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Predictive Models for Tuberculous Pleural Effusions in a High Tuberculosis Prevalence Region

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Abstract
Background Patients with pleural effusions who reside in geographic areas with a high prevalence of tuberculosis frequently have similar clinical manifestations of other diseases. The aim of our study was to develop a simple but accurate clinical score for differential diagnosis of tuberculosis pleural effusion (TPE) from non-TB pleural effusion (NTPE).

Methods This was an unblinded, prospective study of Turkish patients 18 years of age or older with pleural effusion of indeterminate etiology conducted from June 2003 to June 2005. Unconditional logistic regression models were used to discriminate TPE cases from NTPE cases. Standard errors for the area under the curve (AUC) were calculated using the Mann–Whitney method. Data were statistically significance if two-tailed $P < 0.05$.

Results A total of 63.3% (157/248) of the patients had TPE while 36.7% (91/248) of the patients had other etiologies for pleural effusions. We were able to provide a predictive model of TPE that included age <47 years and either pleural fluid adenosine deaminase enzyme (PADA) >35 U/l or pleural serum protein ratio >0.710. However, only the combination of age <47 and PADA >35 U/l was significant (odds ratio [OR]: 7.46; 95% confidence interval [CI]: 3.99–13.96). The generated summary score (range = 0–6) was significantly predictive of TPE (OR: 2.91; 95% CI: 2.18–3.89) and with high AUC (0.79).

Conclusion We propose an affordable model that includes age <47 years and PADA >35 U/l for timely diagnosis of TPE in geographical regions with a high prevalence of TB.

Keywords Adenosine deaminase enzyme · Lactate dehydrogenase enzyme · Pulmonary tuberculosis · Tuberculous pleural effusion

Abbreviations

ADA	Adenosine deaminase enzyme
AUC	Area under curve
BCG	Bacillus Calmette-Guérin
CxR	Chest X-ray
HRCT	High-resolution chest CT
LDH	Lactate dehydrogenase enzyme

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MTB	*Mycobacterium tuberculosis*
NTPE	Non-TB pleural effusion
P/SADA	Pleural serum ADA ratios
P/SLDH	Pleural to serum LDH
PADA	Pleural fluid ADA
PE	Pleural effusion
PLDH	Pleural lactate dehydrogenase enzyme
PPD	Purified protein derivative
ROC	Receiver operator curves
TB	Pulmonary tuberculosis
TPE	TB pleural effusion
TST	Tuberculin skin test
WHO	World Health Organization

Introduction

Pulmonary tuberculosis (TB) is major public health burden in many developing countries [1]. Other than lung involvement, extrapulmonary TB of the lymph nodes and pleura can be the initial presentation in close to 25% of adults [1]. Furthermore, in areas with a high prevalence of TB, more than 50% of pleural effusion (PE) of indeterminate etiology is due to TB [2].

Tuberculous pleuritis is thought to represent primarily a hypersensitivity reaction to tuberculous protein after the rupture of a subpleural lung caseous focus into the pleural space [3], subsequently followed by delayed hypersensitivity reaction [1]. Ultimately, TB pleural effusion (TPE) results from the combination of the increased pleural fluid formation and the decline in pleural fluid removal [4]. Clinically, tuberculous pleuritis usually presents as an acute illness, with the most frequent symptoms being nonproductive cough ($\sim$70%), pleuritic chest pain ($\sim$70%), fever ($\sim$85%), and dyspnea, especially with large effusion [1]. If left untreated, tuberculous pleuritis usually resolves over time, but the patient frequently develops active TB later [1].

The identification of *Mycobacterium tuberculosis* (MTB) in pleural fluid or lung tissue remains the gold standard for diagnosis of TPE [1]; however, biopsy is invasive and frequently not available. Blind pleural biopsy has a low sensitivity and places the patient at risk for pneumothorax, while pleuroscopic biopsy may have improved sensitivity but is not practical for routine use [5, 6]. Additionally, routine smears of the pleural fluid for MTB in immunocompetent individuals are generally negative unless the patient has developed TB-associated empyema [7]. Furthermore, it is imperative to differentiate TPE from other differential diagnoses that may carry high morbidity and mortality and may require substantially different treatment regimens. For example, in the United States, the estimated incidence of malignant pleural effusion is 150,000 cases per year [4]. Thus, derivation of a clinical decision algorithm to differentiate malignant PE from TPE would be of great utility.

Given current diagnostic difficulties and the international morbidity and mortality of MTB, the objective of the present study was to establish an affordable low-complexity model using clinical and laboratory parameters to more accurately diagnose and differentiate TB from non-TB pleural effusion (NTPE).

Materials and Methods

In an unblinded and prospective manner we analyzed the data of all adult patients, 18 years or older, with pleural effusion of indeterminate etiology who presented at the GATA Haydarpaşa Training Hospital in Istanbul, Turkey, from June 2003 to June 2005.

Each patient underwent a thorough physical examination and detailed history assessment, including contact with a TB patient, prior TB disease, Bacillus Calmette-Guérin (BCG) vaccination status, and history of untreated pneumonia or empyema. Tuberculin skin test (TST) by intracutaneous injection of 0.1 ml (5 tuberculin units) of purified protein derivative (PPD) was performed in each patient once and the size of induration was measured 48 h after injection but no later than 72 h. A tuberculin reaction of $\geq$10 mm of induration was classified as positive, indicating a probability of recent TB infection or other clinical conditions that increase the risk for progression to active TB [8].

Peripheral blood and pleural fluid samples were collected at the same visit. Both pleural and serum adenosine deaminase enzyme (ADA) levels were determined by the Giusti method [9]. A Coulter MD II Series Analyzer (Coulter Corporation, Miami, FL, USA) was used to perform complete blood count. Biochemical profiles were obtained by automated analysis (R-A 1000, RA-XT autoanalyzer, Technicon, Tarrytown, NY, USA). Routine analysis of the pleural fluid included total and differential nucleated cell counts, glucose, protein, albumin, lactate dehydrogenase enzyme (LDH), ADA, and cytology for malignant cells. All patients underwent posteroanterior and lateral chest radiography, with localization of the effusion as right, left, or bilateral.

The diagnosis of TPE required the identification of MTB in a pleural fluid or sputum sample by (1) Ziehl–Neelsen staining [10], (2) aerobic and anaerobic cultures in Lowenstein media [10], or (3) the identification of necrotizing granulomatous inflammation with caseous necrosis by histology examination in a blind pleural biopsy specimens obtained by either Abrams [11] or Cope [12] needle. Patients were excluded from final analysis if their ADA enzyme level was not available or no final diagnosis was made.

PE was diagnosed as neoplastic only if it was confirmed by positive histopathology or cytological evaluation. However, PE was considered parapneumonic if positive for bacterial or fungal culture or if it was accompanied by bacterial pneumonia, lung abscess, or bronchiectasis in the presence of negative TB and malignancy evaluations.

We utilized several approaches for predicting PE etiology among TB patients. The first approach utilized age, P-LDH, PADA >35 U/l, pleural fluid-to-serum protein ratio, and parenchymal lesion in CxR. In addition, three separate strategies were used: (1) continuous, (2) median, and (3) best cut point. As parenchymal lesion at CxR and PADA >35 U/l were considered dichotomous, results are presented only for best-cut-point analyses.

The institutional review board at GATA Haydarpaşa Training Hospital approved the study protocol.

Statistical Analysis

Unconditional logistic regression models were used to discriminate TPE cases from NTPE cases and generate odds ratios (OR) and 95% confidence intervals (CI) as estimates of effect size. Independent variables were utilized in logistic regression models in two ways: continuous and binary. Binary values were determined by median values. Best cutoff values were chosen for those continuous variables with values that discriminate TPE cases from NTPE cases using receiver operator curves (ROC). For both continuous and binary independent variables, following initial models that included all variables, a second model that excluded nonstatistically significant variables ($P > 0.05$) was run. The Hosmer–Lemeshow test was used to assess the fit of the logistic regression model. Estimates of sensitivity, specificity, and AUC were determined by final model fit. Standard errors for the AUC were calculated using the Mann–Whitney method. All statistical analyses were performed using SAS ver. 9.2 (SAS Institute, Cary, NC, USA). Statistical significance was at two-tailed $P < 0.05$.

Results

Patient Demographics

We prospectively enrolled 251 patients who consecutively presented with PE and met our enrollment criteria. Of these, 157 (62.5%) and 94 (37.5%) were diagnosed with TPE and NTPE, respectively (Table 1). Patients were younger in the TPE group (23 vs. 51 years, $P < 0.05$) and a male predominance was observed in the TPE group (98% vs. 84%). Similar baseline proportions of BCG vaccination were reported for both groups (68 and 62%); however, TST tested positive via the PPD method more frequently in the TPE group (70% vs. 14%, $P < 0.05$). TPE patients presented with a greater predominance of left-sided pleurisy (57% vs. 22%, $P < 0.05$), whereas NTPE pleurisy was more frequently right-sided (59% vs. 39%, $P < 0.05$) or bilateral (19% vs. 4%, $P < 0.05$).

Table 2 outlines the microbiological and histological findings in the 157 patients who had one or more positive tests for TPE, with observation of caseating granulomas in a pleural biopsy as the most frequent finding (92/157, 58.6%).

Table 1 Patient demographics

	N (%)	Male/female	Age (SD)	PPD (+) (%)	BCG (%)	CxR right side of pleural (%)	Left effusion (%)	Bilateral effusion (%)
TPE	157 (62.5)	154/3	23 ± 5*	70*	68	39	57*	4
NTPE	94 (37.5)	80/14	51 ± 23	14	62	59*	22	19*
Infectious	40 (15.9)	36/4	38.6 ± 23	63	–	–	–	–
Neoplastic	30 (11.9)	21/9	62 ± 15	36	–	–	–	–
CABG	4 (0.02)	3/1	66 ± 4.7	33	–	–	–	–
CHF	8 (0.03)	8/0	75 ± 9	0	–	–	–	–
CRF	2 (0.01)	2/0	58.5 ± 4.9	0	–	–	–	–
Idiopathic	7 (0.03)	7/0	30.7 ± 21	28	–	–	–	–
PE	1 (0.0)	1	–	–	–	–	–	–
Fahr's syndrome	1 (0.0)	1	–	–	–	–	–	–
Hydatid cyst	1 (0.0)	1	–	–	–	–	–	–
Total	251 (100)	234/17	–	–	–	–	–	–

TPE TB pleural effusion, *NTPE* non-TB pleural effusion, *PPD* purified protein derivative, *CABG* coronary artery bypass surgery, *CHF* congestive heart failure, *CRF* chronic renal failure, *PE* pulmonary thromboembolism, *CxR* chest X-ray, *SD* standard deviation

* Statistically significant; $P < 0.05$

Table 2 Histological and microbiological findings for the TPE patients ($n = 157$)

Test	*n*	%
Culture in Lowenstein medium		
Pleural fluid	25/157	15.9
Pleural biopsy tissue	16/157	10.2
Sputum	58/157	36.9
Ziehl–Neelsen staining		
Pleural fluid	3/157	1.9
Pleural biopsy tissue	0/157	–
Sputum	35/157	22.3
Pleural caseating granulomas	92/157	58.6

Pleural Adenosine Deaminase (PADA)

Assessment using Mann–Whitney's statistic revealed significantly elevated PADA levels in TPE patients when compared to NTPE patients ($P < 0.0001$). ROC analysis similarly revealed highly significant results for distinguishing between tuberculous and nontuberculous effusions, with an AUC of 0.88 (95% CI: 0.83–0.93; $P < 0.0001$) (Fig. 1). Table 3 shows the results of multiple threshold values. Selecting the cutoff of 30 U/l allowed for a sensitivity of 0.94 (95% CI: 0.87–0.97), specificity of 0.65 (95% CI: 0.54–0.77) [+LR = 2.69, −LR = 0.1, PPV = 0.72, NPV = 0.89]. Alternatively, the cutoff of 46 U/l showed a sensitivity of 0.72 (95% CI: 0.63–0.80), specificity of 0.92 (95% CI: 0.85–0.97) [+LR = 9.2, −LR = 0.3, PPV = 0.92, NPV = 0.73].

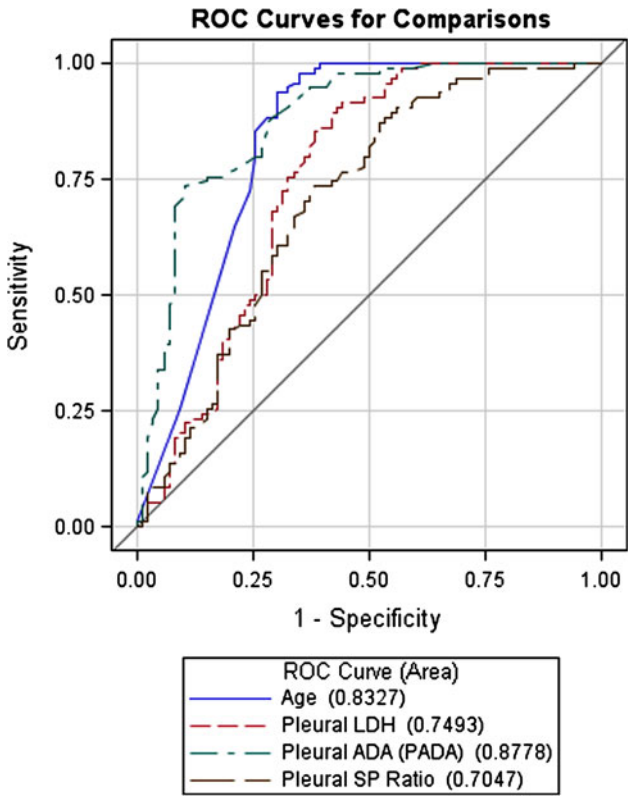

Fig. 1 Overlay of receiver operator curve characteristics for the prediction of TPE. *LDH* lactate dehydrogenase enzyme, *ADA* adenosine deaminase enzyme, *SP* serum protein ratio

Pleural Serum ADA (P/SADA)

Assessment using Mann–Whitney's statistic revealed significantly elevated pleural serum ADA ratios (P/SADA) in TPE patients when compared to NTPE patients ($P < 0.0001$). ROC analysis similarly revealed highly significant results for distinguishing between tuberculous and nontuberculous effusions, with an AUC of 0.78 (95% CI: 0.70–0.86; $P < 0.0001$); however, these results were less significant than measuring absolute PADA levels alone. Table 3 shows the results of multiple threshold values. The cutoff of 1.2 allowed for a sensitivity of 0.80 (95% CI: 0.70–0.87), specificity of 0.65 (95% CI: 0.50–0.78) [+LR = 2.25, −LR = 0.32, PPV = 0.82, NPV = 0.62]. Alternatively, selecting the cutoff of 1.74 resulted in lowering the sensitivity to only 0.30 (95% CI: 0.21–0.41) while increasing the specificity to 0.94 (95% CI: 0.83–0.99) [PPV = 0.90, NPV = 0.41, +LR = 4.82, −LR = 0.75].

Pleural Lymphocytes (P-lymph)

Again, assessment using Mann–Whitney's statistic revealed significantly elevated pleural lymphocyte percentage in TPE patients when compared to NTPE patients ($P < 0.0003$). ROC analysis similarly revealed highly significant results for distinguishing between tuberculous and nontuberculous effusions, with an AUC of 0.76 (95% CI: 0.61–0.91; $P < 0.0004$). Table 3 shows the results of multiple threshold values. A 95% sensitivity was achieved using the cutoff of 60%, sensitivity of 0.95 (95% CI: 0.89–0.98), specificity of 0.47 (95% CI: 0.21–0.73) [+LR = 1.77, −LR = 0.12, PPV = 0.94, NPV = 0.50]. Alternatively, selecting the cutoff of 90% allowed for a sensitivity of 0.58 (95% CI: 0.49–0.67), specificity of 0.73 (95% CI: 0.45–0.92) [PPV = 0.95, NPV = 0.17, +LR = 2.19, −LR = 0.57].

In the meantime, total serum white blood cell (WBC) count was not helpful in distinguishing TPE from NTPE, with ROC analysis revealing an AUC of only 0.33 (95% CI: 0.24–0.41; $P < 1.0$).

Pleural Lactate Dehydrogenase (P-LDH)

Assessment using Mann–Whitney's statistic revealed significantly elevated P-LDH levels in TPE patients when

Table 3 Sensitivity and specificity of laboratory parameter cutoffs in identifying TPE

Variable	Value	Sensitivity (95% CI)	Specificity (95% CI)	+LR/−LR	PPV/NPV
PADA (U/l)	30	0.94 (0.88–0.98)	0.65 (0.54–0.75)	2.69/0.10	0.77/0.89
	35	0.84 (0.76–0.90)	0.73 (0.63–0.82)	3.11/0.22	0.80/0.78
	38	0.80 (0.72–0.87)	0.79 (0.69–0.87)	3.76/0.25	0.83/0.76
P/SADA	1.2	0.80 (0.70–0.87)	0.65 (0.50–0.78)	2.25/0.32	0.81/0.62
	1.3	0.72 (0.62–0.81)	0.73 (0.58–0.85)	2.66/0.38	0.84/0.57
	1.4	0.60 (0.50–0.70)	0.85 (0.72–0.94)	4.13/0.47	0.89/0.53
P-lymph	0.6	0.95 (0.89–0.98)	0.47 (0.21–0.73)	1.77/0.12	0.94/0.50
	0.7	0.87 (0.80–0.93)	0.60 (0.32–0.84)	2.19/0.21	0.95/0.36
	0.8	0.77 (0.69–0.84)	0.73 (0.45–0.92)	2.89/0.31	0.96/0.28
PLDH (U/l)	328	0.99 (0.96–1.00)	0.38 (0.28–0.48)	1.59/0.02	0.69/0.97
	397	0.95 (0.90–0.98)	0.46 (0.36–0.57)	1.77/0.10	0.71/0.88
	512	0.90 (0.83–0.95)	0.56 (0.45–0.66)	2.04/0.18	0.74/0.80

TPE TB pleural effusion, *ADA* adenosine deaminase enzyme, *PADA* pleural fluid ADA, *P/SADA* pleural serum adenosine deaminase enzyme ratios, *PLDH* pleural lactate dehydrogenase enzyme, *P-lymph* pleural lymphocytes, *CI* confidence interval, *+LR* likelihood ratio positive, *−LR* likelihood ratio negative, *PPV* positive predictive value, *NPV* negative predictive value

compared to NTPE patients ($P < 0.0001$). ROC analysis similarly revealed significant results for distinguishing between tuberculous and nontuberculous effusions, with an AUC of 0.74 (95% CI: 0.66–0.81; $P < 0.0001$) (Fig. 1). Table 3 shows the results of multiple threshold values. A 95% sensitivity was achieved using the cutoff of 397 U/l, sensitivity of 0.95 (95% CI: 0.90–0.98), specificity of 0.46 (95% CI: 0.36–0.57) [PPV = 0.71, NPV = 0.88, +LR = 1.77, −LR = 0.10]. Alternatively, selecting the cutoff of 656 U/l allowed for a sensitivity of 0.74 (95% CI: 0.66–0.82), specificity of 0.65 (95% CI: 0.54–0.74) [PPV = 0.74, NPV = 0.65, +LR = 2.09, −LR = 0.37].

Of note, the pleural to serum LDH (P/SLDH) ratio was not helpful in distinguishing tuberculous from nontuberculous pleural effusions, with an ROC analysis yielding an AUC of only 0.40 (95% CI: 0.30–0.50; $P = 0.98$).

Discussion

The differentiation between TPE and NTPE continues to pose a major diagnostic dilemma to many health-care providers worldwide. This is particularly true in countries with a high prevalence of TB such as Turkey. In 2008, the World Health Organization (WHO) estimated the prevalence of TB in Turkey [13] to be 22/100,000 and often presenting as PE. Therefore, the prevalence of TPE in our series was high (62.5%), although it remains slightly lower than the recently reported prevalence of 75.7% by Valdés et al. [14].

Obviously, the main differential diagnosis for TPE is with malignant PE, since both effusions are lymphocytic. To further complicate the diagnostic dilemma, in a large proportion of cases confirmatory diagnosis of NTPE is not attainable by microbiological methods alone, while the cytological studies for malignant PE have low sensitivity (60–66%) [10, 15]. Furthermore, although closed-needle biopsy of the pleura is more diagnostic than PE analysis in establishing TPE, it adds little diagnostic yield to fluid cytology alone in malignant PE [16]. The question is whether this invasive procedure can be avoided, especially since the analysis of PE frequently requires expensive and complex laboratory techniques that are often not readily available. Furthermore, due to the diverse presentation of various pleural diseases, it is unwise to consider only a single factor when determining the most likely etiology of PE. Hence, we performed unconditional logistic regression models to discriminate cases of TPE from NTPE.

In this study, a number of approaches were utilized to predict PE etiology among TB patients. By evaluating the data as *continuous* variables (Fig. 1; Table 4), all univariate models were statistically significant. However, only two of four models presented a high degree of accuracy, and age ($R^2 = 0.42$; AUC = 0.83, 95% CI: 0.77–0.90) and PADA ($R^2 = 0.40$; AUC = 0.88, 95% CI: 0.83–0.93) explained the greatest model variance and presented the largest AUC results. Then using *median* as cut points, once again all models were statistically significant but with a significant loss of accuracy when parameters were treated as continuous variables. Again, age ($R^2 = 0.21$; AUC = 0.80, 95% CI = 0.74–0.85) and PADA ($R^2 = 0.38$; AUC = 0.80, 95% CI: 0.74–0.86) explained the greatest model variance and presented the largest AUC results. However, age as a median cut point predicted 50% less variance than earlier models. In addition, AUC and R^2 PADA results as median were similar to earlier models but

those models were significantly less accurate (67.4% vs. 88.7%).

Lastly, using *best cut points* defined by maximizing AUC revealed that age ($R^2 = 0.37$; AUC = 0.72, 95% CI: 0.65–0.78) and PADA ($R^2 = 0.35$; AUC = 0.80, 95% CI: 0.75–0.86) explained the greatest model variance and presented the largest AUC results. Furthermore, PADA >35 U/l predicted the most variance ($R^2 = 0.42$) and maximized AUC (0.79, 95% CI: 0.83–0.85).

Table 4 (continuous) and Table 5 (best cut point) present results of multivariate logistic regression equations with all parameters (model 1) and only those significant parameters from the earlier model (model 2). Tables 5 (continuous) and 6 (best cut point) present results of multivariate logistic regression equations with all parameters (model 1) and only those significant parameters from the earlier model (model 2). When treated as continuous variables (Table 5) only age ($\beta = -0.104 \pm 0.025$, $P < 0.001$) and PADA ($\beta = 0.058 \pm 0.001$, $P < 0.001$) were significant. When only those terms were included in a model, the resulting model was significantly different from model 1 ($P < 0.05$) but minimal gain was achieved via AUC (0.925 vs. 0.915). Similarly, when treated as best cut points (Table 6), age <47 years ($\beta = 3.483 \pm 0.782$) and PADA >35 U/l ($\beta = 1.825 \pm 0.451$, $P < 0.001$) were statistically significant (model 1). Similar to the continuous variables, when only those significant best cut points parameters were retained (model 2), no significant difference was observed from model 1 ($P < 0.07$).

Lastly, a summary score was created (range = 0–6) after dichotomizing each parameter by the best cut point then summing those values (Table 7). Summary score treated as a continuous variable was significantly predictive of PE etiology among TPE (OR: 2.91; 95% CI: 2.18–3.89) and maximized AUC (0.790). Using a summary score of 2 with no particular parameter included was a significant predictor of PE etiology among TPE (OR: 13.23; 95% CI: 6.37–27.66). Using model selection criteria based on model −2 log-likelihood scores (−2LL), the best two-variable models include age <47 years and either PADA >35 U/l or pleural serum protein ratio >0.710, although only the combination of age <47 years and PADA >35 U/l was statistically significant (OR: 7.46; 95% CI: 3.99–13.96) (Fig. 2).

The performance of some variables in our model is consistent with the results of similar analyses in differentiating TPE from NTPE described in other studies [2, 17–20].

The presence of small lymphocytes in PE is a valuable tool in differentiating TPE from NTPE, with an estimated 50–90% of patients with TB pleuritis having small-size lymphocytes in their PE [3]. Hence, its combination with PADA has been investigated with the intention of increasing specificity by excluding causes of falsely high PADA values, especially empyema [3, 21]. However, the presence of pleural lymphocytes had little impact in our analysis. This may be related to the fact that patients with TPE for less than 2 weeks are more likely to have predominantly polymorphonuclear leukocytes in their PE instead of lymphocytes [22].

Similarly, P-LDH and pleural serum protein ratios did not prove useful in our multivariate analysis, so they were excluded despite their well-known utility in discriminating transudate from exudate [4].

Given the complexity of differentiating TPE from NTPE, a number of other investigators attempted to develop an accurate but simple tool for diagnosing TPE from other entities. In 2001, Carrion-Valero et al. [23] performed a discriminate analysis using 47 variables except ADA for the diagnosis of TPE. They studied 78 patients with TPE and 111 with NTPE. In their model the predictors for the diagnosis of TPE were age, white cell count, TST, and blood-stained exudates; with a sensitivity of 90%, a specificity of 87%, and accuracy of 88%. Then Porcel et al. [15] developed clinical score models for differentiating between TPE and NTPE in a total of 106 tuberculous and 286 neoplastic effusions. One of their models predicted a TPE etiology if ADA >40 U/l, age <35 years, temperature >37.8°C, and RBC count $<5 \times 10^9$/l. In the other model without ADA, no previous history of malignancy and a pleural fluid/serum LDH ratio >2.2 were added to age <35 years, temperature >37.8°C and RBC count $<5 \times 10^9$/l. A proportional score was then utilized to the magnitude of the coefficients of the logistic equations, with a cut-off point of >5 in model 1 and >6 in model 2. Overall, the sensitivity of both models was 95 and 97%, respectively, with specificity 94 and 91%, respectively, and AUC of 0.987 and 0.982, respectively.

Another study by Sales et al. [24] utilized the numerical score of Porcel and Vives [15] in establishing two predictive models for the diagnosis of TPE from malignant PE. Their first model included ADA, globulins, and the absence of malignant cells in the pleural fluid, while the second model included ADA, globulins, and fluid appearance, and both models yielded similar results (accuracy of 97.7% vs. 96.6%).

Recently, Valdés et al. [14] reported data from 218 patients with PE (165 tuberculous, 21 infectious, 11 neoplastic, 16 miscellaneous, and 3 idiopathic). They proposed an algorithm based on a regression tree that classified an effusion as TPE or NTPE. One model included pleural fluid ADA >35 U/l and lymphocytes >31.5% and correctly classified 216/218 effusions (1 false negative, 1 false positive). The sensitivity of that model was 99.4%, specificity 98.1%, and accuracy of 99%. The other proposed model was without ADA and included three variables, lymphocytes >31.5%, fever, and cough, and correctly classified 207/218 TPEs (8 false negatives, 3 false positives).

Table 4 Individual parameter performance from logistic regression models for the discrimination of TPE from NTPE

Run	Variable	*N*	Cutoff	R^2	χ^2 (*P*)	OR (95% CI)	Acc.	AUC (95% CI)	Sens (95% CI)	Spec (95% CI)
(1) Continuous	Age (years)	251	na	0.42	0.001	0.89 (0.86–0.92)	79.0	0.83 (0.77–0.90)	na	na
	Pleural fluid LDH	221	na	0.07	0.001	1.01 (1.00–1.02)	73.5	0.75 (0.67–0.82)	na	na
	Pleural fluid ADA (PADA)	201	na	0.40	0.001	1.09 (1.06–1.11)	88.7	0.88 (0.83–0.93)	na	na
	Pleural serum protein ratio	197	na	0.08	0.001	26.05 (4.07–166.8)	69.9	0.70 (0.63–0.78)	na	na
(2) Median cut point	Age (years)	251	<22	0.21	0.001	2.16 (1.56–2.76)	55.2	0.80 (0.74–0.85)	70.0 (62.9–77.2)	78.7 (70.5–87.0)
	Pleural fluid LDH	221	>742	0.14	0.001	3.93 (2.23–6.94)	44.1	0.66 (0.60–0.73)	64.1 (55.5–72.2)	68.8 (58.9–77.6)
	Pleural fluid ADA (PADA) (U/l)	201	>45	0.38	0.001	3.37 (2.53–4.21)	67.4	0.80 (0.74–0.86)	74.1 (66.0–82.2)	94.1 (85.1–96.7)
	Pleural serum protein ratio	197	>0.650	0.12	0.001	3.48 (1.93–6.27)	42.4	0.65 (0.55–0.64)	85.2 (77.5–91.0)	47.2 (36.9–57.6)
(3) Best cut point	Age (years)	251	<47	0.37	0.001	75.6 (22.55–254.80	58.4	0.72 (0.65–0.78)	98.1 (96.0–100.0)	59.6 (49.7–68.5)
	Pleural fluid LDH	221	>749	0.13	0.001	3.80 (2.16–6.71)	43.5	0.66 (0.60–0.72)	63.3 (54.4–71.6)	68.8 (59.4–78.2)
	Pleural fluid LDH (2/3 over normal)	221	>531	0.29	0.001	9.98 (5.07–19.65)	50.3	0.73 (0.67–0.78)	88.3 (81.8–93.0)	57.0 (46.8–66.8)
	Pleural fluid ADA (PADA) (U/l)	201	>42	0.35	0.001	20.35 (9.73–42.53)	66.3	0.80 (0.75–0.86)	77.7 (69.1–85.4)	85.4 (78.1–92.7)
	Pleural serum protein ratio	197	>0.710	0.12	0.001	3.47 (1.93–6.27)	42.4	0.65 (0.61–0.73)	63.9 (54.5–72.5)	66.3 (56.0–75.5)
	Pleural serum protein ratio	197	>0.650	0.17	0.001	5.14 (2.62–10.09)	42.4	0.65 (0.58–0.72)	85.2 (77.5–91.0)	47.2 (36.9–57.6)
	Parenchyma lesion at CxR	204	–	0.02	0.158	1.46 (0.96–1.96)	31.1	0.56 (0.49–0.67)	47.8 (40.0–55.6)	40.4 (27.2–54.8)
	Pleural fluid ADA (PADA) >35 U/l	201	>35	0.42	0.001	16.55 (8.11–33.80)	62.3	0.79 (0.83–0.85)	86.7 (79.3–92.0)	71.9 (61.9–80.5)

TPE TB pleural effusion, *NTPE* non-TB pleural effusion, R^2 generalized coefficient of determination, χ^2 chi-squared, *OR* odds ratio, *CI* confidence interval, *AUC* area under curve, *na* not applicable, *ADA* adenosine deaminase enzyme, *PLDH* pleural lactate dehydrogenase enzyme, *CxR* chest X-ray, *PADA* pleural fluid adenosine deaminase enzyme

Table 5 Logistic regression coefficients for significance values for models used to discriminate TB from NTB: independent variables as continuous

Variable	Model 1				Model 2			
	β (SE)	P	R^2	AUC	β (SE)	P	R^2	AUC
Age (years)	−0.104 (0.025)	0.001	–	–	−0.109 (0.026)	0.001	–	–
PLDH	0.001 (0.001)	0.750	–	–	–	–	–	–
Pleural fluid ADA (PADA) (U/l)	0.058 (0.013)	0.001	–	–	0.063 (0.013)	0.001	–	–
Pleural serum protein ratio	−0.007 (1.190)	0.996	0.506	0.915	–	–	0.520	0.925
Parenchymal lesion at CxR[a]	–	–	–	–	–	–	–	–
Pleural fluid ADA (PADA) >35 U/l[a]	–	–	–	–	–	–	–	–

Model 1: all variables included, *Model 2* excluding nonstatistically significant variables, *TPE* TB pleural effusion, *NTPE* non-TB pleural effusion, *SE* standard error, R^2 generalized coefficient of determination, *AUC* area under curve, *PLDH* pleural lactate dehydrogenase enzyme, *ADA* adenosine deaminase enzyme, *CxR* chest X-ray

[a] Data were not significant and are not shown

Table 6 Logistic regression coefficients for significance values for models used to discriminate TB from NTB: independent variables as best cut point binary

Variable	Model 1				Model 2			
	β (SE)	P	R^2	AUC	β (SE)	P	R^2	AUC
Age <47 years	3.48 (0.782)	0.001	–	–	3.83 (0.024)	0.001	–	–
Pleural fluid LDH >749	0.58 (0.438)	0.183	–	–	–	–	–	–
Pleural serum protein ratio >0.710	0.72 (0.433)	0.098	–	–	–	–	–	–
Parenchymal lesion at CxR	–	–	–	–	–	–	–	–
Pleural fluid ADA (PADA) >35 U/l	1.83 (0.451)	0.001	0.62	0.88	2.15 (0.443)	0.001	0.621	0.877

Model 1: all variables included, *Model 2* excluding nonstatistically significant variables, *TPE* pleural effusion, *NTPE* non-TB pleural effusion, *SE* standard error, R^2 generalized coefficient of determination, *AUC* area under curve, *CxR* chest X-ray, *ADA* adenosine deaminase enzyme, *LDH* lactate dehydrogenase enzyme

That model had a sensitivity of 95.2%, specificity of 94.3%, and accuracy of 95.0%.

However, our study had key methodological differences from other published models for the diagnosis of TPE. For instance, similar to the studies by Carrion-Valero [23], Porcel [15], and Sales [24], our study used age as one of the discriminate variables for diagnosis of TPE. However, in contrast to the study by Valdés et al. [14], who limited their study to a younger population with high prevalence of TPE, our model included patients with diverse ages (Table 1). Consequently, the high predictive value of the Valdés et al. [14] strategies might not be applicable in an older age group, while our model should have wide applicability in a general patient population presenting with symptomatic PE.

Furthermore, the studies by Sales et al. [24] and Porcel et al. [15, 25] limited their models to differentiating between TPE and neoplastic effusions and did not consider other possible causes for symptomatic PE such as infectious or rheumatologic diseases. That is in contrast to our models where we were able to differentiate between TPE and those other possible etiologies for PE.

Finally, we created a simple-to-use bioclinical scoring rule that utilizes readily available data that assigned a relative score to each of the variables included in the final multivariate diagnostic model. That is in contrast to Gupta et al. [26] who utilized the PADA level in a wide age range group rather than a scoring model for differentiating TPE (56/96) from NTPE (40/96), with a smaller number of NTPE secondary to malignancy (16/40) and infectious etiologies (18/40). Furthermore, the model by Dheda et al. [27] used a bioclinical scoring rule that included interferon-γ which might not be readily available in many developing countries, and Carrion-Valero et al. [23] calculated the final, discriminate function using a rather more complicated equation.

In summary, our best predictive model of TPE included two variables: age <47 years and either PADA >35 U/l or pleural serum protein ratio >0.710, although only the combination of age <47 years and PADA >35 U/l was significant (OR: 7.46; 95% CI: 3.99–13.96). Nevertheless, the model that includes age and PADA may have a similar performance in clinical practice and certainly requires fewer calculations and utilization of resources. In this

Table 7 Individual parameter performance from logistic regression models for the discrimination of TB from NTB

Variable	*N*	R^2	χ^2 (*P*)	OR (95% CI)	Accuracy	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Summary score (range = 0–6)	251	0.365	0.001	2.91 (2.18–3.89)	71.8	0.79 (0.74–0.85)	–	–
Score ≥2: any 2 or more	251	0.299	0.001	13.23 (6.37–27.66)	46.5	0.72 (0.66–0.77)	93.0 (88.2–96.3)	50.0 (40.0–60.0)
Score ≥3: any 3 or more	251	0.217	0.001	6.24 (3.51–11.20)	50.3	0.71 (0.65–0.77)	65.6 (57.9–72.7)	76.6 (67.3–84.3)
Age <47 and pleural fluid ADA (PADA) >35 U/l	251	0.238	0.001	7.46 (3.99–13.96)	50.2	0.719 (0.66–0.77)	60.5 (52.7–67.9)	83.0 (74.4–89.6)
Age <47 and pleural serum protein ratio >0.710	251	0.097	0.001	3.63 (1.95–6.77)	35.4	0.63 (0.57–0.68)	42.7 (35.1–50.5)	82.9 (74.4–89.6)

TPE TB pleural effusion, *NTPE* non-TB pleural effusion, *ADA* adenosine deaminase enzyme, *PADA* pleural fluid adenosine deaminase enzyme, R^2 generalized coefficient of determination, *OR* odds ratio, *CI* confidence interval, *AUC* area under curve

sense, when this model is applicable, needle biopsy of the pleura may be reserved for patients with suspected TPE whose pleural ADA levels are <35 U/l in at least two separate thoracentesis with negative cytology but with malignant etiology still not ruled out.

Limitations

This study may have some limitations. Our model might not be applicable in geographical regions with a lower prevalence of TB, although the minimal limit of such prevalence remains to be determined. In addition, our model did not include data about the use of Interferon-γ Release Assay (IGRA) or the Nucleic Acid Amplification (NAA) assays in differentiating between TPE and NTPE. However, these assays may not be wildly available in many developing countries. In addition, IGRA is useful primarily in identifying patients who have been infected with TB but much less useful in identifying patients with TPE, while the NAA remains an investigational tool [1]. Finally, we applied a scoring system proportional to the magnitude of the coefficients of the logistic equations, and although this might be considered arbitrary, it is in a way similar to the models of Sales et al. [24] and Porcel and Vives [15] and has the added benefits of differentiating between other possible etiologies of symptomatic PE such as infectious diseases. Our data still need further validation in a prospective independent sample of patients who live in other geographical regions.

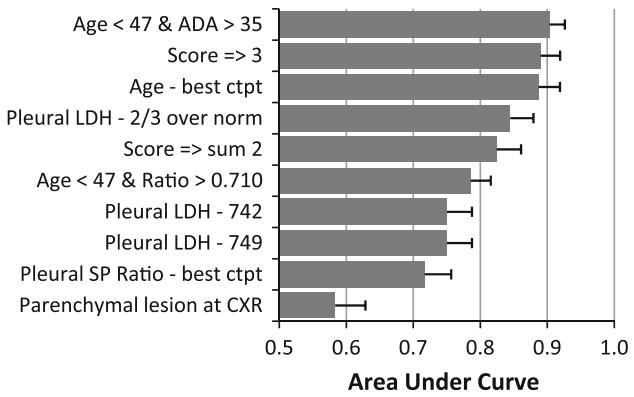

Fig. 2 Final receiver operator curve characteristics for the prediction of TPE. *TPE* TB pleural effusion, *ADA* adenosine deaminase enzyme, *PADA* pleural fluid ADA, *P/SADA* pleural serum ADA ratios, *LDH* lactate dehydrogenase enzyme, *SP* serum/protein ratio, *CxR* chest X-ray

Conclusion

In geographic areas with a high prevalence of TB and in patients <47 years, it is possible to safely diagnose TPE against a wide array of NTPE with either of the two models that we have studied, although using the ADA and age is superior. Our results should be reproducible since all the variables that were utilized are readily available worldwide and affordable.

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