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# Performance of clinical prediction rules for diagnosis of pleural tuberculosis in a high-incidence setting

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**Abstract**

OBJECTIVES Diagnosis of pleural tuberculosis (PT) is still a challenge, particularly in resource-constrained settings. Alternative diagnostic tools are needed. We aimed at evaluating the utility of Clinical Prediction Rules (CPRs) for diagnosis of pleural tuberculosis in Peru.

METHODS We identified CPRs for diagnosis of PT through a structured literature search. CPRs using high-complexity tests, as defined by the FDA, were excluded. We applied the identified CPRs to patients with pleural exudates attending two third-level hospitals in Lima, Peru, a setting with high incidence of tuberculosis. Besides pleural fluid analysis, patients underwent closed pleural biopsy for reaching a final diagnosis through combining microbiological and histopathological criteria. We evaluated the performance of the CPRs against this composite reference standard using classic indicators of diagnostic test validity.

RESULTS We found 15 eligible CPRs, of which 12 could be validated. Most included ADA, age, lymphocyte proportion and protein in pleural fluid as predictive findings. A total of 259 patients were included for their validation, of which 176 (67%) had PT and 50 (19%) malignant pleural effusion. The overall accuracy of the CPRs varied from 41% to 86%. Two had a positive likelihood ratio (LR) above 10, but none a negative LR below 0.1. ADA alone at a cut-off of ≥40 IU attained 87% diagnostic accuracy and had a positive LR of 6.6 and a negative LR of 0.2.

CONCLUSION Many CPRs for PT are available. In addition to ADA alone, none of them contributes significantly to diagnosis of PT.

**keywords** score, adenosine deaminase activity, pleural tuberculosis, *Mycobacterium tuberculosis*

## Introduction

Diagnosis of pleural tuberculosis (PT) is a challenge, particularly in resource-constrained settings. The occurrence of pleural exudates raises clinical suspicion of this condition and patients' pleural fluids are usually evaluated for the presence of acid-fast bacilli (AFB) through Ziehl–Neelsen staining, for malignant cells through haematoxylin–eosin staining and through Gram examination for common bacteria. However, in a large proportion of cases, these tests do not lead to a diagnosis, amongst others because the presence of the tuberculous bacilli in pleural fluid specimens is scarce. Additionally, the diagnostic contribution of molecular techniques, when available, is only modest [1]. Invasive procedures, such as closed pleural biopsy and thoracoscopy, are then recommended. These can establish the diagnosis in most cases, but come at the risk of complications, require high-level expertise and equipment and have an elevated cost [2].

Clinical prediction rules (CPRs), or 'scores', have been developed to contribute to the diagnosis of PT. They combine several clinical signs or symptoms and/or laboratory tests as predictors and could inform clinical decision-making [3]. However, they need to be locally validated before implementation. This validation is usually performed through the evaluation of the standard indicators of diagnostic performance (sensitivity, specificity, predictive values and areas under the ROC curve (AUC)) against a reference diagnostic standard.

Meanwhile, the diagnostic utility of Adenosine deaminase activity (ADA) for PT continues to be controversial, but some recent publications support its use [4, 5]. It has been advocated as helpful in low-to-medium incidence settings [6], although not considered in the clinical guidelines of these countries [7]. In contrast, it is included in guidelines for diagnosis of PT in high-incidence Latin American countries [8]. Its utility, compared to that of CPRs, has still to be evaluated.

Our aim was to identify existing CPRs for the diagnosis of PT, to determine their performance in patients with pleural exudates in Peru and to evaluate their clinical utility in relation to ADA.

## Materials and methods

### Identification of the CPRs for the diagnosis of PT

We performed literature searches in MEDLINE and LILACs to retrieve CPRs for PT. For the MEDLINE search, we followed the procedures suggested by Ingui *et al.*, prioritising sensitivity [9] with some modifications and adding the Mesh terms related to 'tuberculosis' and to 'pleural', both as MeSh terms and as text. The final search strategy was ((((('Sensitivity and Specificity'[Mesh]) OR ('Diagnosis'[Mesh] OR 'diagnosis'[Subheading] OR 'Early Diagnosis'[Mesh] OR 'Diagnosis, Differential'[Mesh] OR 'Clinical Laboratory Techniques'[Mesh]))) AND (('Tuberculosis'[Mesh]) OR 'Mycobacterium tuberculosis'[Mesh])) AND (('Pleurisy'[Mesh]) OR ('Pleura'[Mesh] OR 'Empyema, Pleural'[Mesh] OR 'Tuberculosis, Pleural'[Mesh] OR 'Pleural Effusion'[Mesh] OR 'Pleural Diseases'[Mesh] OR 'Empyema, Tuberculous'[Mesh])). The search was limited to humans and articles published until June 2016. We searched LILACs using (pleural OR derrame) AND tuberculosis, applying the same limits.

We manually searched the 'related articles' displayed in PubMed and the references of the selected retrieved papers for additional CPRs. Two researchers (LS and AS), screened the abstracts of the retrieved papers and independently selected the publications on CPRs to be included. Discrepancies were solved by consensus. The inclusion criteria were as follows: Clinical Prediction Rules (defined as a combination of signs, symptoms and laboratory tests that jointly interpreted lead to a clinical decision) [10] and having PT as an outcome to be predicted. We excluded from subsequent evaluation CPRs derived for specific groups, such as children, HIV positive or inmuno-compromised patients. We also excluded CPRs that included as predictive findings 'high-complexity tests' as defined by the FDA's CLIA (clinical laboratory improvement amendments) [11]. These are, amongst others, molecular methods, interferon-gamma release assays, lysozyme determinations and antibody tests for *M. tuberculosis*, which are not normally available in hospital laboratories, even at referral level, in low-middle income countries.

### Setting, patients and clinical procedures

We performed the validation of the CPRs in patients attending Hospital Nacional Cayetano Heredia and Hospital Nacional Hipolito Unanue, third-level hospitals in Lima, Peru, a Latin American country with a concentrated HIV epidemic and a high incidence ($120/10^5$) of tuberculosis. The sample size needed was calculated based on 90% power to detect an increase of 10% in the overall accuracy of the evaluated CPRs compared to ADA determination, for which we assumed a baseline accuracy of 75%. Allowing for 10% of non-evaluable cases, the required number of participants was 190.

From October 2009 to February 2012, all new adult patients that attended the internal medicine wards of these hospitals and had pleural effusion according to chest X-ray or ultrasound were screened with Light's criteria [12] for distinguishing between exudates and transudates. Patients with exudates were referred to the neumology units for inclusion in the study.

After giving informed consent, demographic and clinical information was collected through direct interviews and physical examination. Mycobacterial culture in Lowenstein-Jensen media and papanicolaou was performed on sputum samples of all patients. Pleural aspirates were obtained, and patients with hemothorax or grossly turbid empyemas were excluded from further study, as their management required therapeutic surgical procedures rather than diagnosis. Pleural fluid specimens were sent for determination of cell count and differential, glucose, lactate dehidrogenase, protein, ADA, Ziehl–Neelsen staining, cultures for mycobacteria in Ogawa and Mycobacterial Growth Indicator Tube (MGIT) media, PCR for *M. tuberculosis* and cytology for malignant cells. Trained neumologists performed on all patients a closed pleural biopsy with Abrams needle according to standard procedures [13], and the pleural tissue was sent for histopathological examination by certified pathologists and for culture in MGIT if tissue quantity sufficed. Specific complementary tests performed when indicated included culture in Sabouread media for fungal infections and immunohistochemistry for connective tissue diseases amongst others. All laboratory results were promptly communicated to the treating physicians, who remained in charge for the subsequent management of the patients.

### Diagnostic classification

We classified the patients into four diagnostic categories:

- Pleural Tuberculosis: our reference standard was positive AFB smear or positivity for *M. tuberculosis* in any of the culture media or positive PCR for *M. tuberculosis* in pleural fluid or tissue; or presence of caseating granulomas in the histopathology; or compatible histopathological results (lymphocytic

infiltration, unspecific granulomas, fibrosis) followed by resolution of the effusion and symptoms within the 3 months after initiation of antituberculous therapy.
- Malignant pleural exudate: the presence of malignant cells in the pleural fluid or biopsy
- Other specific pleurisies (connective tissue diseases, fungal infections and other conditions diagnosed through histopathology or specific complementary tests).
- Pleural exudate of unknown cause: patients for whom no definite diagnosis could be established.

### Data analysis

Each withheld CPR was applied to every patient. For CPRs derived to differentiate PT from other conditions, the diagnostic categories 'malignant pleural effusion' and 'other specific pleurisies' were jointly considered 'Not PT'. For CPRs designed to differentiate PT from malignant pleural exudates, the diagnostic category 'other causes' were excluded from the analysis.

In both situations, patients with two coexisting aetiologies for the pleural exudate and those with pleural exudates of unknown cause were excluded from the analysis.

We compared the results obtained through the CPRs with our reference standard for PT to calculate their sensitivity, specificity, predictive values, likelihood ratios and, for the CPRs based on scoring systems, the areas under their ROC curve (AUC)s. We did the same for ADA at two different cut-off levels: 40 and 60 UI/L. All statistical analyses were performed with STATA ver. 10.

### Ethical aspects

All included patients gave written informed consent for participation. The ethics committees of Universidad Peruana Cayetano Heredia, Hospital Nacional Cayetano Heredia, Hospital Nacional Hipolito Unanue and the Institute of Tropical Medicine, Antwerp approved the study.

## Results

### Identified CPRs

We retrieved 2419 publications using our MEDLINE search strategy and 280 through the LILACs search (Figure 1). This yielded 25 CPRs and three additional ones were found through the revision of the references. Of these, 11 CPRs including one neural network were excluded because they considered 'high-complexity' test amongst their predictive findings, including one neural network. Despite the study being performed at two third-level hospitals, our laboratories were not equipped to perform C-reactive protein test (CRP), complement activation products dosage and pleural globulin level

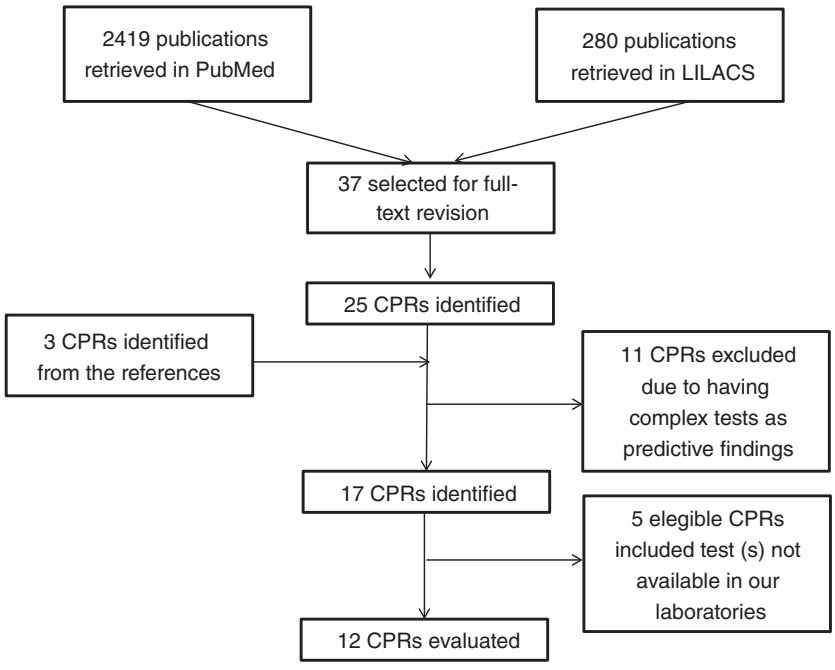


**Figure 1** Clinical Prediction Rules (CPRs) for Pleural Tuberculosis retrieved and assessed.

**Table 1** Characteristics and predictive findings included in the evaluated CPRs for diagnosis of Pleural Tuberculosis

| Characteristics | | | | Predictive findings | | | | |
|---|---|---|---|---|---|---|---|---|
| Author | Year, country | Derivation population | Sample size (prevalence of PT) | ADA (U/L) | Lymphocyte pro portion (%) or *L/N* ratio | Age | Pleural protein (mg/dL) or P/S ratio | Other predictive findings |
| CPRs for diagnosis of PT | | | | | | | | |
| De Oliveira *et al.* [19] | 1994, Brazil | Patients with pleural effusion | 276 (20%) | >40 | >50% | – | – | – |
| Burgess *et al.* [20] | 1996, South Africa | Patients with pleural exudates | 303 (58%) | >50 | >0.75 | – | – | – |
| Melo *et al.* [21] | 2000, Brazil | Patients with pleural effusion | 417 (64%) | ≥30 | >90% | ≤ 45 | ≥45 | – |
| Ghanei *et al.* [23] | 2004, Iran | Patients with pleural effusion | 88 (19.3%) | >47 | >0.75 | – | – | Pleural LDH >220 mg/dL |
| Neves *et al.* [24] | 2004, Brazil | Patients with pleural effusion | 215 (48%) | >39 | >80% | – | – | – |
| Neves *et al.* [25] | 2007, Brazil | Patients with pleural effusion | 215 (48%) | >39 | >81% | – | >41 | Disease duration <45 days), white cell count <6000/mm$^3$ |
| Dheda *et al.* [27] | 2009, South Africa | Patients with "clinical suspicion" of PT | 74 (74%) | – | – | <42 | >53 | – |
| Valdes *et al.* [28] | 2010, Spain | Patients with pleural effusion <40 years old | 218 (76%) | >35 | >31.5 | – | – | – |
| Demirer *et al.* [30] | 2012, Turkey | Patients with pleural effusion | 251 (63%) | >35 | – | <47 | >0.71 | – |
| CPRs for differentiation between PT and cancer | | | | | | | | |
| Porcel *et al.* [22] | 2003, Spain | Patients with diagnosis of PT and cancer | 292 (27%) | ≥40 | – | ≤35 | – | Tempe rapture ≥ 37.8, pleural RBC count ≤ 5 × 10$^9$/L |
| Porcel *et al.* [26] | 2008, Spain | Patients with diagnosis of PT and cancer | 238 (27%) | >38 | – | <35 | – | Fever, pleural LDH >320 mg/dL |
| Yildiz *et al.* [29] | 2011, Turkey | Patients with pleural exudates with >50% lympho | 196 (58%) | >55 | – | >50 | – | – |

determination, all classified as moderate complexity tests by the FDA-CLIA. Neither could we perform the TST on all patients. For this reason, we could not assess five eligible CPRs [14–18]. Figure 1 resumes the procedure of selection of the CPRs.

Table 1 summarises the main characteristics of the 12 CPRs we evaluated [19–30]. Many of them had been derived in study populations with high incidences of PT. The most common predictors included were ADA (in 11 CPRs), lymphocyte proportion (in 7), protein in pleural fluid (in 4) and age (in 6).

### Patient characteristics

We evaluated 383 patients for inclusion. Of these, 101 (26.4%) did not consent to participate in the study, five were lost to follow-up, 12 (3.1%) had pus in the thoracentesis and in three the procedures of thoracentesis or pleural biopsy failed. Finally, 262 patients had a complete workup.

Out of them, 176 (67.2%) had PT,140 had microbiological or histopathological confirmation and 36 showed histopathological signs suggestive of PT and complete resolution of symptoms in response to treatment. Fifty patients had malignant pleural effusion, 12 had other specific pleurisies such as rheumatoid or fungal pleuritis, three had concomitant evidence of PT and malignant pleuritis and 21 (8.1%) had pleural exudates of unknown cause (Figure 2). Table 2 compares demographic, clinical and laboratory findings between patients with PT and not PT (malignant pleural effusion and other specific pleuritis). Younger age, male gender, former contact with a patient with tuberculosis, shorter duration of illness, fever, night sweats and high ADA and protein levels in pleural fluid were positively associated with PT.

### Accuracy of the CPRs

The sensitivity, specificity, predictive values and likelihood ratios for the diagnosis of PT of each of the evaluated CPRs are shown in Table 3. In general, the sensitivities of the CPRs were substantially lower in our setting than reported in the original papers, but the specificities were comparable. While the CPRs designed for diagnosis of PT attained low sensitivities, Melo's and Neves's had a specificity of 100% and together with Dheda's, and Demirer's, attained positive likelihood ratios above 10. CPRs for differentiation with cancer had higher sensitivities but did not attain negative likelihood ratios lower than 0.10. Given the high PT prevalence in our patients, all CPRs attained high-positive predictive values (90–100%), but all had negative predictive values below 70%. ADA alone had the highest overall diagnostic accuracy for diagnosis of TP at a cut-off point of 40 UI/L (87% for diagnosis of PT), with a sensitivity of 86% (95% CI 81–91) and a specificity of 87% (95% CI 77–93) (Table 4).

There were two CPRs expressed as scores, Dheda's and Porcel's (2003). They attained AUC of 0.81 (CI 0.76–0.90) for diagnosis of PT and 0.91 (CI 0.82–0.95) for

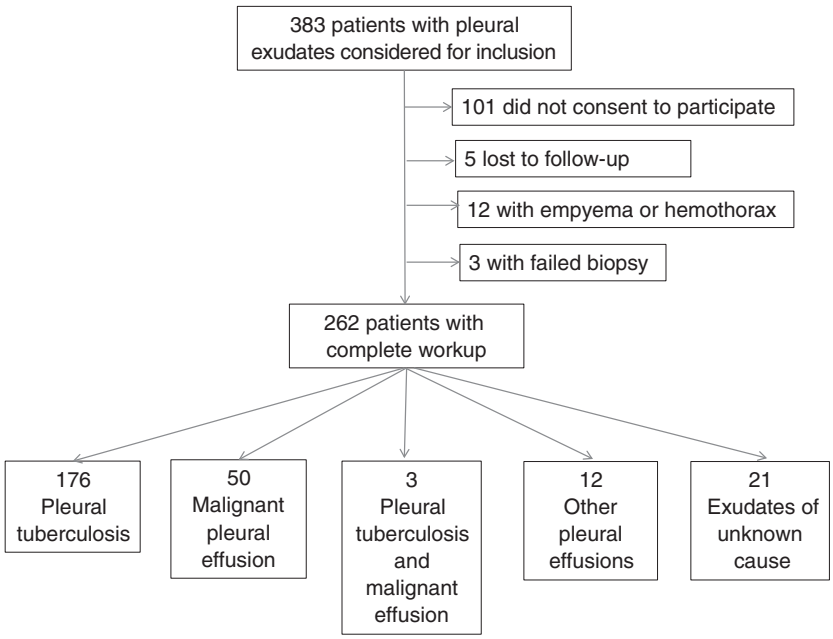


**Figure 2** Flowchart of patient inclusion and their final diagnosis, Lima, Peru.

**Table 2** Demographic, clinical and laboratory findings of patients with pleural tuberculosis (PT) and with other pleurisies, Lima, Peru

| | PT ($n$ = 176) | Not PT ($n$ = 62) | $P$ value |
|---|---|---|---|
| Demographic findings and past history | | | |
| Age in years (median, interquartile range) | 37 (34–40) | 62 (57– 67) | <0.001 |
| Male gender $n$ (%) | 124 (70.5) | 28 (45.2) | 0.001 |
| History of tuberculosis $n$ (%) | 19 (10.8) | 7 (11.3) | 1.00 |
| Contact with a tuberculosis patient $n$ (%) | 88 (50.0) | 14 (22.6) | <0.001 |
| Comorbidity $n$ (%) | 53 (30.1) | 20 (32.3) | 0.75 |
| Clinical findings | | | |
| Duration of illness in days (median, interquartile range) | 35 (31–40) | 77 (54–100) | <0.001 |
| Cough > 14 days $n$ (%) | 61 (34.7) | 23 (37.1) | 0.76 |
| Expectoration $n$ (%) | 75 (42.6) | 28 (45.2) | 0.77 |
| Fever $n$ (%) | 142 (80.7) | 28 (45.2) | <0.001 |
| Night sweats $n$ (%) | 106 (60.2) | 21 (33.9) | <0.001 |
| Weight loss $n$ (%) | 124 (70.5) | 43 (69.4) | 0.87 |
| Laboratory findings | | | |
| Leucocyte count in blood (median, interquartile range) | 7749 (7529–8376) | 8525 (7642–9401) | 0.11 |
| HIV infection $n$ (%) | 13 (7.7) | 3 (5.1) | 0.51 |
| White cell count in pleural fluid (/ml) (median, interquartile range) | 1949 (1136–2762) | 808 (430–1188) | 0.11 |
| Lymphocyte percentage in pleural fluid (median, interquartile range) | 69 (57–80) | 67 (61–74) | 0.91 |
| ADA in pleural fluid (U/l) (median, interquartile range) | 79 (74–85) | 28 (20–36) | <0.001 |
| LDH in pleural fluid (U/l) (median, interquartile range) | 880 (809–951) | 867 (553–1181) | 0.90 |
| Protein in pleural fluid (U/l) (median, interquartile range) | 5.2 (5.0–5.3) | 4.2 (3.8–4.5) | <0.001 |
| Glucose in pleural fluid (U/l) (median, interquartile range) | 71.8 (68.0–75.6) | 79.9 (64.3–95.4) | 0.15 |

differentiation between PT and cancer respectively. These were not significantly different from the AUC for ADA (0.89, CI 0.81–0.95).

## Discussion

We validated 12 clinical prediction rules (CPRs) for diagnosis of pleural tuberculosis (PT), most of them derived during the last decade in countries with moderate or high incidence of tuberculosis. Our validation series consisted of patients with pleural exudates, among whom the prevalence of PT was 67%, not surprising for a country with a high tuberculosis burden. Some CPRs had very high specificity but due to their low-to-moderate sensitivity, attained only modest overall accuracy (the highest at 86%). The Adenosine Deaminase (ADA) test on its own performed the best according this diagnostic indicator (87%), due to its better sensitivity and acceptable specificity (86% and 87% respectively). CPRs added to what was already achieved by ADA only in terms of specificity, strengthening the positive likelihood for diagnosis of PT, but detracting on sensitivity.

Our results constitute the first formal validation of a set of CPRs for PT, most of which had not been previously externally validated. We found, as expected, that they perform less well than in the setting they were developed. This is common to all kinds of CPRs and is the reason why it is important to perform their local validation before application.

We expressly chose not to include CPRs with 'high-complexity tests' among their predictive findings, because is against the nature of CPRs to use such tests and, more importantly, because facilities that can perform them are not common in most high-incidence countries. Still, research on interferon-gamma release assays (IGRAs) tests in pleural fluid show promising results [31] for diagnosis of TP if combined with other biomarkers. This is because in isolation it has important limitations: a recent meta-analysis of 14 studies shows a pooled sensitivity of 72% and a pooled specificity of 78% for the diagnosis of PT [32]. The assessment of other specific markers of inflammation due to *M. tuberculosis* may prove increasingly useful, in line with the physiopathology of pleural tuberculosis.

However, molecular techniques intended to capture the presence of bacilli, which are scarce in PT, have low sensitivity [33] and could, at best, be used if and when available. Other CPRs excluded used lysozyme, antibodies for *M. tuberculosis* or citoquines that are definitively of too high complexity for use in resource-constrained settings or at peripheral level.

A limitation of this study was that we were not able to validate five CPRs that included tests of moderate complexity, which could not be performed at our tertiary

**Table 3** Diagnostic accuracy of clinical prediction rules and adenosine deaminase for pleural tuberculosis, Lima, Peru

| Author, year | Report in the original publication | | Calculated diagnostic performance in our set of patients (95% C. I.) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Specificity | Overall accuracy | Positive predictive value | Negative predictive value | Positive likelihood ratio | Negative likelihood ratio |
| CPRs for diagnosis of PT | | | | | | | | | |
| De Oliveira (1994) [19] | 91% | 98% | 61% (54–68) | 90% (80–95) | 69% (63–75) | 95% (94–95) | 45% (42–46) | 6.1 (2.7–13.6) | 0.4 (0.3–0.6) |
| Burgess (1996) [20] | 88% | 95% | 59% (52–66) | 90% (80–95) | 67% (61–73) | 94% (94–95) | 44% (41–45) | 5.9 (2.6–13–2) | 0.5 (0.4–0.6) |
| Melo (2000) [21] | NR | NR | 20% (15–26) | 100% (94–100) | 41% (34–47) | 100% (100–100) | 31% (29–31) | Infinity | 0.8 (0.7–0.9) |
| Ghanei *et al.* (2004) [23] | NR | 100% | 59% (51–66) | 94% (85–97) | 68% (61–74) | 97% (96–97) | 45% (42–45) | 9.8 (3.3–22.0) | 0.4 (0.4–0.6) |
| Neves *et al.* (2004) [24] | 97.8% | 97.9% | 26% (20–33) | 100% (94–100) | 45% (39–52) | 100% (100–100) | 32% (31–32) | Infinity | 0.7 (0.7–0.9) |
| Neves *et al.* (2007) [25] | NR | NR | 72% (65–78) | 77% (66–86) | 74% (67–79) | 90% (89–91) | 49% (45–52) | 3.1 (1.9–5.6) | 0.4 (0.3–0.5) |
| Dheda *et al.* (2009) [27] | 81% | 58% | 66% (56–74) | 94% (84–98) | 74% (67–81) | 97% (96–97) | 49% (47–50) | 11.0 (3.5–37.0) | 0.4 (0.3–0.5) |
| Valdes *et al.* (2010) [28] | 99.4% | 98.1% | 64% (55–72) | 63% (31–86) | 65% (56–73) | 83% (81–85) | 38% (23–46) | 1.7 (0.8–5.1) | 0.6 (0.3–1.5) |
| Demirer *et al.* (2012) [30] | 60.5% | 83.0% | 69% (62–76) | 95% (87–98) | 76% (70–81) | 98% (97–98) | 52% (50–53) | 13.8 (4.8–38.0) | 0.3 (0.2–0.4) |
| CPRs for differentiation between PT and cancer | | | | | | | | | |
| Porcel and Vives (2003) [22] | 95% | 94% | 86% (81–91) | 86% (74–93) | 86% (81–90) | 95% (94–95) | 68% (65–70) | 6.1 (3.1–13.0) | 0.2 (0.1–0.3) |
| Porcel *et al.* (2008) [26] | 85.1% | 96.9% | 86% (81–91) | 86% (74–93) | 86% (81–90) | 95% (94–95) | 68% (65–70) | 6.1 (3.1–13.0) | 0.2 (0.1–0.3) |
| Yildiz *et al.* (2011) [29] | 87.2% | 95.7% | 64% (56–70) | 96% (87–99) | 71% (64–77) | 98% (98–98) | 48% (46–49) | 16.0 (4.3–70.0) | 0.4 (0.3–0.5) |

NR, Not reported.

**Table 4** Diagnostic performance of adenosine deaminase activity (ADA) for diagnosis of Pleural Tuberculosis (PT) and for differentiation between PT and cancer at two cut-off levels

| | Calculated diagnostic performance in our set of patients (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| Adenosine Deaminase Activity | Sensitivity | Specificity | Overall accuracy | Positive predictive value | Negative predictive value | Positive likelihood ratio | Negative likelihood ratio |
| For diagnosis of TP | | | | | | | |
| ADA ≥ 40 IU/L | 86% (81–91) | 87% (77–93) | 87% (82–90) | 95% (90–97) | 69% (58–78) | 6.7 (3.5–12.8) | 0.16 (0.11–0.23) |
| ADA ≥ 60 IU/L | 73% (66–79) | 89% (78–94) | 77% (72–82) | 95% (90–97) | 54% (44-63) | 6.5 (3.2–13.1) | 0.30 (0.23–0.39) |
| For differentiation between TP and cancer | | | | | | | |
| ADA ≥ 40 IU/L | 86% (81–91) | 88% (76–94) | 86% (81–90) | 95% (90–97) | 64% (52–77) | 7.2 (3.4–15.3) | 0.16 (0.11–0.23) |
| ADA ≥ 60 IU/L | 73% (66–79) | 88% (76–94) | 77% (71–82) | 96% (91–98) | 48% (38–58) | 6.1 (2.9–13.0) | 0.30 (0.23–0.40) |

level hospitals due to laboratory constraints. These tests were C-reactive protein, complement activation products, globulin levels in pleural fluid, and TST. The latter test is a marker of tuberculosis infection, with fluctuating availability globally, and would probably not be useful in a setting where more than 50% of the population is positive [34]. As C-reactive protein is intended to discriminate PT from bacterial infections, which were not present in our patient series, it would have scarcely contributed. A similar situation occurs with pleural globulins and complement activation products. While pleural globulins have been associated with TP [35], other infectious conditions such as pneumonia and some neoplastic disorders like multiple myeloma can significantly raise the level of globulins in the pleural fluid and currently the trend is to study the nature of the globulins rather than to assess them it as a whole [36]. Complement activation products are most of all useful for diagnosis of lupus and other connective tissue diseases, when low levels are found, and less so for TP or cancer diagnosis [37].

The lack of diagnostic thoracoscopy could also be of concern. Twenty-one (8.1%) patients remained without definite diagnosis after pleural biopsy and these patients are, according to current recommendations [38], candidates for thoracoscopy. Notwithstanding, our rate of undiagnosis is similar to the rate of around 10% reported in the literature [39]. Finally, of the few patients with empyema that we excluded from analysis, some could have been tuberculous pleuritis cases. However, diagnosing PT in the presence of purulent fluid poses no major diagnostic challenge, as AFB are generally found [40]. At any rate, empyema calls for surgical intervention. Above all, this study adds evidence on the utility of ADA in the diagnostic approach of TP. Currently, only Latin American guidelines consider its use as part of diagnostic recommendations. An explanation may be that, compared to other forms of extrapulmonary tuberculosis, pleural tissue is relatively accessible and that clinicians often chose to confirm PT through histopathological examination. However, in countries with high incidence of tuberculosis, considerable amounts of resources could be saved and risks avoided with the use of ADA as a decision-making tool. Surprisingly, clinical prediction rules do not or hardly perform better than ADA alone for diagnosis of PT. Designing CPRs intended to improve on what ADA already discriminates would be an interesting development. In resource-constrained settings, where ADA determination is not available, Dheda's CPR, the only evaluated not including ADA as a predictive finding, could be an option, despite its moderate (74%) overall diagnostic accuracy.

In conclusion, we assessed the performance of published CPRs for the diagnosis of PT in a country with high incidence of tuberculosis. We found that they do not contribute significantly over ADA alone in overall diagnostic performance, although some of them improve the specificity. ADA, an inexpensive, simple and accessible test, shows a good diagnostic performance and is an important element in the diagnostic approach to PT.

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