of note that, in general, the sensitivities and specificities published in the original articles were much higher than the ones attained for our patients. On average, we found a difference of –9.6% (range, −22.0% to 53.4%) for sensitivity and of –21.3% (range, −11.4% to 46.8%) for specificity. The exception, with respect to sensitivity, was Pegues's CPR. The CPR with the highest area under the ROC curve (AUC) was Mylotte's score (AUC, 0.91; 95% confidence interval, 0.87–0.95).

Table 2. Sensitivities, Specificities, and Likelihood Ratios of Existing Clinical prediction rules for Pulmonary Tuberculosis in Lima, Peru

Clinical prediction rule	Sensitivity, %	Specificity, %	Positive likelihood ratio	Negative likelihood ratio
Aguilar et al [28]	85.3	27.1	1.17	0.54
Moran et al [29]	98.2	19.5	1.22	0.09
Wang et al [30]	38.5	85.2	2.60	0.72
Rakoczy et al[31]	86.2	22.9	1.12	0.60
Tessema et al [32]	44.0	69.9	1.46	0.80
Wisnivesky et al [33]	92.7	19.5	1.15	0.38
Tattevin et al [34]	91.7	23.3	1.20	0.35
Gaeta et al [35]	89.9	38.1	1.45	0.26
Mylotte et al [36]	89.0	68.6	2.84	0.16
El-Solh et al [37]	79.8	51.3	1.64	0.39
Pegues et al [38]	89.9	17.4	1.09	0.58
Redd et al [39]	58.7	67.8	1.82	0.61
Bock et al [40]	84.4	41.9	1.45	0.37

Table 3 shows the positive predictive value (PPV) and negative predictive value (NPV) in the hypothetical scenarios of 5% and 30% PTB prevalence. As a whole, the NPVs that were attained were good to excellent. However, the PPVs were extremely low in the 5% prevalence scenario and low in the 30% prevalence scenario, in which only Wang's and Mylotte's rules surpassed 50% PPV. Using Mylotte's CPR, which was the best-performing CPR, in the 5% scenario would lead to isolation of

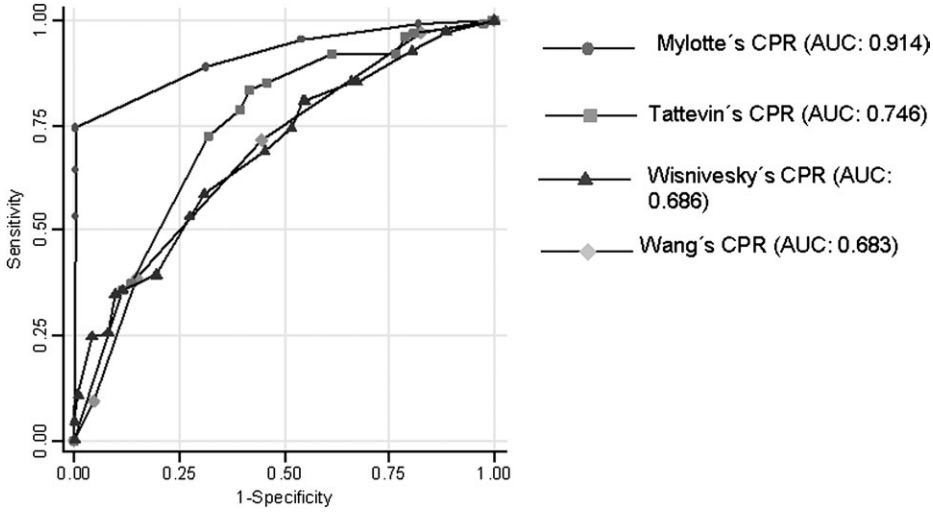

Figure 1. Receiver Operating Characteristic (ROC) curves for the best performing Clinical Prediction Rules (CPR) in the format of scores. AUC: Area Under the Curve

Table 3. Predictive Values and Theoretical Implications of Using the CPRs according to 2 PTB Prevalence Scenarios

	5% Prevalence of PTB among suspected cases				30% Prevalence of PTB among suspected cases			
CPR	PPV	NPV	No. of subjects isolated/ 1000 suspected cases	No. of PTB cases missed/ 1000 suspected cases	PPV	NPV	No. of subjects isolated/ 1000 suspected cases	No. of PTB cases missed/ 1000 suspected cases
Aguilar et al [28]	5.8	97.2	735	7	33.4	81.20	766	44
Moran et al [29]	6.0	99.5	814	1	34.3	96.1	858	6
Wanget al [30]	12.0	96.3	160	31	52.7	76.4	219	184
Rakoczy et al [31]	5.6	96.9	776	7	32.4	79.5	799	41
Tessema et al [32]	7.2	96.0	308	28	38.5	74.5	343	168
Wisnivesky et al [33]	5.7	98.1	811	4	33.0	86.1	842	22
Tattevin et al [34]	5.9	98.2	774	4	33.9	86.8	812	25
Gaeta et al [35]	7.1	98.6	633	5	38.4	89.8	703	30
Mylotte et al [36]	13.0	99.2	342	6	54.9	93.6	486	33
El-Solh et al [37]	7.9	98.0	503	10	41.2	85.6	581	61
Pegues et al [38]	5.4	97.0	830	5	31.8	80.1	848	30
Redd et al [39]	8.8	96.9	335	21	43.9	79.3	402	124
Bock et al [40]	7.1	98.1	594	8	38.4	86.3	660	47

NOTE. CPR, clinical prediction rule; NPV, posterior probability using the negative likelihood ratio; PPV, posterior probability using the positive likelihood ratio; PTB, pulmonary tuberculosis.

342 patients per 1000 individuals with suspected PTB, which would capture 44 patients with true PTB but would miss 6 patients. In the 30% scenario, which was a prevalence quite similar to the one in our setting, application of this CPR would result in a decision to isolate 486 of 1000 individuals with suspected PTB, which would capture 267 patients with true PTB but would miss 33 patients. In our dataset, such patients with false-negative cases had clinical and radiographic characteristics that were similar to those for the individuals with correctly identified PTB, except for a high frequency of hemoptysis, which is associated with negative sputum smear results. In the 30% scenario, Moran's CPR is the only CPR that would miss only a few patients with true PTB (6 patients), but 858 of 1000 individuals with suspected PTB would have to be isolated.

CPRs based on clinical and radiographic parameters alone (ie, those not including sputum smear results) were generally less accurate. However, in the 5% prevalence scenario, Tattevin's and Gaeta's CPR would still reduce the number of patients to be isolated without substantially increasing the number of PTB cases missed.

The data in Table 3 could be compared with what can be achieved on the basis of the results of 2 consecutive sputum smears alone: isolating 38 and 227 patients in the 5% and 30% prevalence scenarios, respectively, but missing 12 and 73 PTB cases, respectively.

DISCUSSION

We found an important number of published CPRs for respiratory isolation of individuals with suspected PTB, although many of them were not labeled as CPRs by their authors. This relative abundance responds to the need for optimization of respiratory isolation procedures, given the imperative of infection control, on the one hand, and the high costs of isolation, on the other hand.

Some predictive variables are common to many CPRs (in particular, the presence of an apical infiltrate or cavity visible on a chest radiograph, weight loss, and fever), whereas others that are rarely encountered (eg, duration of cough, bacillus Calmette-Guérin vaccination, and the result of PPD testing at hospital admission) are probably more specific to a given context. In our set of individuals with suspected PTB, most CPRs achieved quite high sensitivities and NPVs, but all had low specificities and PPVs. This reflects that, in developing them, the implications of missing infectious patients were deemed to be serious [41], but it also reflects that they were derived in settings where the resources needed for isolating inpatients were not heavily constrained. Still, it may be surprising that Mylotte's [36] and Moran's [29] scores are the only ones with negative likelihood ratios below 0.2, which is the threshold for giving strong diagnostic evidence [42], and that these are the only CPRs that provide clear support for a decision not to isolate an individual with suspected PTB. Furthermore, the CPRs show decreased

performance, compared with the original derivation setting. This could be expected, because the external validity of CPRs is always a problem, and they absolutely need local validation prior to application [43].

This study is unique in attempting to evaluate as many existing CPRs for respiratory isolation of individuals with suspected PTB as possible. A previous review [17] has described the characteristics of some of the CPRs included here, but without assessing their external validity. Additionally, we simulate the potential effect of the application of these CPRs in a high-prevalence, resource-constrained setting, where they could find their greatest usefulness. Still, some limitations of our study must be kept in mind. In the first place, there is increasing evidence that liquid culture media are somewhat more sensitive than solid culture media for the diagnosis of TB [44], and we may have missed a few PTB cases. However, given the marginal difference between the yields obtained with both techniques, this could not meaningfully change our conclusions.

Second, we did not perform PPD testing. This test should probably not be included as a predictive finding in CPRs, given the amount of time needed (48–72 h) to obtain the result, which precludes prompt decision making. Notwithstanding this fact, 2 CPRs make use of PPD testing. However, Gaeta [35] only relies on PPD when all other predictive findings are negative. The patient is then tested but is not isolated until the result becomes available. Hence, the PPD result does little to determine the overall performance of this CPR. In Aguilar's score [28], missing values are, in practice, equivalent to negative findings, and as the authors point out, having a history of a positive PPD result is more relevant than having the actual test performed, so the lack of PPD at hospital admission in our dataset should not have affected the validity of the sensitivity and specificity that we calculated for this CPR. Interferon gamma release assays (IGRAs) might solve the problem of PPD timeliness and their potential usefulness for isolation decisions merits additional study. However, IGRAs are not an option in resource-poor settings.

Only Mylotte's CPR [36] performs acceptably well in our context. It includes the result of sputum smears as a predictive finding. Tattevin's [34] CPR is the best performer among the 11 CPRs that do not include sputum smears, which makes them more suitable for health care facilities in which smear results are not readily available. It includes cough as a predictive variable and has a high sensitivity but a low specificity. Because transmission from smear-negative patients can be considerable [45, 46], good sensitivity, compared with that of culture, is a must. The priority is to minimize non-isolation of patients with infectious TB. However, the unnecessary isolation of high numbers of patients with false-positive results should also be avoided. The latter seems particularly difficult to achieve without including smear results in the CPR. Nucleic acid amplification techniques for *Mycobacterium tuberculosis,* which seem to be promising [47], could constitute an alternative, but they still have a prohibitive cost for many settings.

When we simulated the potential effect of applying the 13 CPRs, we found that Mylotte's [36] and Tattevin's [37] were, indeed, the most interesting ones. In the 5% prevalence scenario, they save resources while missing few PTB cases. In the 30% prevalence scenario, however, a quite significant number of PTB patients are missed. Notwithstanding this fact, in high-prevalence settings with no isolation policy, limited resources, and constrained isolation space, decision-makers could still consider their use. Additionally, introduction of CPRs would be beneficial because it leads to the standardization of processes [48].

Nosocomial transmission of PTB is a public health problem, and its importance will increase with the epidemics of multidrug-resistant and extensively drug-resistant infections, so any tool that can reduce TB transmission in health care settings must be disseminated. Medicine today has a strong tendency to substitute clinical judgment for the results of laboratory tests, but every effort to find the accurate weight that each should have for solving a medical problem is mandatory in order to achieve the best decision making. In this case, it is a clinical prediction rule that includes the results of sputum smear which leads to the best decisions. Mylotte's CPR for TB prediction [36] attains good performance for decision-making regarding respiratory isolation in hospitals in Peru, but many clinicians and public health officers are not familiar with prediction models and may be reluctant to use them until they have been properly tested in their own setting. This study illustrates that external validation is indeed a necessary step before implementation, as has been argued before [49]. Additional validation and implementation studies of the CPRs that we have identified are needed, in different kinds of hospitals and in different epidemiological settings. Eventually, formal cost-effectiveness analysis should assess their economic benefit, and impact analysis should provide evidence of their genuine usefulness.

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