ORIGINAL ARTICLE

Systematic Review With Meta-Analyses and Critical Appraisal of Clinical Prediction Rules for Pulmonary Tuberculosis in Hospitals

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OBJECTIVE. To systematically review studies evaluating clinical prediction rules (CPRs) for adult inpatients suspected to have pulmonary tuberculosis.

DESIGN. Systematic review with meta-analyses.

SETTING. Hospitals.

PATIENTS. Inpatients at least 15 years of age admitted to acute care.

METHODS. A search was conducted in 5 indexed electronic databases with no language or year of publication restrictions. We performed a meta-analysis for those CPRs with at least 2 validation studies. Results were reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

RESULTS. Of the 461 abstracts selected, 36 articles were fully analyzed and 11 articles were included, yielding 8 CPRs derived in 4 countries. Broad validation studies were identified for 2 CPRs. The most frequent clinical predictors were fever and weight loss. All CPRs included chest imaging signs. Most CPRs were derived in countries with a low prevalence of pulmonary tuberculosis and included homeless, immigrants, and those who reacted to the purified protein derivative test. Both of the CPRs derived in countries with a high prevalence of pulmonary tuberculosis strongly relied on chest radiograph predictors. Accuracy of the different CPRs was high (area under receiver operating characteristic curve, 0.79–0.91). Meta-analysis of 4 validation studies for Wisnivesky´s CPR indicates optimistic pooled results: sensitivity, 94.1% (95% CI, 89.7%–96.7%); negative likelihood ratio, 0.22 (95% CI, 0.12–0.40).

CONCLUSION. On the basis of a critical appraisal of the 2 best validated CPRs, the presence of weight loss and/or fever in inpatients warrants obtaining a chest radiograph, regardless of the presence of productive cough. If the chest radiograph is abnormal, the patient should be placed in isolation until more specific test results are available. Validation in different settings is required to maximize external generalization of existing CPRs.

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INTRODUCTION

Although tuberculosis (TB) seems to be decreasing worldwide, a large proportion of cases is occurring in adults with comorbidities.[1] AIDS, neoplasms, diabetes mellitus, transplantation, chronic renal diseases, connective tissue diseases, and immunosuppression are risk factors for the occurrence of the disease, including the more severe clinical forms where diagnosis is difficult and may require hospitalization.[2] In addition, progressive aging of the population[3,4] and the advent of mycobacterial resistance have increased the need for complex health services.

Delay in pulmonary tuberculosis (PTB) diagnosis can result in increased patient morbidity and in-hospital disease transmission, especially among healthcare workers.[5] Patients with active PTB are the major source of disease transmission. Because institutional risk seems to be related to patients care indicators[6] and location,[7] prompt identification and isolation of patients with active PTB are imperative.

The diversity of clinical presentations, decrease in patients with evident symptoms, and increase in patients with atypical radiologic patterns hinder early detection.[3,6,8] In these contexts, bacillary load is usually lower,[9] making it

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difficult to use microbiologic examination as a single screening criterion.

Depending on the method used, smear microscopy can accurately detect 25% to 65% of cases. Patients with negative smear results and positive culture results are therefore frequent and, although being less efficient transmitters of the PTB, may cause up to 17% of new cases of PTB.[10]

Mycobacterium tuberculosis culture, the diagnostic reference standard, can take up to 42 (Mycobacteria Growth Indicator Tube [BD]) or 60 (Lowestein Jensen medium) days to provide final results. Thus, rapid and high-sensitivity molecular laboratory tests have been increasingly gaining importance as diagnostic tools. The test currently recommended by the World Health Organization, Xpert MTB / RIF, allows rapid detection of up to 99% of smear-positive and 67% of smear-negative culture-confirmed TB cases.[11] Nevertheless, there are constraints related to its widespread use in low- and middle-income countries on account of cost and test logistics. Implementation requires identifying target groups and defining diagnostic algorithms.

Independent of the healthcare setting, request of specific tests for TB will always rely on clinical suspicion.[12] Clinical prediction rules (CPRs) quantify the contributions of several components of the clinical-epidemiologic history, physical examination, and basic laboratory tests to diagnosis, providing stratification algorithms[13] and generating scores with cut-offs indicative of risk of having the disease. The World Health Organization[1] currently recommends the use of algorithms for systematic screening of active TB in priority groups, specifically those with conditions that are risk factors for the disease, but makes no special recommendations for in-hospital screening.

Wisnivesky et al[14] and Solari et al[15] reported that CPRs for PTB diagnosis have greater sensitivity than direct microbiologic examination of sputum smear alone. A positive screening by a CPR could guide the request of both simple (eg, chest radiograph) and more complex tests (eg, molecular biology tests) and optimize the use of respiratory isolation rooms.

The development and application of a CPR involves a 4-step method using prospective, blind designs for accuracy and cost-effectiveness studies[16,17]: (1) derivation (definition of the most important predictors in a specific population); (2) external validation in similar populations (temporal or narrow validation) or different populations (broad or geographical validation)[18]; (3) the assessment of its impact on the physician's behavior or patient outcome, to determine its ability to accurately define the targeted disease, reduce costs, and improve care; and (4) actual dissemination of the CPR in daily practice to guide health professionals with disease management, which is optimized with simpler rules.[13,19]

Several studies have been conducted to derive and/or validate CPRs for the diagnosis of active PTB in outpatient,[20] emergency care,[21,22] and inpatient[23–30] settings. However, the CPR's performance can vary with healthcare setting,[7] warranting the specific assessment of CPRs for inpatient diagnosis of PTB.

CPRs for PTB diagnosis in adults reported in the literature have varied regarding predictors, accuracy, and epidemiologic contexts.[20,27] We aimed to summarize studies of CPRs for active PTB in adult patients (at least 15 years old) admitted to general hospitals, identify level of evidence (derivation or validation), and compare their accuracy and predictors, highlighting implications for practice and further research.

METHOD

This is a systematic review of CPRs in adult patients admitted to acute care hospitals. Procedures adopted and results reported follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[31]

The search was conducted in indexed databases PubMed-MEDLINE, Scopus, Web of Knowledge, Latin-American and Caribbean Center on Health Sciences Information, and EMBASE, and by using the "alert" resource to keep the search updated. The Zotero Standalone software, version 3.0.3 for Windows, was used for searching and storage of references. A librarian experienced in conducting systematics reviews (M.F.M.M.) developed the search strategies.

Keywords were combined according to the proper syntax of each base and included the following expressions: "inpatient"; "hospitalization"; "predict"; "sensitivity and specificity"; "tuberculosis pulmonary"; "mycobacterium tuberculosis"; and "TB". The search strategy at PubMed was "((Inpatient* [Title/Abstract]) OR hospitalization [Title/Abstract]) AND ((("predictive value of tests"[MeSH Terms]) OR predict* [Title/Abstract]) OR sensitivity and specificity [MeSH Terms]) AND (("tuberculosis, pulmonary"[MeSH Terms]) OR "mycobacterium tuberculosis/isolation and purification"[MeSH Terms])". There was no restriction regarding language and publication date and studies up to January 2013 were included.

Three pairs of reviewers (B.D.G.-S.R.L.P., B.D.G.-F.C.Q.M., and B.D.G.-C.A.F.A.) read and selected the abstracts and full texts independently and blind to authorship and journal. In case of discrepancies between the members of any pair, one member of the other 2 pairs gave an opinion. A data extraction sheet was developed and piloted, including characteristics of the studies, clinical and laboratorial predictors, cutoffs for the score, and accuracy parameters used. We also reviewed cross-references and alerts of the indexed databases.

The eligibility criteria were as follows: articles including patients in general care hospitals, aged at least 15 years and assessed regarding signs and symptoms as well as laboratory and imaging tests; articles aimed at defining CPRs (combination of 2 or more clinical, laboratory, or radiologic predictors) for active PTB diagnosis and using positive culture results for *M. tuberculosis* as the reference standard. Cross-sectional, cohort, or case-control studies were included as long as their accuracy measures were stated. Articles with the following characteristics were excluded: those having no parameters for comparison with other rules (ie, neural networks or decision tree); studies focusing on specific populations (ie, homeless, elderly, prisoners, or pneumonia or AIDS patients); and studies restricted to assessing cases with negative microbiologic

examination; studies of isolated inpatients; as well as studies aiming to compare TB patients having positive versus negative smear results.

We used the following criteria from Standards for Reporting of Diagnostic Accuracy to evaluate methodologic quality of the articles: prospective design, with consecutive or randomized selection of the population included and masking to the result of the reference test. Criteria employed aimed to avoid possible biases and confounders.[30] Accuracy results of the derivation and validation studies for the same CPR are shown as long as populations were different. However, because the predictors were the same, each rule was considered only once. Accuracy parameters included were sensitivity, specificity, and the area under the receiver operating characteristic curve, which allows assessment of sensitivity and specificity variation of different cutoff values for the result. Positive likelihood ratios (LRs) (true-positive rate / false-positive rate) were estimated by us for all CPRs on the basis of data provided in the original studies. The larger the positive LR, the greater the likelihood of disease. Positive LR values between 5 and 10 indicate moderate and greater than 10 indicates strong increases in posttest probability of disease. Negative likelihood ratio is given by the probability of a negative test result in those with disease, compared with the probability of a negative test result in those without disease. Thus, the smaller the negative LR, the greater the likelihood of disease.

We also performed a meta-analysis using WinPepi[32] version 11.29 for those CPRs with at least 2 validation studies. We compared studies with respect to test performance: sensitivity, specificity, LR of positive and negative test results, and diagnostic odds ratio. We inspected the forest plot for visual appraisal of heterogeneity and considering test I-squared greater than 0.70 as statistical heterogeneity. Overall pooled and Dersimonian-Laird (random effects) estimates values of the measures of test performance were computed.

RESULTS

Selection and Characteristics of the Studies Included

The search yielded 461 registries, of which 438 were found in electronic databases, 19 by use of cross-references, and 4 by the alert system of indexed databases. After discarding duplicates and ineligibles, we fully analyzed 36 articles, ultimately resulting in 11 approved articles (Figure 1).

The articles included met almost all quality criteria, allowing comparison of population and accuracy data; in 4, however, there was no reference to masking in any stage of data collection and assessment[20,27,28,30] (Table 1).

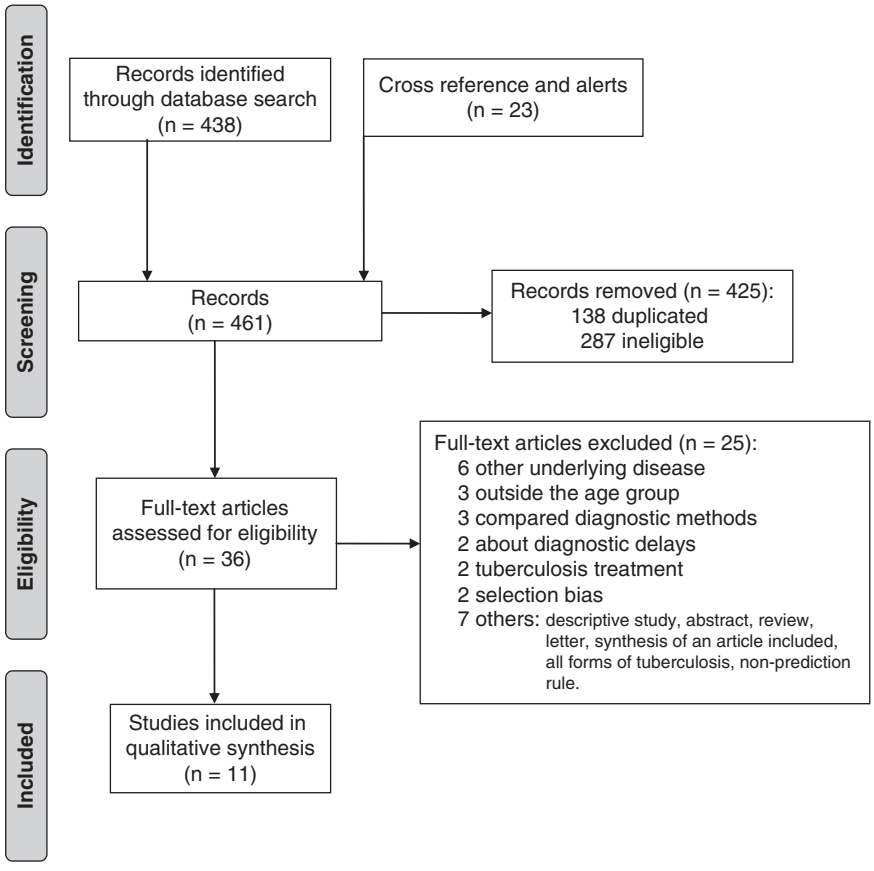

FIGURE 1. Flow diagram of the systematic review (PRISMA Model 2009[31])

TABLE 1. Quality Assessment Parameters for Studies Included (Adapted From Standards for Reporting of Diagnostic Accuracy)

Author, year, country	Mylotte (1997) USA[23]	Redd (1997) USA[21]	Tattevin (1999) France[24]	Wisnivesky (2000) USA[25]	Wisnivesky (2005) USA[26]	Rakoczy (2008) USA[27]	Solari (2008) Peru[22]	Aguilar (2009) USA[28]	Lagrange-Xélot (2011) France[29]	Solari (2011) Peru[15]	Aguiar (2012) Brazil[30]
METHODS											
1. Participants: consecutive series (yes or no)	Yes	Yes	Yes	Yes	Yes	Yes (controls paired to cases)	No	Yes (consecutive cases and random controls)	Yes	No	No
2. Clear description of reference standard	Yes	Yes (culture medium description lacking)	Yes	Yes	Yes	Yes (culture medium description lacking)	Yes	Yes (culture medium description lacking)	Yes	Yes	Yes
3. Masking of clinical data available to readers	No	No	Yes	Yes (CXR)	Yes	No (derivation) Yes (validation)	Yes	No	Yes	Yes (for data collection in 2008)	Yes (CXR)
RESULTS											
4. Reporting of estimates of diagnostic accuracy and measures of statistical uncertainty	AUC only	Yes (CI lacking)	Yes (CI lacking)	Yes (CI for sensitivity and specificity)	Yes (CI for sensitivity and specificity)	Yes (CI lacking)	Yes (CI for AUC only)	Yes	Yes (CI lacking)	Yes (CI for AUC only)	Yes (validation)

NOTE. AUC, area under receiver operating characteristic curve; CI, confidence interval; CXR, chest radiograph.

TABLE 2. Characteristics of Clinical Prediction Rule Derivation Studies for Hospitalized Adult Patients With Suspected Pulmonary Tuberculosis (PTB)

Author, year, country	Design	No. of participants	Male sex	Age, mean ± SD, y		Patients with PTB No. (%)	Smear-positive No. (%)	No. of predictors
				PTB	non-PTB			
Mylotte,[23] 1997-USA	Sectional	296	–	42 ± 15		31 (10.5)	–	4
Redd,[21] 1997-USA	Case-control	141	86	36.6 ± 11.0	38.4 ± 13.1	28 (19.9)	12 (44.0)	4
Tattevin,[24] 1999-France	Sectional	211	–	46.2		47 (22.3)	31 (14.7)	6
Wisnivesky,[25] 2000-USA	Case-control	112	82	40 ± 2	40 ± 2	56 (50.0)	30 (54.0)	6
Rakoczy,[27] 2008-USA	Case-control	98	62	60.0	51.8	49 (50.0)	–	5
Aguilar,[28] 2009-USA	Case-control	660	398	51.3 ± 18.5	55.3 ± 15.9	132 (20.0)	–	14
Solari,[22] 2008-Peru	Sectional	345	222	27	36	109 (31.6)	82 (78.0)	6
Aguiar,[30] 2012-Brazil	Sectional	290	173	43.2 ± 1.7		77 (26.5)	48 (62.3)	12

TABLE 3. Characteristics of Clinical Prediction Rule (CPR) Validation Studies for Hospitalized Adult Patients With Suspected Pulmonary Tuberculosis (PTB)

Author	Design	No. of participants	Male sex	Age, mean ± SD, y		Patients with PTB No. (%)	Smear-positive No. (%)	CPR validated
				PTB	non-PTB			
Mylotte,[23] 1997- USA	Sectional	220	–	44.0 ± 16		8 (3.6)	–	Mylotte[23]
Wisnivesky,[26] 2005- USA	Sectional	516	285	45.8 ± 9.6	46.3 ± 11.4	19 (3.7)	14 (74.0)	Wisnivesky[25]
Rakoczy,[27] 2008-USA	Sectional	247	–	–	–	32 (13.0)	–	Rakoczy[27] and Wisnivesky[25]
Lagrange-Xélot,[29] 2011- França	Sectional	134	94	37 ± 12	45 ± 14	26 (19.4)	14 (53.8)	Wisnivesky[25]
Solari,[15] 2011- Peru	Sectional	345	222	27	36	109 (31.6)	82 (78.0)	Mylotte,[23] Tattevin,[24] and Wisnivesky[25]
Aguiar,[30] 2012- Brazil	Sectional	191	–	–	–	32 (16.6)	15 (48.0)	Aguiar[30]

The 11 articles, published between 1997 and 2012, reported on 8 CPRs derived in 4 countries (United States, France, Peru, and Brazil). Three narrow validation[24,27,30] and 2 broad validation studies[23,25] were performed. The studies as a whole included 3,461 patients, active PTB being confirmed in 646 (18.7%). The number of patients included and PTB prevalence in individual studies ranged from 98 to 660 patients and 10.5% to 50.0% for derivation studies, and from 134 to 516 patients and 3.6% to 31.6% prevalence in validation studies. Mean age ranged from 27.0 to 55.3 years, male population predominating in all studies. Sputum smear result was positive in 14.7% to 78.0% of the patients with positive microbiologic culture result. Presence of comorbidities, especially AIDS, ranged from 24.6% to 60% (Tables 2 and 3).

Calculation of the final CPR score was mostly based on angular coefficients or odds ratios of final predictors obtained using logistic analysis for all studies except one using the Classification And Regression Tree model.[30]

CPR derivation studies had 2 types of retrospective design: case-control and cross-sectional. Five CPRs[23,25,27,28,30] used comparators restricted to controls isolated on admission to the hospital. All the validation studies had cross-sectional or prospective designs (Tables 2 and 3).

Only 2 CPRs[23,25] were validated by authors other than those deriving them, thus generating evidence sufficient to consider for use in practice (level 2). Lagrange et al[29] and Rakoczy et al[27] validated CPR by Wisnivesky et al.[25] Solari et al[15] reviewed 13 CPRs, including Wisnivesky et al,[25] and applied them to a

TABLE 4. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of Prediction Rules for the Diagnosis of Pulmonary Tuberculosis in Hospitalized Adults

Rules	Author	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	AUC (95% CI)	Positive LR
DERIVATED	Mylotte,[23] 1997-USA	–	–	–	–	0.86 (0.82–0.90)	–
	Redd,[21] 1997-USA	96 (86–100)	54 (45–63)	34 (24–46)	98 (91–100)	–	2.1
	Tattevin,[24] 1999-França	100 (94–100)	48 (41–57)	36 (27–44)	100 (95–100)	–	1.9
	Wisnivesky,[25] 2000-USA	98 (95–100)	46 (33–59)	65 (54–75)	96 (81–100)	–	1.8
	Rakoczy,[27] 2008-USA	98 (89–100)	37 (23–52)	61 (49–72)	95 (74–100)	–	1.6
	Aguilar,[28] 2009-USA	99 (96–100)	34 (30–38)	27 (23–32)	99 (97–100)	–	1.5
	Solari,[22] 2008-Peru	93 (86–97)	42 (36–49)	43 (36–49)	93 (86–97)	0.81 (0.76–0.86)	1.6
	Aguiar,[30] 2012-Brazil	60 (40–77)	76 (68–82)	33 (21–47)	90 (84–95)	0.79 (0.70–0.88)	2.5
VALIDATED	Mylotte,[23] 1997-USA	–	–	–	–	0.86 (0.79–0.93)	–
	Wisnivesky,[26] 2005-USA	95 (74–100)	35 (31–40)	5 (3–8)	99 (97–100)	–	1.5
	Rakoczy,[27] 2008-USA	97 (84–100)	42 (35–49)	20 (14–27)	99 (94–100)	–	1.7
	Lagrange-Xélot,[29] 2011-França	96 (80–100)	21 (14–30)	23 (15–32)	96 (79–100)	–	1.2
	Solari,[15] 2011-Peru	89 (82–94)	69 (62–74)	56 (49–64)	93 (88–96)	0.91(0.87–0.95)	2.9
	Aguiar,[30] 2012-Brazil	60 (40–77)	76 (68–82)	33 (21–47)	90 (84–95)	0.79 (0.70–0.88)	2.5

NOTE. AUC, area under receiver operating characteristic curve; CI, confidence Interval; LR, likelihood ratio.

population presenting to the emergency department that they had studied earlier[22] (Table 3). The best validation results of Solari et al[15] were obtained for the CPR of Myllote et al,[23] with results presented in Table 4.

Predictors and Accuracy of CPRs

Individual CPRs included from 4 to 14 predictors and 28 to 132 patients with PTB (Table 2). Only 4 CPRs adhered to the recommendation of keeping a predictor: case ratio of 1:10.[22,25,27,28] The cutoff point of scores recommending respiratory isolation ranged from 1 or greater to 18 or greater (Table 5). Wisnivesky´s CPR[25] presented the lowest cut-off ($\geq$1) and, paradoxically, the highest maximum score (36). Data about homeless, immigrants, and purified protein derivative testing predominated in studies from countries with a low prevalence of TB, and older age, male sex, alcoholism, and smoking history in high-prevalence countries.

Clinical signs most often included as predictors were weight loss (7 of 8 CPRs) and fever (5 of 8 CPRs). The CPRs of Mylotte et al[23] and Solari et al[22] included weight loss as their sole clinical predictor. Cough was included as a predictor in 3 CPRs and sputum production in 1. Only 3 CPRs[25–27] provided any detail for clinical predictor description.

In 4 studies[24,25,27,30] clinical PTB signs and symptoms were grouped into a single aggregate predictor named "chronic symptoms" or "typical symptoms." In 3 of these,[25,27,30] the weight of this aggregate predictor exceeded the cut-off (Table 5).

All models included chest radiography imaging predictors, mainly disease in upper lobe or typical CRX (Table 5). In 3 CPRs[24,25,28] imaging predictors, independently of other predictors, could yield scores sufficient to recommend isolation.

One CPR included sputum smear microscopy for the detection of *M. tuberculosis* in respiratory specimens[23] as a predictor and 3 CPRs derived in low–TB prevalence countries included tuberculin (purified protein derivative) skin testing, used to assess previous contact with *Mycobacterium.*[21,25,28] The BCG (bacillus Calmette-Guérin) vaccine, used to protect against TB, was listed as a predictor in a rule from the 1990s[24] (Table 5).

Regarding accuracy measures (Table 4), all studies showed high sensitivities and area under the curve and low specificities, but none presented LRs. The positive LRs estimated by us were low and varied from 1.5 to 2.9, demonstrating that CPRs would not significantly change the number of culture-confirmed cases among patients included by their predictors. These CPRs are therefore more adequate to triage than to confirm cases.

For derivation studies, sensitivity ranged from 60% to 100%, specificity from 34% to 76%, and area under the curve from 0.79 to 0.81. For validation studies, sensitivity ranged from 60% to 97%, specificity from 21% to 76%, and area under the curve from 0.79 to 0.91.

Meta-analysis of four retrieved validation studies[15,26,27,29] for the CPR of Wisnivesky et al[14] (the only rule with more than 1 validation study) indicate optimistic pooled results: sensitivity, 94.1% (95% CI, 89.7%–96.7%); LR negative, 0.22 (95% CI, 0.12–0.40); and odds ratio diagnostic, 5.81 (95% CI, 3.11–10.85).

However, due to high heterogeneity (I-squared 90.9% and 71.2%, respectively) both specificity-weighted estimate 25.3% (95% CI, 22.7%–27.9%) and LR-positive Dersimonian-Laird 1.24 (95% CI, 1.13–1.36) should be viewed with caution.

The CPR of Myllote et al,[23] derived in the United States, has 2 validation studies (1 from Solari et al[15] in Peru) with excellent performance—area under the curve, 0.86—and is an easy-to-use rule with only 4 predictors. The remaining CPRs were derived and validated only once or not at all, preventing meta-analyses.

TABLE 5. Clinical Prediction Rule Derivation Studies for In-Hospital Pulmonary Tuberculosis: Predictors and Weights

Author/Year	Mylotte[23] 1997	Redd[21] 1997	Tattevin[24] 1999	Wisnivesky[25,a] 2000	Rakoczy[27] 2008	Aguilar[28] 2009	Solari[22] 2008	Aguiar[30,b] 2012
Epidemiologic data	USA	USA	France	USA	USA	USA	Peru	Brazil
Age						0	0 = < 35 − 1 = 35–60 − 2 = ≥ 61	•
Sex								•
Race						1		
BCG immunization > 10 years			1 = Yes or 2 = No					
PPD positive (reported or tested)		1		5		1 = History 4 = Tested		
Exposure to TB/TB previous active						2 (each)	− 3	•
Immigrant			0 = No, 1,2 = Yes (Country)	risk factors	2			
Institutionalized / homeless	2	1	1					
Clinical symptoms								
Hemoptoic			6 (compatible) or 12 (typical)					•
Cough								•
Malaise / hyporexia				4 = (1 risk factor or chronic symptoms)	6	3		
Night sweats						3		
Weight loss	1					3	5	•
Sputum						1		
Fever		1		0 = < 38.5°C 3 = 38.5–39°C 6 = > 39°C				•
Shortness of breath				− 3	− 2			•
Pulmonary crackles				− 3				
Predisposing factors								
HIV / AIDS			5			− 2		•
Immunosuppression[c]					4			
Alcoholism								•
Smoking history								•
Laboratory								
White blood cells (4–10 or > 10mil)						2 or − 2		
Smear-positive	3							

Chest radiograph (CXR)												
Positive or abnormal CXR	2	1					4					
CXR Suggestive or compatible				7								
CXR typical				14								
Disease in upper lobe						6		2			9	
Cavitation									3		5	
Consolidation									4			
Miliary											10	
Positive thoracic CT scans									3			
Cut-off (points)	**>2**	**≥2**		**≥18**		**≥1**		**>4**		**≥4**	**≥3**	–
Maximum points	**8**	**4**		**36**		**21**		**14**		**33**	**21**	–
Ratio cut-off: maximum points	**1:4**	**1:2**		**1:2**		**1:21**		**1:3,5**		**1:8,2**	**1:7**	–

NOTE. BCG, bacillus Calmette-Guérin; CT, computed tomography; HIV, human immunodeficiency virus; PPD, purified protein derivative RT 23.
[a]Wisnivesky grouped as risk factors or chronic symptoms with weighting 4 points.
[b]Aguiar included marked symptoms.
[c]Immunosuppression: liver disease, chronic renal diseases, diabetes mellitus, cancer, use of steroid drug and alcohol ≥3 months.

DISCUSSION

This study summarized 8 CPRs for PTB diagnosis focusing on hospital settings and adult inpatients. As required for screening algorithms, which favor avoiding false-negative results, accuracy of the CPRs was high and mainly based on high sensitivity at the expense of lower specificity.

Signs of PTB traditionally used as surveillance parameters[1] in many countries—that is, a history of persistent cough (only 3 CPRs[24,27,30]) and sputum production (in one[28])—were not alone good predictors in hospital settings compared with primary care settings, as previously pointed out by Greenway et al.[6]

Clinical symptoms most often included were fever and weight loss, suggesting these signs could guide the correct decision in terms of respiratory isolation and of request for more specific laboratory tests. Future CPRs should investigate more specific patterns for these signs—for example, more precise definitions of weight losses and fever´s intensity and duration.

All CPRs included radiologic abnormalities and in some,[22,24,25] scoring weights were higher than for other predictors. A previous meta-analysis of patients with TB and human immunodeficiency virus[33] showed that an abnormal chest radiograph result increases the sensitivity of a CPR in 11.7% but decreases specificity in 10.7%, highlighting the trade-offs of using imaging studies as predictors.

Despite the fact that CPRs need successive assessments in different settings and populations to enhance their level of evidence,[13,19] only 2 of the 8 CPRs[22,30] were derived or validated in developing (high-prevalence) countries and both in the past 6 years. Only 5 CPRs were evaluated by prospective validations[15,23,26,27,29,30] and 2 of them have undergone broad validation[18] by authors other than those who proposed them.[15,29]

We identified 2 previous systematic reviews of CPRs for PTB diagnosis over the past 8 years.[14,15] Main differences from ours include years of publication up to 2003[14] and 2009[15]; inclusion of outpatients, emergency care, exclusively AIDS patients, homeless, or prisoners; and analysis of accuracy not discriminating derivated from validated rules. This explains the higher sensitivities (81%–100%)[14] compared with ours (60%–97%), because validation data tend to be more conservative than derivation data. Our review included 5 and 7 new studies compared with those of Solari et al[15] and Wisnivesky et al,[14] respectively. The latter[14] did not include the CPR of Mylotte et al,[23] which proved to be the most accurate CPR in the validation study of Solari et al.[15]

Limitations of our study could be losses due to syntax aspects and publication bias of negative or gray literature results. Nevertheless, our syntax is similar to that suggested in specialized literature.[34] We also used alerts and cross-references to minimize losses.[21] Our study also has the strengths of scoping larger publication intervals, no restriction regarding language, and strict appraisal of studies´ quality.

Further validation studies are needed to maximize CPR generalization potential and strengthen their evidence level in

settings different from the original studies, especially for countries with limited resources. Methodologic approaches to strengthen CPRs' external generalization could include (a) using the entire population of inpatients as controls in place of only isolated patients, thus increasing heterogeneity between groups; (b) performing studies in high-prevalence settings so as to avoid overfitting due to predictor: case (outcome) ratios (under 1:10); (c) including reliability studies in original CPRs designs; and (d) performing meta-analysis of individual data of validated CPRs.[35]

At the time of writing, no CPR to diagnose PTB on hospital admission has been successfully implemented into clinical practice (maximum level of evidence)[16] or been shown to change health professionals´ behavior.[13] Personal experience of the attending healthcare worker remains the basis for adoption and correct use of validated CPRs.[35]

Two of the CPRs[23,26] warrant consideration for clinical practice and further assessment (evidence level 2) by impact studies and implementation, especially that of Wisnivesky et al.[26] Our meta-analysis of this CPR showed good performance to rule out true-negative patients but low accuracy to confirm cases, tending to over-refer patients to isolation.

On the basis of a critical appraisal of the 2 best performing or validated rules, the presence of consumptive symptoms (weight loss and/or fever) in inpatients, regardless of the existence of productive cough, suggests the need of a chest radiograph.[14,15] Should an abnormal chest radiograph be found, mainly in the upper lobe with or without cavitation, isolation measures are warranted until results of a more specific test are available. The elevated prevalence of sputum smear–negative and culture-confirmed cases in the reviewed CPRs suggests that hospital inpatients could be a potential target group for Xpert MTB/RIF (Cepheid) on an add-on basis[11] following use of this algorithm. Further validation and cost-effectiveness studies are in order to test this recommendation.

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