International Journal of Infectious Diseases 69 (2018) 103–107

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Development of a clinical prediction rule for the diagnosis of pleural tuberculosis in Peru

Lely Solari[a,b], Alonso Soto[c,d,*], Patrick Van der Stuyft[a,e]

[a] Unit of General Epidemiology and Disease Control, Institute of Tropical Medicine, Antwerp, Belgium
[b] Instituto Nacional de Salud, Lima, Peru
[c] Escuela de Medicina, Universidad Peruana de Ciencias Aplicadas, Chorrillos, Lima, Peru
[d] Departamento de Medicina, Hospital Nacional Hipolito Unanue, Lima, Peru
[e] Department of Public Health, Ghent University, Ghent, Belgium

ARTICLE INFO

Article history:
Received 8 September 2017
Received in revised form 21 January 2018
Accepted 23 January 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Clinical prediction rules
Aadenosine deaminase
Pleural effusion
Peru

ABSTRACT

Objectives: To develop a clinical prediction rule (CPR) for the diagnosis of pleural tuberculosis (PT) in patients with pleural exudates in Peru.
Methods: Clinical and laboratory information was collected from patients with exudative pleural effusion attending two reference hospitals in Lima, Peru. Predictive findings associated with PT in a multiple logistic regression model were used to develop the CPR. A definite diagnosis of PT was based on a composite reference standard including bacteriological and/or histological analysis of pleural fluid and pleural biopsy specimens.
Results: A total of 238 patients were included in the analysis, of whom 176 had PT. Age, sex, previous contact with a TB patient, presence of lymphadenopathy, and pleural adenosine deaminase (ADA) levels were found to be independently associated with PT. These predictive findings were used to construct a CPR, for which the area under the receiver operating characteristics curve (AUC) was 0.92. The single best cut-off point was a score of ≥60 points, which had a sensitivity of 88%, specificity of 92%, a positive likelihood ratio of 10.9, and a negative likelihood ratio of 0.13.
Conclusions: The CPR is accurate for the diagnosis of PT and could be useful for treatment initiation while avoiding pleural biopsy. A prospective evaluation is needed before its implementation in different settings.

Introduction

Pleural tuberculosis (PT) is one of the most common forms of extrapulmonary TB and a common cause of exudative pleural effusion in developing countries (Sharma and Mohan, 2004). The differential diagnosis of exudative pleural effusion includes several conditions, the most important one being neoplasms with pleural involvement (Porcel and Vives, 2003). Bacteriological studies of pleural fluid to confirm the presence of *Mycobacterium tuberculosis* have low sensitivity (Gopi et al., 2007), and even molecular tests are only helpful in a small group of patients (Denkinger et al., 2014). Consequently, reaching a definite diagnosis in many cases requires performing an invasive procedure such as pleural biopsy or thoracoscopy for histopathological examination. However, access to these procedures is frequently restricted, particularly in settings with constrained resources and a high incidence of TB. Moreover, these procedures are not exempt from complications such as bleeding or pneumothorax, which, even if infrequent, can have serious consequences (Cao et al., 2015).

In some high incidence settings, clinical features and pleural fluid analyses are the only available tools for decision-making. In alignment with this, guidelines have been issued to standardize the use of laboratory tests. The World Health Organization (WHO) proposes 'coagulation ability of the pleural fluid' and 'presence of mononuclear predominance in pleural fluid' as parameters suggesting a diagnosis of PT when assessing a pleural exudate (WHO, 2007). Locally, Peruvian guidelines do not propose a structured approach, but instead only consider microbiological procedures as criteria for the diagnosis of PT (MINSA, 2013). Although currently not endorsed by the WHO, the use of adenosine deaminase (ADA) for the diagnosis of extrapulmonary TB and

* Corresponding author at: Escuela de Medicina, Universidad Peruana de Ciencias Aplicadas, Avenida Alameda San Marcos cuadra 2, Chorrillos, Lima, Peru.
E-mail addresses: lsolari@ins.gob.pe (L. Solari), pcmeasot@upc.edu.pe (A. Soto), Patrick.VanDerStuyft@UGent.be (P. Van der Stuyft).

https://doi.org/10.1016/j.ijid.2018.01.026

specifically for PT is supported by several meta-analyses (Morisson and Neves, 2008; Liang et al., 2008; Greco et al., 2003; Goto et al., 2003).

Several clinical prediction rules (CPRs) or scores (tools that use simple clinical and/or laboratory findings to assess the likelihood of a condition or to inform a clinical decision) (Laupacis et al., 1997) have been proposed to guide the diagnosis of PT in different settings and populations, but most of all in low-incidence countries (Porcel and Vives, 2003; Antonangelo et al., 2007; Burgess et al., 1996; De Oliveira et al., 1994; Demirer et al., 2012; Ghanei et al., 2004; Neves et al., 2007; Porcel et al., 2008). In Latin America, the only country in which CPRs have been developed is Brazil (De Oliveira et al., 1994; Neves et al., 2007). Considering the importance of the setting for the strength of particular predictive findings, it would be useful to develop additional CPRs in other high-incidence Latin American countries, in order to compare the predictive findings included and their diagnostic performance. These local CPRs could constitute an adequate tool to support clinical decision-making. The objective of this study was to derive a CPR for the diagnosis of PT in patients with pleural exudates in Lima, Peru.

Methods

Patients

Clinical information was obtained from patients attending Hospital Nacional Cayetano Heredia and Hospital Nacional Hipolito Unanue, two reference hospitals in Lima, Peru, a country with a TB incidence of 119/100 000 (http://www.who.int/tb/publications) (WHO, 2016) and a concentrated HIV epidemic. All adult patients with pleural effusion diagnosed through chest X-ray or ultrasound, attending the two hospitals between October 2009 and February 2012, were screened using Light's criteria for pleural exudates (Light et al., 1972). Those meeting the criteria for pleural exudates were referred to the pulmonology units for inclusion in the study until the required sample size was attained.

After giving informed consent, demographic and clinical information was collected through direct interviews and physical examination by certified physicians. Standard blood tests were performed. Trained pulmonologists performed a thoracentesis and a blind closed pleural biopsy with an Abrams needle according to recommended procedures (McLeod et al., 1989). Cell count and differential, glucose, lactate dehydrogenase (LDH), protein, and ADA levels (using the Giusti method) in the pleural fluid were determined.

In addition, Ziehl–Neelsen acid-fast bacillus (AFB) staining, Gram staining, and cultures for mycobacteria in Ogawa medium and Mycobacterial Growth Indicator Tube (MGIT) medium, as well as PCR for *M. tuberculosis* and cytology for malignant cells were performed. The pleural biopsy was sent for histopathological examination and read by certified pathologists.

The required sample size was 259 participants based on an estimated accuracy of 80% for the clinical prediction rule, a precision of 5%, and a confidence level of 95%, and allowing for up to 5% of missing data.

Reference standard

The diagnosis of PT was based on a composite reference standard consisting of the following elements: positive AFB or culture for *M. tuberculosis* in any of the culture media or positive PCR for *M. tuberculosis* (all of these in pleural fluid) or presence of caseating granulomas in the histopathology of the pleural biopsy, or histopathological findings compatible with TB (fibrosis, lymphocytic infiltration, unspecific granulomas) followed by complete resolution of the effusion and all of the clinical symptoms within the 3 months after initiating anti-TB therapy.

Malignant pleuritis was defined by the presence of malignant cells in the pleural fluid or biopsy. Other causes of pleural exudate diagnosed through immunohistochemistry or cultures included connective tissue diseases and bacterial and fungal infections. Patients for whom neither the pleural fluid analysis, nor the pleural biopsy, nor specific complementary tests allowed a diagnosis to be reached within 3 months of follow-up, were considered to have 'pleural exudates of unknown cause' and were excluded from the analysis. Diagnostic thoracoscopy could not be performed.

Development of the prediction rule

The aim was to differentiate patients with PT from those with other pathologies. Predictive findings that were identified as relevant in previously published clinical prediction rules for the diagnosis of PT, or that had a strong association with TB in general, were used (Porcel and Vives, 2003; Antonangelo et al., 2007; Burgess et al., 1996; De Oliveira et al., 1994; Demirer et al., 2012; Ghanei et al., 2004; Neves et al., 2004; Neves et al., 2007; Porcel et al., 2000; Porcel et al., 2008; Valdes et al., 2010; Yildiz et al., 2011). The following were selected as relevant predictive anamnestic and clinical findings for evaluation: age (in years), sex, having had previous contact with a patient with TB (defined as living in the same dwelling or working in the same area as a person with a diagnosis of TB during the last 2 years), disease duration (duration of symptoms in days), and presence of fever (as reported by the patient, not necessarily confirmed at the examination), night sweats, haemoptysis, and lymphadenopathy (presence of lymph nodes at any site, observed by the patient or detected during physical examination). The laboratory predictive findings that were withheld were the white blood cell count, pleural protein, pleura/serum protein ratio, pleural LDH, percentage of lymphocytes in pleural cells, and pleural ADA.

Univariate logistic regression was performed to assess the association of the predictor variables with PT. Those predictors found to be associated with an odds ratio (OR) >2 or <0.5 and/or a p-value of <0.10 were retained and used to develop a multiple logistic regression model. Variables with the highest p-values were dropped from the full model in a backward fashion until only variables with a p-value of <0.05 were kept. A bootstrapped linear regression of the expected individual PT probabilities (based on the final logistic regression model) on the withheld variables was then performed. The beta coefficients for the predictors in this linear regression model were multiplied by 100 and rounded to the nearest integer to assign the specific number of points for each predictor in the final score.

The objective for defining the cut-off point of the score was to reach a positive likelihood ratio (LR) of ≥ 10 or a negative LR of ≤ 0.1. These values are considered adequate for diagnostic purposes (Deeks, 2004). If no single cut-off point fulfilled this objective, three categories were to be defined: low likelihood of PT for those scores with a negative LR of ≤ 0.1, high likelihood of PT for those scores with a LR of ≥ 10, and intermediate likelihood for the scores in between.

The sensitivity, specificity, predictive values, and LRs of the score were calculated for the selected cut-off point(s). Additionally a receiver operating characteristics (ROC) curve analysis was used, and the area under the ROC curve (AUC) for the score was compared to that for pleural ADA alone. All calculations were performed using STATA version 11 for Windows (StataCorp., College Station, TX, USA).

Written informed consent was obtained from all participants. The study was approved by the ethics committees of Universidad Peruana Cayetano Heredia, Hospital Nacional Cayetano Heredia,

Table 1
Clinical and laboratory predictive findings and their association with pleural tuberculosis in the univariate and multiple logistic regression models; Lima, Peru.

Predictive findings	Patients		Univariate logistic regression		Final multiple logistic regression model	
	Pleural TB ($n=176$)	Other conditions ($n=62$)	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Clinical						
Mean age, years (95% CI)	37.1 (34.4–39.8)	61.9 (56.6–64.6)	0.94 (0.92–0.96)	<0.001	0.96 (0.94–0.98)	<0.001
Mean disease duration, days (95% CI)	35 (33–37)	77 (74–82)	0.90 (0.85–0.95)	<0.001	Not withheld in the final model	
Fever % (95% CI)	81 (74–86)	45 (32–58)	5.07 (2.71–9.47)	<0.001	Not withheld in the final model	
Male % (95% CI)	70 (66–80)	45 (32–58)	2.90 (1.60–5.25)	<0.001	2.77 (1.16–6.67)	0.02
Contact with a patient with TB % (95% CI)	50 (42–58)	23 (13–25)	3.43 (1.76–6.66)	<0.001	3.25 (1.30–8.07)	0.01
Night sweats % (95% CI)	60 (53–68)	34 (22–47)	2.96 (1.61–5.42)	<0.001	Not withheld in the final model	
Haemoptysis % (95% CI)	7 (4–12)	15 (7–26)	0.43 (0.17–1.08)	<0.07	Not withheld in the final model	
Lymphadenopathy % (95% CI)	16 (11–22)	32 (21–45)	0.40 (0.20–0.78)	<0.01	0.18 (0.06–0.56)	0.003
Laboratory						
Mean WBC count in blood, $\times 10^9$/l (95% CI)	7.750 (7.267–8.232)	8.525 (7.642–9.409)	0.99 (0.99–1.00)	0.11	Not considered for inclusion in the model	
Mean proteins in pleural fluid, g/dl (95% CI)	5.16 (5.03–5.29)	4.16 (3.83–4.49)	2.53 (1.79–3.57)	<0.001	Not withheld in the final model	
Pleural/serum protein ratio (95% CI)	0.58 (0.53–0.62)	0.61 (0.54–0.68)	0.67 (0.24–1.89)	0.49	Not considered for inclusion in the model	
Mean LDH in pleural fluid, g/dl (95% CI)	880.2 (809.1– 951.4)	866.9 (553.2–1180.6)	1.00 (1.00–1.00)	0.90	Not considered for inclusion in the model	
Mean lymphocyte proportion in pleural fluid (95% CI)	63 (58–68)	67 (61–74)	0.66 (0.25–1.72)	0.40	Not considered for inclusion in the model	
Mean ADA in pleural fluid, U/l (95% CI)	79.2 (73.7–84.6)	28.0 (19.9–36.1)	1.06 (1.04–1.07)	<0.001	1.05 (1.03–1.06)	<0.001

TB, tuberculosis; OR, odds ratio; CI, confidence interval; WBC, white blood cell; LDH, lactate dehydrogenase; ADA, adenosine deaminase.

Hospital Nacional Hipolito Unanue, and the Institute of Tropical Medicine, Antwerp.

Results

Three hundred and eighty-three patients were eligible for inclusion in the study. Of these, 101 did not consent to participate and a further 41 were excluded: 21 because a definite diagnosis could not be reached, 12 had empyema, and eight had incomplete data for analysis. Three had concomitant evidence of TB and malignancy. Of the 238 patients eventually included in the analysis, 176 had a diagnosis of PT. One hundred and forty were confirmed through microbiology or the presence of caseating granulomas on histopathology and 36 were diagnosed through histopathological findings compatible with TB followed by complete resolution of the symptoms after treatment. Sixty-two had other causes of pleural exudates, out of which 50 were neoplastic, seven were associated with connective tissue diseases, three had a bacterial aetiology, and two had a fungal origin.

The mean age of the 238 included patients was 43.6 years (95% confidence interval (CI) 40.9–46.3 years). One hundred and fifty-two (64%) were male, 28 (12%) had a previous history of TB, and 102 (43%) reported having had contact with a patient with TB. The mean duration of symptoms was 46.3 days (95% CI 39.0–53.6 days). Fourteen (6%) of the tested patients were infected with HIV (12 patients refused testing).

Table 2
Clinical prediction rule (score) for pleural tuberculosis; Lima, Peru.

Offset	+70
Predictive findings	
Age in years	$-0.7 \times$ (number of years)
Sex (male)	+12
Contact with a patient with TB (presence of)	+13
Lymphadenopathy (presence of)	−19
ADA in IU/l	$+0.4 \times$ (ADA)

TB, tuberculosis; ADA, adenosine deaminase.

The univariate logistic regression analysis found that age, sex, contact with a patient with TB, duration of illness, fever, night sweats, hemoptysis, lymphadenopathy, ADA, and proteins in the pleural fluid were associated with PT at a p-value of ≤0.10 (Table 1). After developing the multiple logistic regression model, only age, sex, contact with a TB patient, lymphadenopathy, and pleural ADA remained significantly and independently associated with PT at a p-value of ≤0.05. The corresponding ORs and individual p-values are shown in Table 1.

Table 2 shows the final CPR and the number of points assigned to each predictive finding.

Figure 1 shows the scores that patients with PT and those with other conditions obtained with the application of this CPR.

Based on the ROC curve analysis, the best single cut-off point for the score was ≥60 points and for ADA was ≥30 IU/l (Figure 2). This cut-off point for the score had an overall accuracy (patients correctly classified) of 89.1%, a sensitivity of 88.1% (95% CI 82.3–92.5%), a specificity of 91.9% (95% CI 82.2–97.3%), a positive

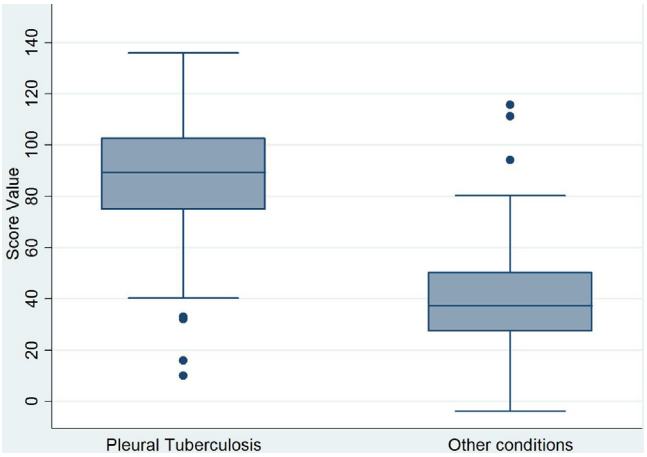

Figure 1. Scores in patients with pleural tuberculosis and in those with other conditions.

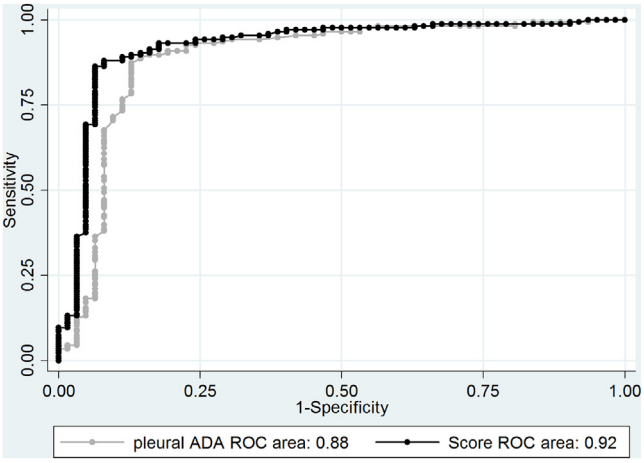

Figure 2. ROC curves for the clinical prediction rule developed and for adenosine deaminase.

predictive value of 96.9% (95% CI 93.0–98.6%), a negative predictive value of 73.1% (95% CI 64.4–80.3%), a positive LR of 10.92 (95% CI 4.7–25.4), and a negative LR of 0.13 (95% CI 0.09–0.2).

In spite of coming close, this single best cut-off point did not simultaneously attain a positive LR >10 and a negative LR <0.1. Defining an additional cut-off point at ≤53 points and moving the higher cut-off to ≥62 points instead of ≥61 points, allowed the patients to be categorized as having a high, medium, or low probability of having PT. In patients scoring ≥62, the condition would be 'ruled in'. In patients scoring ≤53, the CPR attained a sensitivity of 93%, a negative LR of 0.08, and a negative predictive value of 94%, which would allow PT to be 'ruled out'. With this approach, 26% were classified as having a low probability of PT and 67% of patients as having a high probability of PT, and these patients could be managed accordingly.

Discussion

A CPR for PT was developed based on anamnestic findings, clinical symptoms, and ADA levels, in a simple pleural fluid analysis. This CPR attained an overall accuracy of 89% and AUC of 0.92, indicating a good diagnostic performance in this study population. It constitutes a simple and affordable tool for the diagnosis of PT, allowing correct decision-making in most patients in the present study population.

However, although the score had a fair overall accuracy, no single cut-off point achieved high positive and negative LRs simultaneously. The negative predictive value of the best single cut-off point would be too low for decision-making. The approach using two cut-off points is more interesting in terms of clinical utility. This CPR, which is intended for use in high-incidence, resource-constrained settings, could then guide the initiation of anti-TB treatment in patients with a high probability of PT, without the need to perform a pleural biopsy. Likewise, in patients with a low probability of PT, further diagnostic work-up could be directed towards other diagnoses, particularly neoplasms.

Several CPRs have already been derived for the diagnosis of pleural TB, but most of them have been investigated in settings that differ significantly from Latin America in general and Peru in particular, a country with a high incidence of TB and a concentrated HIV epidemic. CPRs are usually context-specific, and it was considered relevant to develop a local CPR and to compare the predictive findings it included with those of other CPRs. The predictive findings in the present study were found to be consistent, at least in part, with those used in several other CPRs.

Among the variables included, male sex and contact with a TB patient were positively associated with PT. Age had a negative association with PT, as found in many other studies (Porcel and Vives, 2003; Antonangelo et al., 2007; Demirer et al., 2012): PT was more likely to be present in younger patients and conversely malignancy was more frequent in older patients. Lymphadenopathy was also found to be negatively associated with PT, as it was found more often in cases of pleural effusion associated with neoplastic metastatic disease with lung and lymphatic involvement.

Of note, ADA activity was the only pleural fluid analysis, and even laboratory finding, associated with PT. Pleural protein and in particular the percentage of lymphocytes in pleural cells, which is a predictive finding included in several CPRs (Sales et al., 2009), was not independently associated with PT in the present study patients. Since *M. tuberculosis*-induced lymphocytic activation is the main mechanism for ADA generation, the predictive ability of lymphocytes may be limited when ADA levels have already been taken into consideration. With respect to the protein levels, this study population consisted of patients with pleural exudates, so its discriminatory power was not expected to be high. Currently, one of the few available recommendations on tuberculous pleuritis suggests strongly taking into account the results of pleural fluid analyses when determining the diagnosis (Light, 2010).

It is also of note that this CPR performed better than ADA alone (7% more sensitive and 5% more specific). This is in contrast with earlier findings (Solari et al., 2017), possibly because the present study made comparisons using a locally derived CPR instead of an external one. The former perform better than those developed in different epidemiological settings, as the strength of association between the predictive findings and PT varies.

A limitation of this study is the quite high proportion of patients who could not be included due to refusal of the pleural biopsy. In addition, the possible contribution of molecular tools as potential predictive findings, in particular of GeneXpert and interferon gamma release assays (IGRAs), was not evaluated. In principle, CPRs should only include results from anamnesis, physical examination, and simple tests, and both of these tests are considered high complexity ones by the food and drug administration clinical laboratory improvement amendments FDA-CLIA (FDA, 2018). Their availability in hospitals in resource-constrained settings such as ours is very limited. Furthermore, evidence on their utility for PT is still being debated. Recent papers have failed to provide conclusive evidence concerning the diagnostic accuracy of GeneXpert for PT (Denkinger et al., 2014), and a systematic review showed suboptimal performance of IGRAs in the diagnosis of PT (Aggarwal et al., 2015). More recently, the measurement of serum and pleural interleukins such as IL-31 (Gao et al., 2016) has shown sensitivities and specificities over 90% for the diagnosis of pleural TB, but once more these are high complexity tests that need further evaluation.

In conclusion, the CPR derived in this study is a useful tool for the diagnosis of PT. As is this case for every CPR, it requires further validation before being implemented, particularly in different settings. In Peru, it could be used immediately as a tool for decision-making in patients with pleural exudates and would allow the management of such patients to be standardized, avoiding invasive procedures, preventing their complications, and saving resources.

Funding

This work was supported by the Damien Foundation. The sponsors were not involved in the analysis and interpretation of the data or in the publication process. LS holds a Belgian Development Cooperation PhD scholarship.

Conflict of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

Roberto Acinelli and Dante Vargas are thanked for their support in the data collection at Hospital Nacional Cayetano Heredia and Hospital Nacional Hipolito Unanue, respectively. Juan Agapito is thanked for support in the laboratory procedures.

References

Aggarwal AN, Agarwal R, Gupta D, Dhooria S, Behera D. Interferon gamma release assays for diagnosis of Pleural tuberculosis: a systematic review and meta-analysis. J Clin Microbiol 2015;53(8):2451–9.

Antonangelo L, Vargas FS, Seiscento M, Bombarda S, Teixera L, Sales RK. Clinical and laboratory parameters in the differential diagnosis of pleural effusion secondary to tuberculosis or cancer. Clinics (Sao Paulo) 2007;62(5):585–90.

Burgess LJ, Maritz FJ, Le RI, Taljaard JJ. Combined use of pleural adenosine deaminase with lymphocyte/neutrophil ratio. Increased specificity for the diagnosis of tuberculous pleuritis. Chest 1996;109(2):414–9.

Cao Y, Fan N, Xing F, Xu L, Qu Y, Liao M. Computed tomography-guided cutting needle pleural biopsy: accuracy and complications. Exp Ther Med 2015;9(1):262–6.

Deeks JJ, Altman D. Diagnostic tests 4: likelihood ratios. BMJ 2004;329(7458):168–9.

Demirer E, Miller AC, Kunter E, Kartaloglu Z, Barnett SD, Elamin EM. Predictive models for tuberculous pleural effusions in a high tuberculosis prevalence region. Lung 2012;190(2):239–48.

Denkinger C, Schumacher S, Boehme C, Dendukuri N, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Resp J 2014;44(2):435–46.

De Oliveira HG, Rossatto ER, Prolla JC. Pleural fluid adenosine deaminase and lymphocyte proportion: clinical usefulness in the diagnosis of tuberculosis. Cytopathology 1994;5(1):27–32.

FDA. Clinical laboratory improvement amendments (CLIA) — FDA. 2018 Available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm.

Gao Y, Ou Q, Wu J, Zhang B, Shen L, Chen S, et al. Potential diagnostic value of serum/pleural fluid IL-31 levels for tuberculous pleural effusion. Sci Rep 2016;, doi: http://dx.doi.org/10.1038/srep20607.

Ghanei M, Aslani J, Bahrami H, Adhami H. Simple method for rapid diagnosis of tuberculosis pleuritis: a statistical approach. Asian Cardiovasc Thorac Ann 2004;12(1):23–9.

Gopi A, Madhavan SM, Sharma SK, Sahn SA. Diagnosis and treatment of tuberculous pleural effusion in 2006. Chest 2007;131(3):880–9.

Goto M, Noguchi Y, Koyama H, Hira K, Shimbo T, Fukui T. Diagnostic value of adenosine deaminase in tuberculous pleural effusion: a meta-analysis. Ann Clin Biochem 2003;40(Pt 4):374–81.

Greco S, Girardi E, Masciangelo R, Capoccetta GB, Saltini C. Adenosine deaminase and interferon gamma measurements for the diagnosis of tuberculous pleurisy: a meta-analysis. Int J Tuberc Lung Dis 2003;7(8):777–86.

Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. JAMA 1997;277(6):488–94.

Liang QL, Shi HZ, Wang K, Qin SM, Qin XJ. Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. Respir Med 2008;102(5):744–54.

Light RW, MacGregor MI, Luchsinger PC, Ball Jr. WC. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77(4):507–13.

Light RW. Update on tuberculous pleural effusion. Respirology 2010;15(3):451–8.

McLeod DT, Ternouth I, Nkanza N. Comparison of the Tru-cut biopsy needle with the Abrams punch for pleural biopsy. Thorax 1989;44(10):794–6.

Morisson P, Neves DD. Evaluation of adenosine deaminase in the diagnosis of pleural tuberculosis: a Brazilian meta-analysis. J Bras Pneumol 2008;34(4):217–24.

MINSA. Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis. Norma Técnica de Salud para la Atención integral de las personas afectadas por tuberculosis. Ministerio de Salud del Perú; 2013.

Neves DD, Dias RM, da Cunha AJ, Preza PC. What is the probability of a patient presenting a pleural effusion due to tuberculosis?. Braz J Infect Dis 2004;8(4):311–8.

Neves DD, Dias RM, Cunha AJ. Predictive model for the diagnosis of tuberculous pleural effusion. Braz J Infect Dis 2007;11(1):83–8.

Porcel JM, Vives M, Gazquez I, Vicente de Vera MC, Perez B, Rubio M. Usefulness of pleural complement activation products in differentiating tuberculosis and malignant effusions. Int J Tuberc Lung Dis 2000;4(1):76–82.

Porcel JM, Vives M. Differentiating tuberculous from malignant pleural effusions: a scoring model. Med Sci Monit 2003;9(5):CR175–80.

Porcel JM, Aleman C, Bielsa S, Sarrapio J, Fernandez de ST, Esquerda A. A decision tree for differentiating tuberculous from malignant pleural effusions. Respir Med 2008;102(8):1159–64.

Sales RK, Vargas FS, Capelozzi VL, Seiscento M, Genofre EH, Teixeira LR, et al. Predictive models for diagnosis of pleural effusions secondary to tuberculosis or cancer. Respirology 2009;14(8):1128–33.

Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res 2004;120(4):316–53.

Solari L, Soto A, Van der Stuyft P. Performance of clinical prediction rules for diagnosis of pleural tuberculosis in a high-incidence setting. Trop Med Int Health 2017;22(10):1283–92.

Valdes L, San Jose ME, Pose A, Gude F, Gonzalez-Barcala FJ, Alvarez-Dobano JM, et al. Diagnosing tuberculous pleural effusion using clinical data and pleural fluid analysis. A study of patients less than 40 years-old in an area with a high incidence of tuberculosis. Respir Med 2010;104(8):1211–7.

World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents. Geneva: World Health Organization; 2007.

World Health Organization. Global tuberculosis report 2016. World Health Organization. Downloaded the 25th of June 2017 from http://www.who.int/tb/publications/global_report/en/.

Yildiz PB, Yazar EE, Gorgun D, Secik F, Cakir G. Predictive role of adenosine deaminase for differential diagnosis of tuberculosis and malignant pleural effusion in Turkey. Asian Pac J Cancer Prev 2011;12(2):419–23.