Diagnostic scoring systems for tuberculous pleural effusion in patients with lymphocyte-predominant exudative pleural profile: A development study

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ABSTRACT

Background: Diagnosing tuberculous pleural effusion (TPE) in patients presenting with Lymphocyte-Predominant Exudative pleural effusion (LPE) is challenging, due to the poor clinical utility of TB culture. Adenosine deaminase (ADA) has been recommended for diagnosis, but its high cost and limited availability hinder its clinical utility. We aim to develop diagnostic prediction tools for Thai patients with LPE in scenarios where pleural fluid ADA is available but yields negative results and in situations where pleural fluid ADA is not available.
Methods: Two diagnostic prediction tools were developed using retrospective data from patients with LPE at Surin Hospital. Model 1 is for ADA-negative results, and Model 2 is for situations where pleural fluid ADA testing is unavailable. The models were derived using multivariable logistic regression and presented as two clinical scoring systems: round-up and count scoring. The score cut-point that achieves a positive predictive value (PPV) comparable to the post-test probability of a pleural fluid ADA at a cut-point of 40 U/L was used as a threshold for initiating anti-TB treatment.
Results: A total of 359 patients were eligible for analysis, with 166 diagnosed with TPE and 193 diagnosed with non-TPE. Age <40 years, fever, pleural fluid protein ≥5 g/dL, male gender, pleural fluid color, and pleural fluid ADA ≥20 U/L were identified as final predictors. Both models demonstrated excellent discriminative ability (AuROC: 0.85 to 0.89). The round-up scoring demonstrated PPV above 90% at cut-off points of 4 and 4.5, while the count scoring achieved cut-off points of 3 and 4 for Model 1 (Lex-2P2A) and Model 2 (Lex-2P-MAC), respectively.
Conclusion: These diagnostic tools offer valuable assistance in differentiating between TPE and non-TPE in LPE patients with negative pleural fluid ADA (Lex-2P2A) and in settings where pleural

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fluid ADA testing is not available (Lex-2P-MAC). Implementing these diagnostic scores may have the potential to improve TPE diagnosis and facilitate prompt initiation of treatment.

1. Introduction

Diagnosing tuberculous pleural effusion (TPE) in patients presenting with Lymphocyte-Predominant Exudative pleural effusion (LPE) is challenging. Among all pleural effusion cases, the prevalence of TPE varies across different geographical regions. In countries with a high tuberculosis (TB) incidence, such as India, China, and South Africa, TB stands out as the primary cause of pleural effusion, accounting for a substantial portion, ranging from 23.5% to 82.4% of all pleural effusion diagnoses [1]. Currently, the reference standard for TB diagnosis remains the isolation of *Mycobacterium tuberculosis* from pleural tissue or fluid sample culture [2]. However, the practical application of TB culture is limited by prolonged incubation time, suboptimal sensitivity, and invasiveness [3,4], which can result in the possibility of delayed or missed diagnoses. Since early confirmation is necessary for timely treatment and favorable outcomes, it is crucial to explore alternative non-invasive diagnostic approaches that provide improved sensitivity.

The Infectious Diseases Society of America (IDSA) guideline recommends using adenosine deaminase (ADA) for diagnosing TPE [5], considering a threshold of 40 U/L as an indicator for initiating anti-tuberculosis treatment [6,7]. Although pleural fluid ADA is recommended for TPE diagnosis, with a particular focus on its use in high-incidence Latin American countries [8], it comes with practical limitations, including high costs and restricted availability in resource-limited settings. This is especially notable in Southeast Asia, where TB continues to exert a significant burden across various dimensions [9–11]. Thus, the application of routinely available clinical information might be more attractive and cost-saving. Several clinical factors, including age, gender, presence of fever, pleural fluid lymphocyte percentage, and pleural fluid lactate dehydrogenase (LDH) levels, have been identified as significant predictors associated with TPE [6,10–14] which can potentially help in distinguishing TPE from other conditions, such as malignancy.

Over the years, several diagnostic prediction models have been developed by combining information from multiple predictors to estimate the absolute probability of TPE for each individual patient [11–15]. The discriminative performance of these models was quite promising, ranging from an area under the receiver operating characteristics curve (AuROC) of 0.94–0.99 [12–15]. However, some of the studies may be subjected to certain types of bias resulting from the inclusion of patients with transudate pleural effusion and the utilization of predictors incorporated within Light's criteria. Such biases may contribute to an overestimation of the diagnostic performance observed in these studies.

Studies that have restricted the patient domain to only LPE may be less affected by spectrum bias. However, pleural fluid ADA was incorporated into all of these models [16–18]. The study by Porcel J.M et al. [16] developed two scoring models: model 1 included predictors such as no history of malignancy, age ≤35 years, presence of fever, and pleural fluid red blood cell count (RBC) ≤5 × 10⁹ cells/L; and model 2 additionally incorporated pleural/serum LDH ratio ≥2.2 and pleural fluid protein ≥50 g/L, excluding pleural fluid ADA. The study demonstrated outstanding discriminative ability (AuROC: 0.98–0.99). However, a recent external validation study conducted in Thai patients reported a decrease in the model performance (AuROC: 0.74–0.81) [11]. Furthermore, more than half of the patients with TPE in this study had pleural fluid ADA levels below 40 U/L, highlighting the limitations of pleural fluid ADA as a diagnostic marker. Therefore, the objective of this study is to develop diagnostic prediction tools for Thai patients with LPE in scenarios where pleural fluid ADA is available but yields negative results, as well as in situations where pleural fluid ADA is not available.

2. Methods

2.1. Study design and study patient

We conducted a diagnostic prediction study with a retrospective cross-sectional design. The study domain were patients with LPE who were suspected of having TPE by their attending physicians and treated at Surin Hospital between January 2017 and December 2021. Surin Hospital is a tertiary hospital where incidence of LPE cases accounted for approximately 50% of all pleural effusion cases. The study received approval from the Institutional Review Board and Ethics Committee of Surin Hospital (37/2565).

2.2. Procedure for patient suspected with TPE

All patients with suspected TPE underwent routine investigations, including sputum examination for acid-fast bacilli (AFB), pleural fluid culture, and standard pleural fluid biochemistry panel. The panel included assessments for color, protein, glucose, white blood cell (WBC) count, WBC differentiation, RBC count, and LDH. There was no different in laboratory procedures and clinical data collection during the pandemic of COVID-19. Exudative pleural effusion was defined as having at least one of three criteria: a pleural fluid/serum protein ratio greater than 0.5, a pleural fluid/serum LDH ratio greater than 0.6, or pleural fluid LDH levels that were more than two-thirds of serum LDH levels [19]. LPE was defined as having a percentage of lymphocytes in pleural fluid that exceeded 50% of the total WBC count in exudative background [19].

2.3. Data collection

Demographic data, radiographic characteristics, and clinical laboratory parameters were retrospectively collected from electronic

medical records. Patients without a confirmed diagnosis, those who died before undergoing testing, those with abnormal cell differentiation, and those with a known case of pleural metastasis were excluded from the study.

2.4. Candidate predictors

We selected candidate predictors for the model based on their previously proposed association with TPE [6,10–17] and their availability in resource-limited settings. To address the limitations of pleural fluid ADA testing, we aimed to develop two diagnostic prediction models. Model 1 is designed for situations where pleural fluid ADA is available and produces negative results, while Model 2 is intended for cases where pleural fluid ADA testing is unavailable. In Model 1, pleural fluid ADA levels would be used as a predictor with a cut-off of ≥20 U/L [10]. Demographic data; age (<40 years), and gender, clinical data; smoking status (non-current smoking or current smoking), and fever (presence), clinical Laboratory parameters; pleural fluid color (serosanguinous, straw, and other), pleural fluid/serum LDH ratio (≥2.2), pleural fluid protein (≥5 g/dl), pleural fluid glucose (mg/dl), and serum protein (g/dl) were included as predictors. Radiographic characteristics were not included as model predictors, considering that the model is intended for use by general practitioners who may lack confidence in interpreting lung lesions on plain film.

2.5. Reference standard

The diagnosis of tuberculous pleuritis is defined as having at least one of the following criteria: The biopsy reported by the pathologist revealed the presence of granulomatous formations [5,7], either with or without caseous formations, or the official cytology results consistent with tuberculosis or highly indicative of it, or *Mycobacterium tuberculosis* was detected in the pleural fluid through polymerase chain reaction (PCR) testing, or culture of the pleural fluid confirmed the presence of *Mycobacterium tuberculosis*, or the patient experienced recovery following a trial treatment.

2.6. Statistical methods

All statistical analyses were performed using Stata 17 (StataCorp, Lakeway, Texas, USA). Categorical variables were described using frequency and percentages. Numerical data were assessed for distribution using histograms, and described using means and standard deviations (SD) or medians and interquartile ranges (IQR) based on their distributions. Fisher's exact test was used for comparison of categorical variables, *t*-test and Mann Whitney *U* test were used for continuous variables comparison as appropriate.
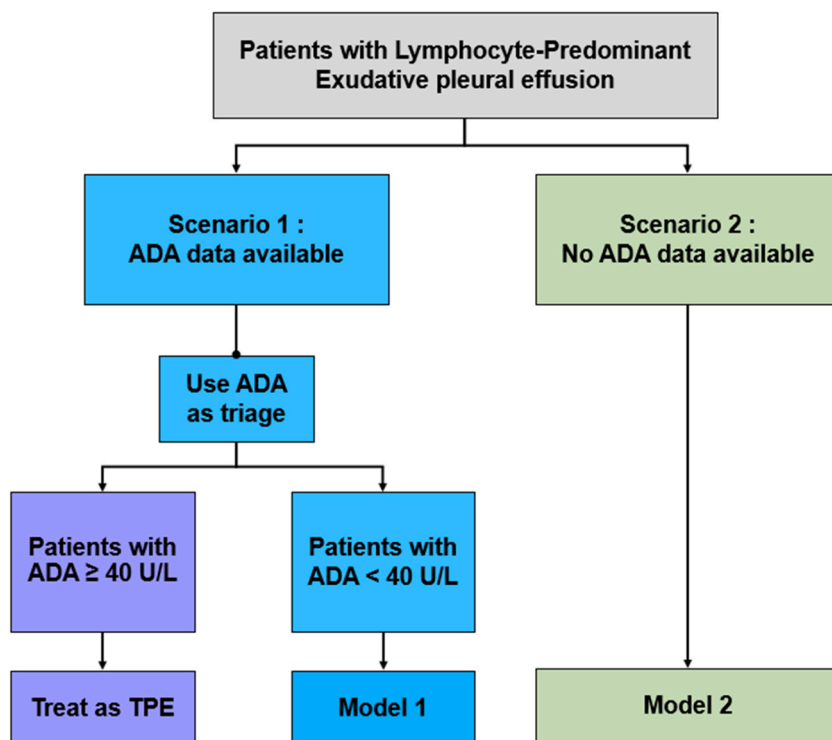

Fig. 1. Proposed implementation of diagnostic models within the clinical diagnostic flow of patients presenting with Lymphocyte-Predominant Exudative (LPE) pleural effusion.
Abbreviation: ADA, adenosine deaminase; TPE, tuberculous pleural effusion.

Statistical test results were considered significant if the p-values were less than 0.05.

2.7. Model development

2.7.1. Modeling development and model presentation

Two diagnostic prediction models were developed using multivariable logistic regression with a stepwise backward elimination approach. Each predictor in the model was initially tested to evaluate its contribution, and a significance level of 0.05 was set to exclude noncontributing predictors. Model 1 was constructed based on patients with pleural fluid ADA levels less than 40 U/L, while Model 2 was developed using all included patients (Fig. 1). All steps involved in generating the final model were executed on the imputed multiple imputation (MI) dataset using the *mi estimate* function in Stata [20,21]. For clinical applicability, the model was presented as two clinical scoring systems: the round-up scoring and the count scoring. The round-up scoring was based on regression coefficients [22], while the count scoring took a conservative approach to minimize the risk of overfitting by assigning a uniform score of one for each predictor, regardless of the magnitude of the coefficient.

2.7.2. Missing data handling

Acknowledging that complete case analysis requires substantial assumptions for unbiased findings and could decrease analytical efficiency, we infer that the missingness mechanism was missing at random (MAR), which is a more plausible assumption in the context of our study [23]. Therefore, we employed multiple imputation with chained equation (MICE) to generate 10 imputed datasets [24] using a fully conditional specification (FCS) approach [25]. For continuous variable, predictive mean matching (PMM) with K-nearest neighbor (where K=10) is used for generating the imputed datasets. A binary logistic regression and multinomial logistic regression were used to imputed binary and multinomial variables. TPE diagnosis, gender, age, red blood cell count, and lymphocyte percentages were used as auxiliary variables to help estimating the uncertainty of imputed data sets. Since Model 1 requires pleural fluid ADA data for patient selection, pleural fluid ADA was not imputed.

2.7.3. Model performance and internal validation

The model performance based on each scoring system was measured in term of discriminative ability and calibration. The model discriminative ability was evaluated using AuROC. According to Hosmer and Lemeshow [26], an AuROC of 0.70–0.80, 0.80–0.90, and above 0.90 was considered acceptable, excellent, and outstanding, respectively [26]. Model calibration was evaluated via the agreement between prediction event and observe event through a modified calibration plot. For internal validation, a bootstrap re-sampling with 1000 replicates was used to assess the model optimism.

2.7.4. Cut-point selection

The diagnostic indices, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR-), were calculated for all score categories. Our objective is to identify the score cut-point that achieves PPV values comparable to the post-test probability of a pleural fluid ADA at a cut-point of 40 U/L, which can be confidently used as a threshold for initiating anti-tuberculosis treatment.
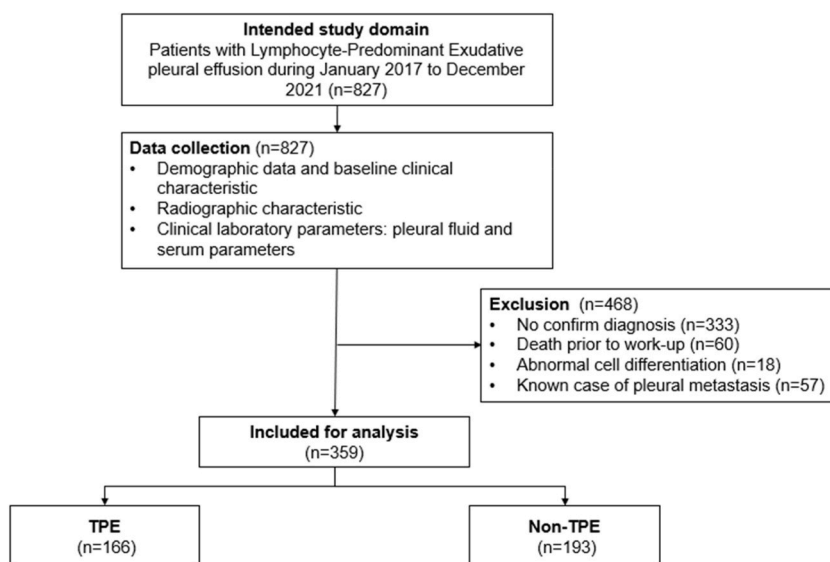

Fig. 2. Study flow diagram.
Abbreviation: ADA, adenosine deaminase; TPE, tuberculous pleural effusion.

3. Results

3.1. Patient characteristics

From January 2017 to December 2021, a total of 827 patients presented with exudative pleural effusion. Among these patients, 468 were excluded from the study for various reasons: 333 patients had unidentified causes of pleural effusion (due to multiple etiologies, referral before complete identification of the cause, or absence of definitive diagnostic findings), 60 patients had passed away before investigations could be conducted, 18 patients had abnormal cell differentiation, and 57 patients had a documented history of pleural metastasis. The remaining 359 patients were eligible for analysis, with 166 diagnosed with TPE and 193 diagnosed with non-TPE (Fig. 2). Among the non-TPE cases, 187 had cancer, while 4 had parapneumonic effusion, and another 2 had other conditions.

Among the included patients, 102 had a pleural fluid ADA level higher than 40 U/L. In our setting, the post-test probability, or PPV, of pleural fluid ADA was 91.2%. In terms of demographics, the majority of TPE patients were men (75.9%) with a mean age of 55.0 years ($\pm$17.5). Approximately half of the TPE patients presented with fever. Several candidate predictors, including gender, age, fever, pleural fluid protein, pleural fluid ADA, pleural fluid/serum LDH ratio, pleural fluid glucose, and serum protein, were found to be significantly different between TPE and non-TPE patients (Table 1). Further details regarding the patient characteristics are provided in Table 1.

Table 1
Baseline characteristic of patients with lymphocyte-predominant exudative pleural fluid profile.

Characteristic	Missing value n (%)	TPE (n = 166) n (%)	Non-TPE (n = 193) n (%)	p-value
Clinical characteristic				
Gender	0 (0)			
Male		126 (75.9)	96 (49.7)	<0.001
Female		40 (24.1)	97 (50.3)	
Age (year), Mean (SD)	0 (0)	55.0 (17.5)	64.6 (13.5)	<0.001
<40 years, n (%)		38 (22.9)	7 (3.63)	<0.001
≥40 years, n (%)		128 (77.1)	186 (96.4)	
HIV positive status	1 (0.3)	7 (4.2)	0 (0)	0.022
Smoking history	4 (1.1)	54 (32.9)	34 (17.8)	0.001
TB history	0 (0)	6 (3.6)	13 (6.7)	0.239
Cancer history	0 (0)	1 (0.6)	13 (6.7)	0.002
Fever presence	4 (1.1)	87 (53.1)	25 (13.1)	<0.001
Radiographic characteristic				
Infiltration	1 (0.3)	24 (14.6)	52 (26.9)	0.004
Mass	0 (0)	2 (1.2)	36 (18.7)	<0.001
Pleural fluid amount	0 (0)			
Massive		60 (36.1)	96 (49.7)	0.011
Non-massive		106 (63.9)	97 (50.3)	
Laboratory investigation				
Pleural fluid color	1 (0.3)			
Serosanguinous		13 (7.9)	28 (14.5)	0.114
Straw		85 (51.5)	86 (44.6)	
Others		67 (40.6)	79 (40.9)	
Pleural fluid glucose (mg/dl), Med (IQR)	68 (18.9)	90 (70–112)	107 (88–123)	<0.001
Pleural fluid protein (g/dl), Mean (SD)	7 (2.0)	5.24 (0.85)	4.49 (1.06)	<0.001
≥5 g/dl, n (%)		110 (67.9)	59 (31.1)	<0.001
<5 g/dl, n (%)		52 (32.1)	131 (69.0)	
Pleural fluid LDH (U/L), Med (IQR)	7 (2.0)	800 (518–1214)	713 (443–1317)	0.577
Pleural fluid ADA (U/L), Med (IQR)	40 (11.1)	44 (32–59)	13 (8.7–20.4)	<0.001
≥40 U/L, n (%)		93 (58.5)	9 (5.6)	<0.001
<40 U/L, n (%)		66 (41.5)	151 (94.4)	
Pleural fluid WBC count (cell/mm^3), Med (IQR)	0 (0)	480 (150–1280)	370 (138–1150)	0.507
%PMN in pleural fluid, Med (IQR)	0 (0)	1 (0–7)	3 (0–13)	<0.001
%Lymphocyte in pleural fluid, Mean (SD)	0 (0)	93.83 (11.80)	88.62 (14.40)	<0.001
RBC count in pleural fluid (cell/mm^3)	3 (0.8)	2000 (700–5184)	4680 (1500–30,000)	<0.001
<10,000 cell/mm^3		138 (83.64)	117 (61.26)	<0.001
≥10,000 cell/mm^3		27 (16.36)	74 (38.74)	
Serum protein (g/dl), Mean (SD)	5 (1.4)	7.22 (0.88)	6.79 (0.86)	<0.001
Serum LDH (U/L), Med (IQR)	57 (15.9)	461 (365–570)	539 (407–900)	<0.001
Pleural fluid/serum LDH ratio	58 (16.2)	1.69 (1.1–2.6)	1.23 (0.8–1.7)	<0.001
≥2.2, n (%)		52 (35.6)	27 (17.4)	<0.001
<2.2, n (%)		94 (64.4)	128 (82.6)	

Abbreviation: ADA, adenosine deaminase; IQR, interquartile range; LDH, lactate dehydrogenase; Med, Median; WBC; White blood cell; PMN, polymorphonuclear leukocyte; RBC, Red blood cell; SD, standard deviation; TPE, tuberculous pleural effusion.

3.2. Candidate predictor contribution

Among 359 patients, data from only 257 patients with pleural fluid ADA levels below 40 U/L were used to develop Model 1, while data from all patients were used to develop Model 2, which did not include pleural fluid ADA values. In Model 1, which excluded patients with pleural fluid ADA >40, pleural fluid ADA ≥20 U/L, age <40 years, presence of fever, male gender, pleural fluid protein ≥5 g/dL, and current smoking showed significant associations with TPE (Table 2). There was no statistically significant association between TPE and pleural fluid color (straw: p-value 0.382, other: p-value 0.561), as well as pleural fluid/serum LDH ratio (p-value 0.401). On the other hand, Model 2, which included all patients, revealed statistically significant associations for these variables. The magnitude of effect was similar in both models, except for pleural fluid protein (2.91 vs 4.83 in Model 1 and Model 2, respectively) (Table 2). Overall, the AuROCs for each predictor were slightly higher in Model 2 than in Model 1.

3.3. Model performance

In terms of discriminative ability, Tables 3 and 4 present the AuROC and the weighted scores assigned to each predictor based on different scoring systems for both Model 1 and Model 2. A higher score indicates a higher probability of being diagnosed with TPE. For Model 1, four final predictors were identified: age <40 years, presence of fever, pleural fluid protein ≥5 g/dL, and pleural fluid ADA ≥20 U/L. The round-up scoring and count scoring methods demonstrated excellent AuROC values of 0.89 (95% CI 0.83–0.94) and 0.87 (95% CI 0.81–0.92), respectively. In Model 2, five predictors were found to be independent predictors, including age <40 years, male gender, presence of fever, pleural fluid protein ≥5 g/dL, and pleural fluid color. The AuROC values for round-up scoring and count scoring were slightly lower than in Model 1, with values of 0.85 (95% CI 0.81–0.89) and 0.84 (95% CI 0.80–0.87), respectively (Table 4). The calibration of both derived models demonstrated good agreement between the observed and predicted probabilities, as shown in Figs. 3 and 4. Internal validation for Model 1 and Model 2 revealed apparent performances of 0.905 and 0.855, bootstrap performances of 0.890 and 0.836, and optimism values of 0.015 and 0.019, respectively.

3.4. Cut-oft threshold

In Model 1, the round-up scoring method demonstrated PPV values above 90% with specificities of 98.6%, 98.6%, and 100% at cut-points of 4, 4.5, and 6 points, respectively (Table S1). In the count scoring method, cut-points above 3 and 5 showed PPV values higher than 90% with specificities of 98.6% and 100%, respectively (Table S2). Similarly, in Model 2, the round-up scoring method showed a diagnostic PPV above 90% at cut-points above 4.5, with specificities of 98% or higher (Table S3). For the count scoring method, a score

Table 2

Prognostic characteristics and predictive performance of each candidate predictor in Model 1 and Model 2.

Predictors	Model 1 (n = 257)			Model 2 (n = 359)		
	uOR (95% CI)	p-value	AuROC (95% CI)	uOR (95% CI)	p-value	AuROC (95% CI)
Age			0.59 (0.54–0.64)			0.60 (0.56–0.63)
≥40 years	Reference	–		Reference	–	
<40 years	8.33 (3.11–22.29)	<0.001		7.89 (3.42–18.22)	<0.001	
Gender			0.63 (0.57–0.69)			0.63 (0.58–0.68)
Female	Reference	–		Reference	–	
Male	3.12 (1.70–5.72)	<0.001		3.18 (2.02–5.01)	<0.001	
Smoking status			0.57 (0.51–0.63)			0.58 (0.53–0.62)
Non-current smoking	Reference	–		Reference	–	
Current smoking	2.06 (1.11–3.82)	0.023		2.27 (1.38–3.71)	<0.001	
Fever			0.70 (0.64–0.76)			0.70 (0.66–0.75)
Absence	Reference	–		Reference	–	
Presence	7.16 (3.80–13.51)	<0.001		7.60 (4.51–12.80)	<0.001	
Pleural fluid color			0.53 (0.46–0.60)			0.55 (0.49–0.60)
Serosanguinous	Reference	–		Reference	–	
Straw	1.48 (0.61–3.58)	0.382		2.15 (1.04–4.42)	0.038	
Other	1.30 (0.53–3.20)	0.561		1.83 (0.88–3.82)	0.105	
Pleural fluid/serum LDH ratio			0.52 (0.46–0.59)			0.58 (0.53–0.63)
<2.2	Reference	–		Reference	–	
≥2.2	1.36 (0.66–2.80)	0.401		2.55 (1.53–4.24)	<0.001	
Pleural fluid protein			0.63 (0.56–0.70)			0.69 (0.64–0.74)
<5 g/dl	Reference	–		Reference	–	
≥5 g/dl	2.91 (1.66–5.12)	<0.001		4.83 (3.08–7.56)	<0.001	
Pleural fluid ADA			0.79 (0.73–0.85)			
<20 U/L	Reference	–		Not apply		
≥20 U/L	21.6 (5.25–88.93)	<0.001*				
Pleural fluid glucose (mg/dl)	0.99 (0.99–1.00)	0.098	0.57 (0.49–0.65)	0.99 (0.99–1.00)	0.007	0.63 (0.58–0.69)
Serum protein (g/dl)	1.58 (1.14–2.18)	0.005	0.61 (0.53–0.69)	1.76 (1.37–2.27)	<0.001	0.64 (0.58–0.70)

Abbreviation: ADA, adenosine deaminase; CI, confidential interval; LDH, lactate dehydrogenase; AuROC, area under the receiver operating characteristic; uOR, unadjusted odds ratio.

Table 3
The effect estimated of odds ratio, beta-coefficient, and score categorization for each predictor in final Model 1.

Predictor	Adjusted OR (95% CI)	β	P-value	Round-up Scoring	Count Scoring
Age (year)					
≥40 years	Reference	–	–	0	0
<40 years	6.48 (1.50–27.95)	1.87	0.012	1.5	1
Fever presence					
Absence	Reference	–	–	0	0
Presence	5.73 (2.46–13.37)	1.75	<0.001	1.5	1
Pleural fluid protein					
<5 g/dl	Reference	–	–	0	0
≥5 g/dl	2.96 (1.33–6.61)	1.09	0.008	1	1
Pleural fluid ADA					
<20 U/L	Reference	–	–	0	0
≥20 U/L	11.64 (5.26–25.73)	2.45	<0.001	2	1
Total score				6	4
AuROC (95%CI)				0.89 (0.83–0.94)	0.87 (0.81–0.92)

Abbreviation: ADA, adenosine deaminase; β, beta-coefficient; CI, confidence interval; OR, odds ratio; AuROC, area under the receiver operating characteristic.

Table 4
The effect estimated of odds ratio, beta-coefficient, and score categorization for each predictor in final Model 2.

Predictor	Adjusted OR (95% CI)	β	P-value	Round-up Scoring	Count Scoring
Age (year)					
≥40 years	Reference	–	–	0	0
<40 years	4.84 (1.78–13.15)	1.671	0.001	1.5	1
Gender					
Female	Reference	–	–	0	0
Male	3.00 (1.68–5.23)	1.126	<0.001	1	1
Fever presence					
Absence	Reference	–	–	0	0
Presence	7.03 (3.76–13.15)	1.940	<0.001	2	1
Pleural fluid color					
Serosanguinous	Reference	–	–	0	0
Straw	3.46 (1.40–8.522)	1.183	0.009	1	1
Other	3.07 (1.25–7.56)	1.057	0.020	1	1
Pleural fluid protein					
<5 g/dl	Reference	–	–	0	0
≥5 g/dl	5.66 (3.23–9.91)	1.740	<0.001	1.5	1
Total score				7	5
AuROC (95%CI)				0.85 (0.81–0.89)	0.84 (0.80–0.87)

Abbreviation: ADA, adenosine deaminase; β, beta-coefficient; CI, confidence interval; OR, odds ratio; AuROC, area under the receiver operating characteristic.
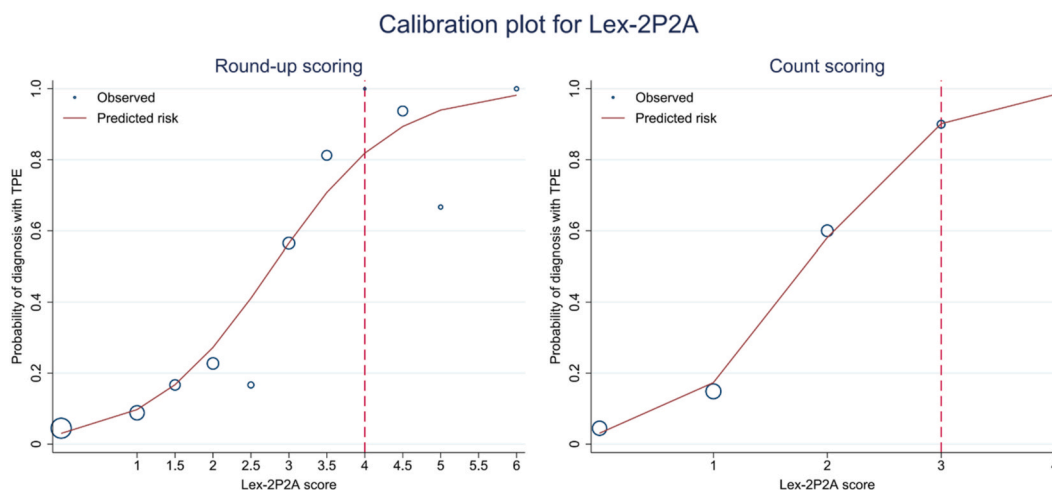

Fig. 3. Calibration plot for the Round-up (left) and the Count (right) scoring for Lex-2P2A (Model 1).
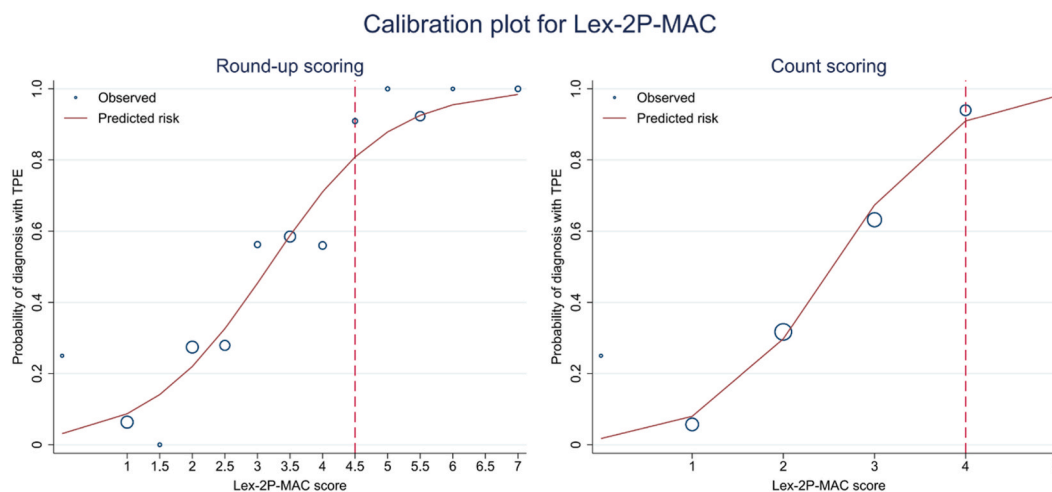
Fig. 4. Calibration plot for the Round-up (left) and the Count (right) scoring for Lex-2P-MAC (Mode 2).

above 4 demonstrated a PPV above 90% and a specificity above 98% (Table S4). Detailed information on diagnostic indices for specific cut-points can be found in Tables S1, S2, S3, and S4.

4. Discussion

In this study, we developed two simple diagnostic scoring systems to assist in the diagnosis of TPE. These scoring systems were designed for situations where pleural fluid ADA testing is available but yields a negative result (Model 1, Lex-2P2A), and for situations where pleural fluid ADA testing is not available (Model 2, Lex-2P-MAC). Both models demonstrated excellent discriminative ability, with AuROC values ranging from 0.85 to 0.89. They incorporated commonly used predictors, including age <40 years, male gender, presence of fever, pleural fluid color, pleural fluid protein ≥5 g/dL, and pleural fluid ADA ≥20 U/L.

Over the past few decades, extensive research has been conducted to develop diagnostic tools that combine clinical data and laboratory profiles. However, many of these studies have focused on patients with nonspecific pleural effusion, including both exudative and transudative cases [10,11,14]. The impact of specific predictors may vary depending on the specific patient population being studied. In the context of LPE pleural effusion patients, our study and other relevant studies have found that both LDH and lymphocyte percentage have limited discriminatory power [16,18]. Nonetheless, certain predictors, such as younger age, male gender, and pleural protein, consistently demonstrate independent predictive ability for TPE across multiple studies, irrespective of the fluid profile [17,27,28].

In our study, we observed that the association between male gender and TPE became insignificant in patients with pleural fluid ADA levels below 40 U/L. We did not find any evidence to support the influence of gender on pleural fluid ADA levels [29]. These discrepancies may be attributed to variations in the distribution of gender among non-TPE patients in our mixed population [30]. Given the low reported occurrence of malignancy history, we did not include it as a predictor in our model. We chose a pleural fluid ADA cut-off of 20 U/L since our aim was to improve diagnostic performance in cases where pleural fluid ADA yielded negative results (below 40 U/L). Our selection of pleural fluid ADA and age cut-offs was based on a study conducted by Jiang C.G. et al. [10]. Their findings demonstrated that in individuals younger than 40 years, the prevalence of non-TPE was significantly low, and pleural fluid ADA (with a cut-off of 21.4 U/L) exhibited outstanding performance in this age group, with an AuROC of 1.00, sensitivity of 100%, and specificity of 100% [10].

All predictors used in our study were categorical variables, and the cut-off points were determined based on previous evidence. To enhance generalizability and minimize overfitting, we employed both a count scoring approach and the use of specific cut-off points. The discriminative ability of our models, although slightly lower than in previous studies (AuROC 0.85–0.89 versus 0.92–0.99) [16–18], aligns with our primary objective of identifying positive cases for timely treatment initiation. Therefore, our focus was on achieving high PPV and specificity to determine optimal cut-off points. In our study, the round-up scoring approach demonstrated PPV above 90% at cut-off points of 4 and 4.5, while the count scoring approach achieved PPV above 90% at cut-off points of 3 and 4 for Lex-2P2A and Lex-2P-MAC, respectively. These cut-off points can serve as threshold indicators for initiating anti-tuberculosis treatment, as their PPV is comparable to that of pleural fluid ADA levels ≥40 U/L in our setting. With its high specificity, the model provides confidence in identifying positive cases and supports healthcare professionals in making appropriate management decisions.

5. Strengths and limitations

This study is the first to develop diagnostic tools for TPE in Thai patients with lymphocyte-predominant exudative pleural effusion. However, it is important to acknowledge the strengths and limitations of our study. One notable strength is the meticulous inclusion of

cases that were definitively intended for diagnosis as TPE, which would minimize spectrum bias. Secondly, our tools utilize simple and routinely-available predictors, making them applicable even in resource-limited settings. Additionally, our study had a relatively large sample size compared to recent relevant studies [11,16,18], and it included a balanced representation of both TPE cases and non-case individuals.

However, there are certain limitations that should be considered. Firstly, the model was constructed using retrospective data. Although a standardized form was used for data collection and imputation was employed to minimize bias, the retrospective nature of the data introduces inherent limitations. Further validation studies using prospective data are necessary. Secondly, out of the total eligible patients, 333 patients (44.6%) were excluded due to unidentified causes of pleural effusion. Due to resource limitations and the complex nature of identifying pleural effusion causes, especially in cases with multiple factors, some patients in our study remained undiagnosed. Previous study in China [31], where a high prevalence of TPE was observed, reported that compound causes of pleural effusion were common, ranging from 23% to 37%. Although this exclusion might affect the internal validity of our findings, it mirrors a naturally occurring phenomenon in practice, where pleural effusions with multiple etiologies are common. Even with a perfectly designed study, there will still be patients whose final diagnosis remains uncertain. A future prospective validation study could address this concern by encompassing all effusion cases suspected of TPE and making efforts to verify cases with multiple etiologies to determine if TPE is one of the causes. If TPE cannot be entirely ruled out, conducting sensitivity analyses by classifying these cases as either TPE or non-TPE may offer additional insights. In addition, it is important to note that most of the excluded cases in this category presented with severe symptoms, and the initiation of anti-TB treatment may have been delayed due to unstable hemodynamics or respiratory conditions. Therefore, the potential impact of this limitation on the predictive model, which focuses on prompt treatment initiation, may be less substantial. Lastly, the models were constructed using data from a single center in Thailand. Plus, a majority of non-TPE cases were attributed to cancer. In settings where the case mix of pleural effusion cases is different from ours, the accuracy of the model could be significantly affected. To ensure robust diagnostic performance, external validation studies are recommended before applying the diagnostic score. Overall, further challenges for clinical implementation to consider include clinicians' attitudes toward the models and their recognition of the models' utility. These challenges could be addressed with appropriate implementation strategies, such as offering education within the clinician's organization or incorporating the derived models into local practice guidelines [32].

Ethics approval and consent to participate

The study received approval from the Institutional Review Board and Ethics Committee of Surin Hospital (37/2565). Informed consent is not required.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Jeerawat Kaewwinud: Writing - review & editing, Writing - original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sireethorn Pienchitlertkajorn:** Investigation, Data curation, Conceptualization. **Kamolphop Koomtanapat:** Investigation, Data curation, Conceptualization. **Lalita Lumkul:** Writing - review & editing, Methodology, Investigation, Formal analysis, Data curation. **Pakpoom Wongyikul:** Writing - review & editing, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Phichayut Phinyo:** Writing - review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT 3.5 in order to check and correct grammatical errors during the manuscript writing process. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23440.

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