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Diagnostic predictors of tuberculosis in exudative pleural effusion patients with intermediate adenosine deaminase values: a retrospective diagnostic prediction model study

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Abstract

Adenosine deaminase (ADA) in pleural fluid is widely used to support the diagnosis of tuberculous pleural effusion. However, ADA levels between 40 and 60 IU/L represent a gray area where both tuberculous and non-tuberculous conditions can coexist. It can potentially lead to empirical antitubercular therapy and a delay in the diagnosis of other conditions. The aim of this study was to create and validate a prediction model to improve the diagnosis of tuberculosis (TB) in patients with exudative pleural effusions and intermediate ADA levels. This retrospective diagnostic modeling study included 125 consecutive adults with exudative pleural effusions, meeting Light's criteria, and pleural fluid ADA levels between 40 and 60 IU/L. These patients were referred to a tertiary respiratory care center in northern India. Univariable receiver operating characteristic curve analysis was used to shortlist candidate predictors with an area under the curve (AUC) of ≥0.60 and p≤0.05. A multivariable logistic regression model was developed using the forward stepwise procedure, including ADA, pleural fluid protein, and patient age. The performance of the model was assessed for discrimination, calibration, and classification and compared to the performance of ADA alone. Internal validation was done using 10-fold stratified cross-validation. Of 125 patients, 77 (62%) had TB and 48 (38%) had non-TB aetiologies (malignancy ≈30%; acute inflammatory/parapneumonic effusion ≈12%; chronic inflammatory conditions ≈6%). The 3-predictor model achieved an AUC of 0.89 [95% confidence interval (CI) 0.83-0.95] and an overall accuracy of 85%, with sensitivity 89%, specificity 79%, positive predictive value 84% and negative predictive value 86% at a probability cut-off of 0.50. ADA alone yielded an AUC of 0.72 (95% CI 0.62-0.82) and accuracy of 68%, with sensitivity 70% and specificity 65%. Ten-fold stratified cross-validation showed stable performance (mean cross-validated AUC 0.87±0.04; optimism 0.02). Independent predictors were ADA [odds ratio (OR) 1.24 per IU/L], protein (OR 1.65 per g/dL) and age (OR 0.93 per year; all p<0.001). In exudative pleural effusions with an ADA level of intermediate values, a simple model combining ADA, pleural protein concentration, and patient age improves the diagnostic discrimination for TB over ADA alone, with a marked improvement in negative predictive probability. External validation in a prospective multicenter study is needed before its use in clinical practice.

Key words: tuberculosis, pleural effusion, adenosine deaminase, logistic models, ROC curve.

Introduction

Pleural effusion occurs in a wide range of clinical conditions including tuberculosis, malignancy, parapneumonic infection and other inflammatory conditions [1,2]. In TB-endemic regions, tuberculous pleural effusion (TPE) is one of the most common causes of exudative pleural effusion. It is an important manifestation of extrapulmonary TB [1,3]. However, establishing a definitive diagnosis of TPE is often challenging in routine practice. Microbiological confirmation from pleural fluid is frequently insensitive, and pleural biopsy or thoracoscopy may not be always immediately available. Therefore, clinicians rely on a combination of clinical assessment, pleural fluid analysis and supportive biomarkers [1,2,4,5].

Pleural fluid adenosine deaminase (ADA) is one of the most widely used biomarkers for TPE. Multiple studies and meta-analyses have reported that a pleural fluid ADA cut-off of approximately 40 IU/L provides high sensitivity and specificity. It can be around 90% for the diagnosis of TPE in appropriate clinical settings [1,3,6-9]. In many high-burden regions, ADA ≥40 IU/L is therefore interpreted as strongly suggestive of TB. Thus it is commonly used to justify initiation of antitubercular therapy (ATT) in the absence of definitive microbiological or histological proof [1,3,5-10].

Despite this overall performance, a substantial diagnostic grey zone exists when ADA values lie between 40 and 60 IU/L. In this intermediate range, multiple non-tuberculous condition such as malignant effusions, parapneumonic effusions, chronic inflammatory diseases and other granulomatous disorders exists. These can produce similar ADA elevations [2,3,8,10]. Large series evaluating the aetiology of pleural effusions and the distribution of ADA values have shown considerable overlap between TPE and non-TB effusions in this interval [2,3,8,10]. As a result, clinicians are often confronted with significant uncertainty when managing patients whose ADA values fall between 40 and 60 IU/L [1-3,10].

In daily practice, this uncertainty has important concerns. Many such patients are started empirically on ATT while awaiting further investigations. It is mainly seen in settings where TB prevalence is high and access to invasive diagnostic procedures is limited [1-3,10]. Although this strategy might decrease the chances of late treatment in actual tuberculosis (TB) patients, it also puts non-TB patients at risk for unnecessary toxicity from anti-tubercular therapy (ATT), such as hepatotoxicity, neuropathy, and drug interactions, and might hinder the early diagnosis

and treatment of other conditions, such as occult malignancies [1-3,10]. On the other hand, a too-conservative approach might result in a delay in anti-tubercular therapy in a patient with actual tuberculous pleural effusion (TPE) [1-3].

A number of important descriptive and comparative studies have outlined the etiological spectrum and pleural fluid biochemistry for patients with intermediate ADA levels [2,3,10]. These studies have emphasized the importance of differences between tuberculous pleural effusions (TPE) and non-TB effusions, but have mainly provided cross-tabulated results and simple diagnostic odds ratios, without attempting to translate these results into multivariable prediction models [2,3,10]- As such, there is a need for quantitative models that combine available clinical and pleural fluid variables to predict the probability of tuberculosis in individual patients with ADA levels in the gray zone [2,3,10,11].

Our study fills a gap in current literature by creating and internally validating a diagnostic predictive model to distinguish tuberculous from non-tuberculous exudative pleural effusions in patients with pleural fluid adenosine deaminase (ADA) levels between 40 to 60 IU/L. Using routinely measured variables like pleural ADA, pleural protein and patient age, our model aims to provide clinicians with an objective, quantitative tool to supplement ADA-alone interpretation. It can thereby reduce diagnostic uncertainty and guide risk-stratified decisions regarding further investigation and initiation or deferral of ATT.

Materials and Methods

Study design and setting

This retrospective diagnostic modeling study was carried out in the Department of Pulmonary Medicine at Indira Gandhi Medical College (IGMC), Shimla, Himachal Pradesh, India. IGMC is a government teaching institution and tertiary care respiratory referral center for high-burden, tuberculosis-endemic areas of the Himalayan foothills. The high annual case load of the center provides a representative population for assessing the diagnostic methods in this context. The current analysis is a secondary diagnostic modeling of a population that was previously assessed in a prospective descriptive etiological study of exudative pleural effusions (concurrent unpublished manuscript). The reporting follows the STROBE criteria for observational studies [4].

Ethics approval

The Institutional Ethics Committee of IGMC approved the study protocol (IRB-2023-045). The study was conducted in accordance with the local regulations and the STROBE guidelines [4]. All personal identifiers were removed before analysis.

Study population

Patients were eligible if they met both of the following criteria,

1. Presence of pleural effusion classified as exudative according to Light's criteria [12], and
2. Pleural fluid ADA values between 40 and 60 IU/L on diagnostic evaluation.

Patients with transudative effusions or incomplete clinical or biochemical data were excluded. In addition, only patients with complete diagnostic confirmation of pleural effusion aetiology, as defined below, were included in the final analysis.

Study variables

Data were abstracted from clinical records and laboratory information systems. Three categories of variables were recorded.

1. Demographic and clinical variables

   Age (years), sex, smoking history (never/former/current), indoor air pollution exposure (yes/no), duration of symptoms prior to presentation (days), predominant symptoms (cough, dyspnoea, fever, chest pain) and relevant comorbidities (diabetes, hypertension, prior malignancy, immunosuppression).
2. Pleural fluid biochemical and cytological variables

   ADA (IU/L), total protein (g/dL), albumin (g/dL), glucose (mg/dL), lactate dehydrogenase (LDH; IU/L), lymphocyte percentage (%), total and differential cell counts, and gross appearance (clear, blood-stained or purulent).
3. Diagnostic confirmation variables

   Acid-fast bacilli (AFB) smear results, cartridge-based nucleic acid amplification test (CBNAAT) on pleural fluid and sputum, mycobacterial culture results (if performed) and pleural histopathology findings.

In the case of the predictors that were ultimately retained in the final model (ADA, pleural protein, and age), there were no missing values.The complete-case analysis was possible without imputation. The reference standard classification of pleural effusion etiology was defined as follows.

Diagnostic criteria: The reference standard classification of pleural effusion aetiology was defined as follows.

- Definite TB
  - Pleural biopsy demonstrating caseating granulomas, with or without positive TB culture or
  - Positive mycobacterial culture from pleural fluid or
  - Positive CBNAAT or AFB smear from pleural fluid or
  - Positive CBNAAT or AFB smear from sputum with pleural fluid characteristics and clinical features compatible with TPE.
- Non-TB aetiologies
  - Pleural biopsy or cytology confirming malignancy, specific non-TB infections, granulomatous diseases other than TB or benign inflammation or
  - Negative pleural AFB smear, CBNAAT and culture, with clinical and radiologic follow-up supporting an alternative diagnosis or benign inflammatory resolution.

In the primary analysis, both definite TB and probable TB (sputum microbiological confirmation with compatible pleural disease) were considered to be TB.

Statistical analysis and model development

The Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on distribution as determined by Shapiro-Wilk test. Also the Categorical variables were described using frequency and percentage. To compare between groups (tuberculosis [TB] vs non-TB), continuous variables were compared using independent t-test or Mann-Whitney U test. Also, the categorical variables were compared using chi-square test or Fisher's exact test.

Sample size considerations were based on events per variable (EPV) for logistic regression. With our total of 125 patients, 77 TB events and three predictors retained in the final model, the EPV

was 25.7. It exceeded the conventional recommendations of 10-15 events per predictor. Thereby it reduces the risk of overfitting and unstable coefficient estimation [11].

Univariable ROC analysis

The Receiver operating characteristic (ROC) curves were made for each continuous variable (ADA, pleural protein, albumin, glucose, LDH, lymphocyte percentage and age). The AUC with 95% confidence intervals (CI) was measured using the trapezoidal method [10]. Variables with AUC ≥ 0.60 and $p \leq 0.05$ in univariable analyses were considered candidate predictors. ADA, pleural protein and age met these criteria and were entered into multivariable modelling (Figure 1).

Multivariable logistic regression model

A binary logistic regression model was fitted using forward stepwise variable selection (entry $p<0.10$, retention $p<0.05$). Model performance was assessed in terms of: 1) Discrimination: which meant AUC with 95% CI; 2) Calibration: Nagelkerke R^2 and the Hosmer–Lemeshow goodness-of-fit test ($p>0.05$ indicating adequate fit); 3) Classification: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy at a predicted probability cut-off of 0.50.

The final model equation for the probability of TB was:

$$P(TB) = \exp(-7.851 + 0.215 \times ADA + 0.500 \times Protein - 0.073 \times Age)$$

divided by

$$1 + \exp(-7.851 + 0.215 \times ADA + 0.500 \times Protein - 0.073 \times Age)$$

where ADA is in IU/L, protein in g/dL and age in years.

Internal validation and comparison with ADA alone

Internal validation used 10-fold stratified cross-validation. The sample was split into ten equal-sized subsets, or folds, each retaining the same proportion of TB to non-TB cases (62%:38%). For each of the ten iterations, the model was trained and tested on different subsets: nine folds (90% of the sample) for training and one fold (10%) for testing. The average cross-validated AUC, sensitivity, specificity, and accuracy were calculated over the ten iterations, and the

optimism was calculated as the difference between the apparent (fitted) AUC and the average cross-validated AUC [11].

To compare the performance of the model with that of current practice, the model was compared to ADA-alone interpretation based on ROC-derived optimal cut-offs for ADA. McNemar's test for paired proportions was used to compare the sensitivity and specificity of the two methods. All analyses were done using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). A two-sided p-value < 0.05 was taken to indicate statistical significance.

Results

Study population and aetiologic spectrum

All 125 patients with exudative pleural effusions and adenosine deaminase (ADA) levels ranging from 40 to 60 IU/L satisfied the predefined inclusion criteria. Of this group, 77 patients (62%) were classified as tuberculosis (TB), and 48 patients (38%) were classified as non-TB. Of the non-TB diagnoses, approximately 30 patients (24% of the total group) had malignancies (primarily lung and breast adenocarcinomas), 12 patients (10%) had acute inflammatory or parapneumonic effusions, and 6 patients (5%) had chronic inflammatory conditions.

Clinical characteristics

Selected demographic and clinical features are summarised in *Supplementary Table 1*. TB patients were significantly younger than non-TB patients (median age 35 vs 63 years, $p<0.01$), consistent with the typical age distribution of TB versus pleural malignancy in high-burden regions [1,3,11]. Fever was more common in patients with tuberculosis (57% vs. 31%, $p<0.01$), whereas the proportion of cough, dyspnea, and chest pain was similar between the two groups. There were no differences in the distribution of sex, smoking, exposure to indoor air pollution, and duration of symptoms.

Pleural fluid biochemistry

Pleural fluid biochemical characteristics are shown in *Supplementary Table 2*. Although all patients had ADA within the 40–60 IU/L range by design, TB patients had significantly higher

median ADA levels than non-TB patients (48.3 vs 43.6 IU/L $p<0.001$). Mean pleural protein was also higher in TB effusions (5.42 vs 4.91 g/dL, $p<0.01$). Differences in albumin, glucose, LDH and lymphocyte percentage were not statistically significant and showed substantial overlap between aetiologic groups.

Univariable ROC analysis

The univariable ROC analysis is summarised in *Supplementary Table 3* and illustrated in Figure 1. Age showed good discrimination for TB versus non-TB (AUC 0.81, $p<0.01$), reflecting the marked age difference between the two groups. ADA demonstrated fair discriminatory ability (AUC 0.72, $p<0.001$), while pleural protein contributed modestly (AUC 0.65, $p<0.01$). Albumin, glucose, LDH and lymphocyte percentage did not achieve an AUC ≥0.60 and were not retained for multivariable modelling.

Multivariable model development

In the multivariable logistic regression, ADA, pleural protein and age remained independent predictors of TB (*Supplementary Table 4*). Each 1 IU/L increase in ADA was associated with a 24% increase in the odds of TB (OR 1.24, 95% CI 1.14–1.35; $p<0.001$). Each 1 g/dL increase in protein increased the odds of TB by 65% (OR 1.65, 95% CI 1.19–2.29; $p<0.01$). Conversely, each additional year of age decreased the odds of TB by 7% (OR 0.93, 95% CI 0.89–0.97; $p<0.001$).

The model explained 52% of the variance in TB diagnosis (Nagelkerke $R^2=0.52$). The Hosmer–Lemeshow test indicated good calibration ($\chi^2=5.18$, $p=0.74$).

Model performance vs. ADA-alone

Discrimination and classification performance of the multimarker model versus ADA-alone are summarised in *Supplementary Table 5* and illustrated in Figures 2 and 3. The three-predictor model achieved an AUC of 0.89 (95% CI 0.83–0.95), compared with 0.72 (95% CI 0.62–0.82) for ADA-alone, representing a 0.17 absolute increase. Overall accuracy improved from 68% with ADA-alone to 85% with the multimarker model (+17 percentage points).

At the chosen probability cut-off of 0.50, sensitivity increased from 70% to 89% and specificity from 65% to 79%. This corresponds to a 65% reduction in missed TB diagnoses (from 23 to 8 of 77 TB patients) and a 41% reduction in false-positive TB classifications (from 17 to 10 of 48 non-TB patients). The NPV improved from 57% to 86%, while PPV increased from 74% to 84%.

Internal validation

Ten-fold stratified cross-validation confirmed the robustness of the model (*Supplementary Table 6*). The mean cross-validated AUC was 0.87 (SD 0.04), close to the apparent AUC of 0.89, yielding an optimism estimate of 0.02. Mean cross-validated sensitivity and specificity were 86% and 77%, respectively, with overall accuracy of 82% (SD 4.8%). These findings suggest that model performance is not materially inflated by overfitting.

Clinical algorithm and nomogram

On the basis of the final model, a practical clinical algorithm was developed to guide risk-stratified management of patients with exudative pleural effusions and intermediate ADA values. The algorithm outlines sequential steps: confirming an exudate by Light's criteria; measuring ADA; applying the model only when ADA lies between 40 and 60 IU/L; calculating an estimated TB probability using the regression equation or a simplified nomogram; and classifying patients into low- (<30%), intermediate- (30–70%) or high-probability (≥70%) risk categories to guide further investigation and treatment decisions (Figure 4).

A nomogram-style table was also constructed to allow bedside estimation of TB probability using categories of ADA, age and pleural protein without a calculator. Base TB risk is derived from the ADA level, then adjusted according to age band and pleural protein band to yield a final probability estimate (Figure 5).

Discussion

Our study describes the creation and internal validation of a simple multivariable prediction model which aims to distinguish tuberculous from non-tuberculous exudative pleural effusions in patients with intermediate pleural adenosine deaminase (ADA) activity levels of 40-60 IU/L.

By Using only three variables: ADA, pleural protein, and age, the model significantly improved the diagnostic discrimination compared to ADA alone, as shown by improvements in sensitivity, specificity, overall accuracy, and most importantly, negative predictive value.

The literature has already highlighted the diagnostic dilemma presented by the intermediate values of ADA [2,3,8]. While highly elevated ADA concentrations (e.g., >70 IU/L) are highly suggestive of TPE and low levels (<40 IU/L) make TB unlikely in most situations, the range of 40-60 IU/L represents a continuum of malignant, parapneumonic, and inflammatory effusions whose biochemistries often overlap with those of TPE [2,3,8,10]. While previous large-scale studies have noted this overlap, they have not always provided a quantitative framework for individual-level probability estimation [2,3,10]. The current study fills this need in the context of a high TB prevalence setting.

The independent role of adenosine deaminase (ADA) in the intermediate range (40-60 IU/L) suggests that small increases remain useful for TB diagnosis. Pleural protein concentration was identified as an independent predictor, consistent with the lymphocyte-predominant exudative process of tuberculous pleural effusion (TPE), which often presents with protein concentrations higher than those found in most cases of malignant or parapneumonic effusions [1-3,10]. Age showed a very strong negative correlation with TB, as expected in TB endemic areas where TPE predominates in younger patients, in contrast to malignant effusions, which are more common in older patients [1,3,10].

The combination of these three partially independent signals such as biochemical (ADA, protein) and epidemiologic (age) has given a marked increase in AUC from 0.72 for ADA-alone to 0.89 for the multimarker model. Even though pleural protein had only modest univariable discrimination (AUC 0.65), its inclusion improved overall model performance. Therefore it shows that predictors with limited individual discrimination can still add value in a multivariable context [10,11].

From a clinical point of view, the improvement in NPV from 57% to 86% is mainly important. In routine practice, many patients with intermediate ADA values are empirically started on ATT because the perceived probability of TB is considered high, yet a good proportion ultimately prove to have non-TB aetiologies such as malignancy or other inflammatory diseases [2,3,8,10]. A model that reliably identifies a low-probability subgroup (for example, predicted TB

probability <30%) can support more confident exclusion of TB and timely pursuit of alternative diagnoses. This will potentially avoid weeks of unnecessary ATT exposure and reduce the delays in cancer work-up.

Conversely, patients with high predicted TB probability (for example, ≥70%) can be prioritised for prompt initiation of ATT while further diagnostic confirmation proceeds in parallel. The intermediate-risk group (30–70%) shows those who may benefit most from invasive diagnostics (repeat CBNAAT, pleural biopsy, cross-sectional imaging). The following clinical algorithm and nomogram translate these risk categories into practical bedside guidance by using only measurements that are already part of standard pleural fluid evaluation in many centres.

The model is designed to be frugal in its approach by using only those variables that are easily accessible in centers where pleural fluid analysis is being performed. This eliminates the need for sophisticated imaging or biomarkers and thus improving the potential applicability of the model in resource-limited settings. These places are where the prevalence of tuberculosis is highest and the availability of diagnostic tools is limited. Also, the strong internal validation provided by 10-fold cross-validation, high events per variable, and good calibration metrics together put forward that the model captures a real signal and is not prone to artifacts of over fitting [4,11].

However, there are a few limitations that require consideration. Firstly, the single-center study in a tertiary referral hospital could potentially limit generalizability. Also, especially if there are differences in case mix and disease severity between primary care or non-referral settings. Secondly, the retrospective analysis could potentially be vulnerable to unmeasured confounding and information bias, although the data were drawn from a prospectively defined cohort using standardized diagnostic criteria. Thirdly, the strong age effect is a reflection of regional epidemiology and in low-prevalence settings. TB is increasingly seen in older patients with comorbidities and immunosuppression, and therefore the age coefficient may need to be recalibrated before use [1-3,10]. Finally, although internal validation was rigorous, external validation in independent, ideally multicentre cohorts remains the gold standard for assessing transportability [11].

Despite these limitations, the present study provides internally consistent evidence that a simple multimarker model can substantially improve diagnostic discrimination for TB in the

intermediate ADA range. By converting routinely available parameters into quantitative probability estimates, the model offers a more nuanced alternative to binary ADA thresholds and may help clinicians balance the competing risks of delayed TB treatment and unnecessary ATT in non-TB patients.

Conclusions

In adults with exudative pleural effusions and pleural fluid ADA values between 40 and 60 IU/L, a three-predictor model incorporating ADA, pleural protein and age significantly improves discrimination between tuberculous and non-tuberculous aetiologies compared with ADA-alone. This model achieves higher sensitivity, specificity and overall accuracy. Also it has a particularly notable increase in negative predictive value. These findings support the potential clinical utility of this multimarker approach for risk-stratified management in TB-endemic settings. External multicentre validation, including assessment in regions with differing TB epidemiology, is warranted before routine clinical adoption.

List of abbreviations

ADA, Adenosine deaminase
ATT, Antitubercular therapy
AUC, Area under the curve
CBNAAT, Cartridge based nucleic acid amplification test
LDH, Lactate dehydrogenase
NPV, Negative predictive value
PPV, Positive predictive value
ROC, Receiver operating characteristic
TB, Tuberculosis
TPE, Tuberculous pleural effusion

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Online supplementary material

Supplementary Table 1. Patient demographics and clinical characteristics.

Supplementary Table 2. Biochemical characteristics of pleural fluid.

Supplementary Table 3. Univariable ROC analysis for diagnostic predictors.

Supplementary Table 4. Multivariable logistic regression model.

Supplementary Table 5. Performance comparison: ADA-alone *vs.* multimarker model.

Supplementary Table 6. Internal validation: 10-fold stratified cross-validation.

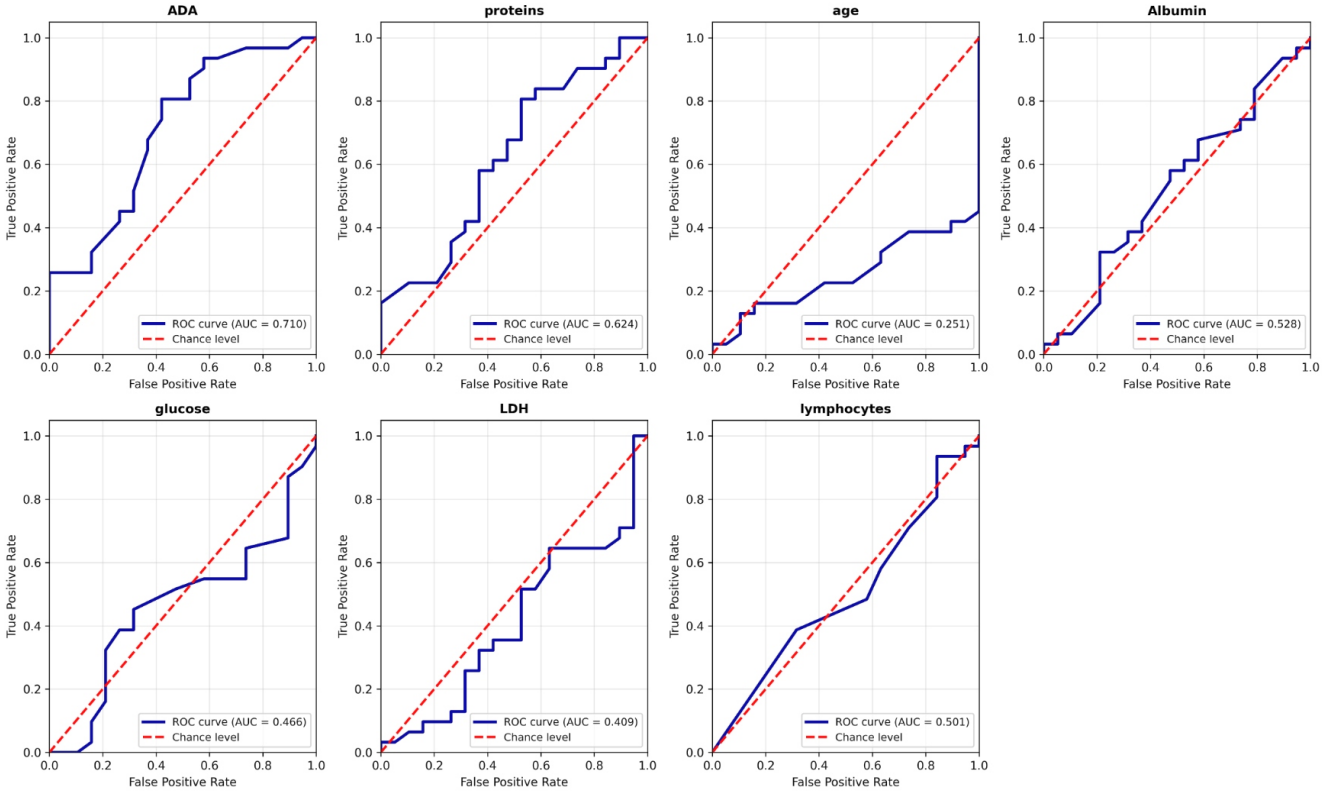

Figure 1. Individual ROC curves for diagnostic predictors. Receiver operating characteristic curves are shown for pleural adenosine deaminase (ADA), protein, age, albumin, glucose, lactate dehydrogenase (LDH) and lymphocyte percentage in discriminating tuberculous from non-tuberculous pleural effusions within the intermediate ADA range.

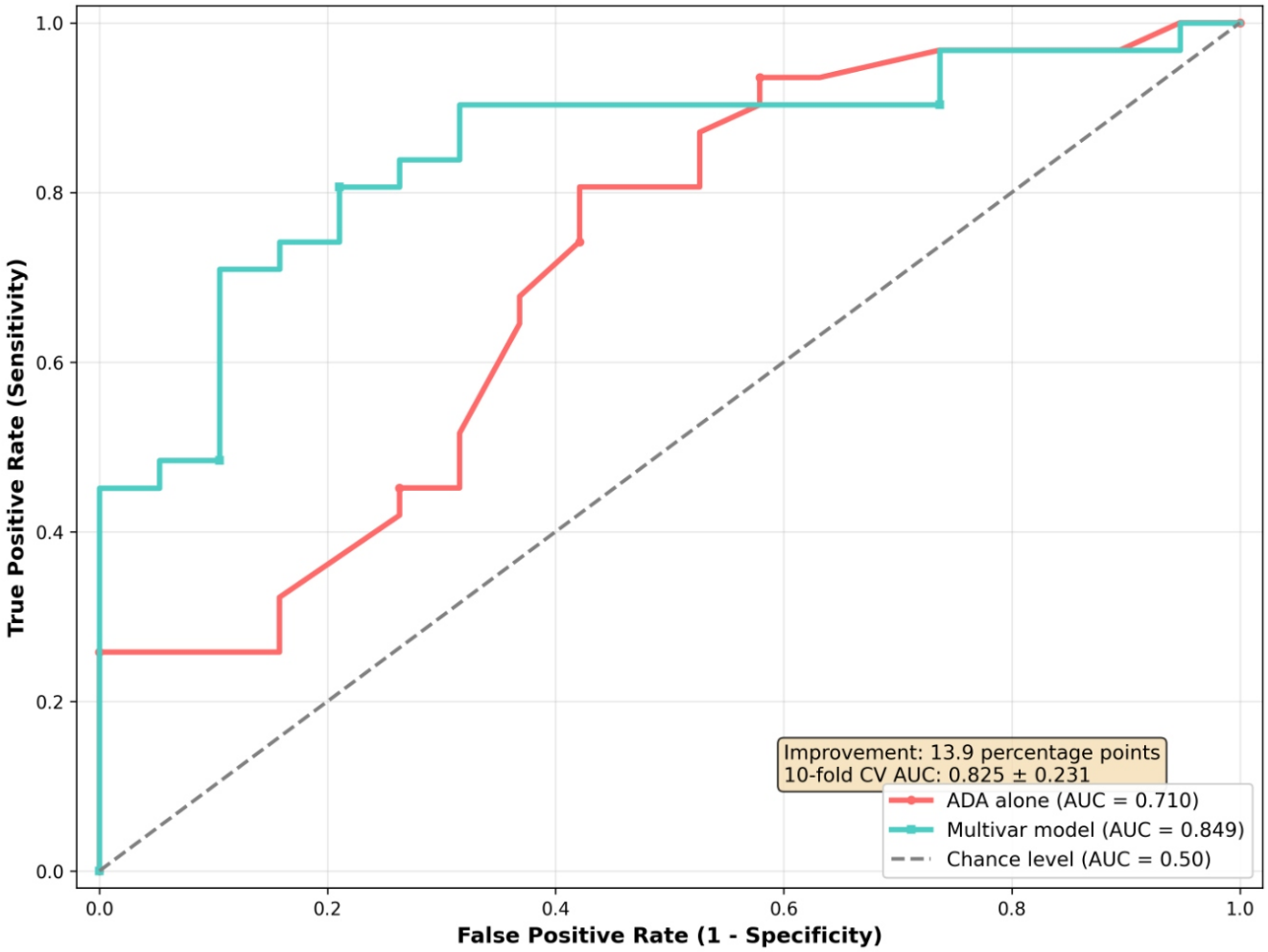

Figure 2. Comparison of diagnostic models. ROC curves comparing pleural ADA-alone with the multivariable logistic regression model (ADA, protein, age) for predicting tuberculous pleural effusion in patients with ADA 40–60 IU/L.

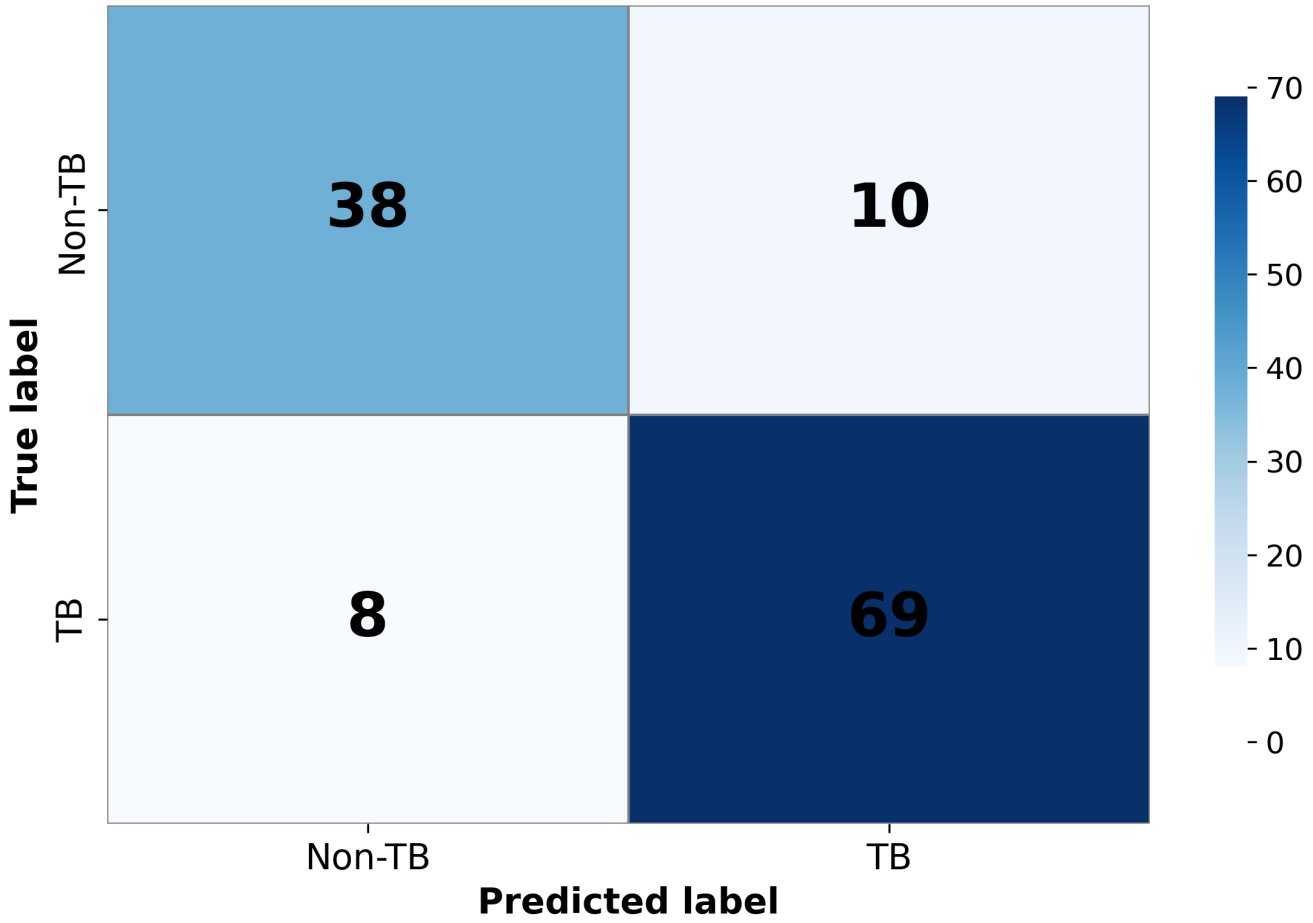

Figure 3. Confusion matrix for the multivariable logistic regression model. Confusion matrix showing the numbers of true-positive, true-negative, false-positive and false-negative classifications for tuberculous versus non-tuberculous effusions using the final model at a probability cut-off of 0.50.

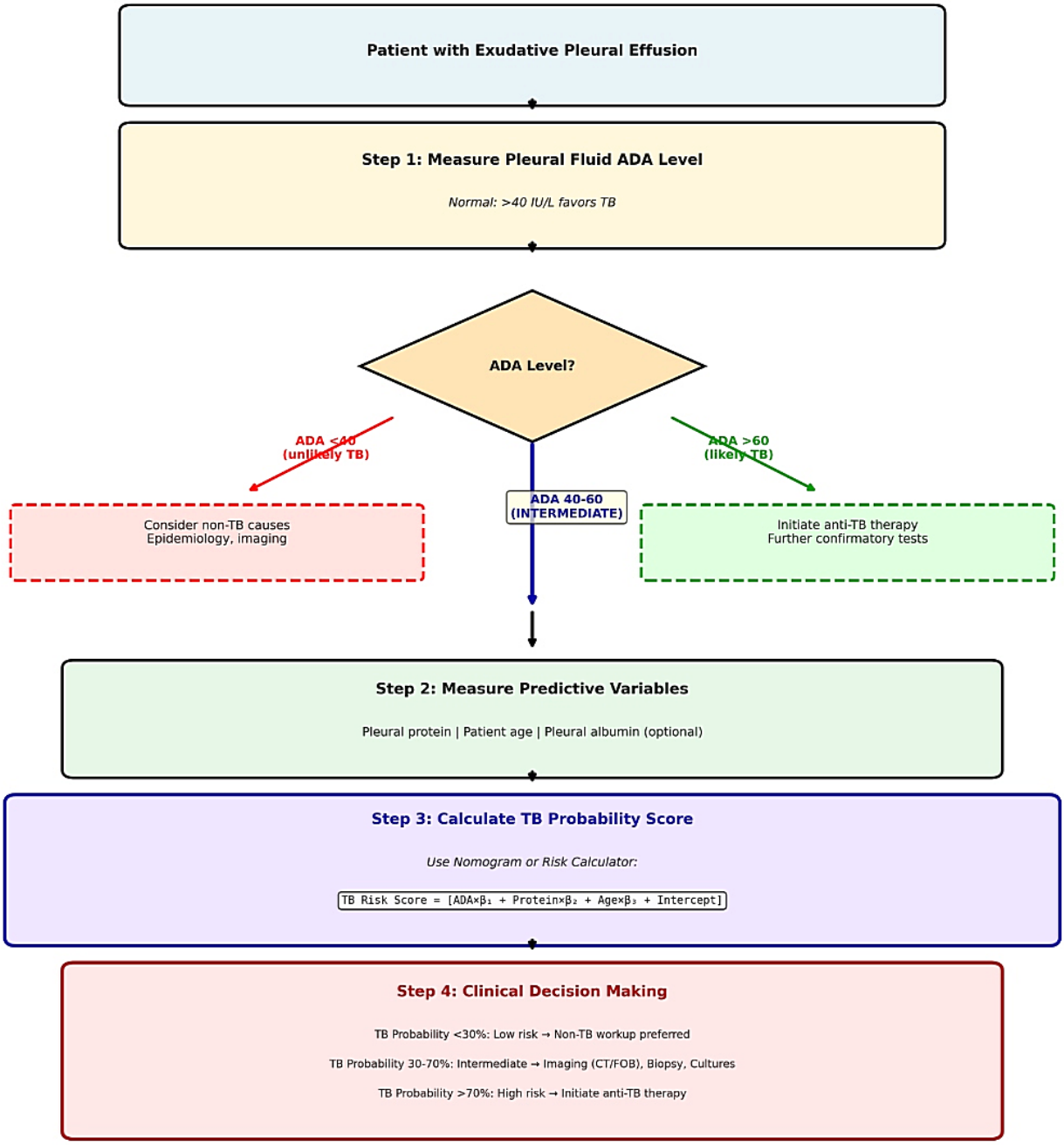

Figure 4. Clinical algorithm for TB prediction in intermediate ADA pleural effusions. Stepwise clinical algorithm outlining the application of the multivariable model and risk categories (low, intermediate, high probability) to guide diagnostic work-up and treatment decisions in patients with exudative pleural effusions and ADA 40–60 IU/L.

Table 1: Base TB Risk by ADA Level

ADA (IU/L)	Base TB Risk %
40-42	28%
42-44	31%
44-46	34%
46-48	37%
48-50	40%
50-52	43%
52-54	46%
54-56	49%
56-58	52%
58-60	55%

Table 2: Age Adjustment

Age (years)	TB Risk Adj
<25	+8%
25-35	+5%
35-45	0%
45-55	-5%
55-65	-10%
>65	-15%

Table 3: Pleural Protein Adjustment

Pleural Protein (g/dL)	TB Risk Adj
<4.0	-12%
4.0-4.5	-8%
4.5-5.0	-4%
5.0-5.5	+4%
5.5-6.0	+8%
>6.0	+12%

```
INSTRUCTIONS FOR USE:
1. Start with Base TB Risk from Table 1 (using ADA level)
2. Adjust by Age (Table 2) - ADD or SUBTRACT the adjustment
3. Further adjust by Pleural Protein (Table 3) - ADD or SUBTRACT the adjustment
4. Final TB Risk = Base Risk ± Age adjustment ± Protein adjustment

EXAMPLE: ADA=48 IU/L, Age=40 years, Protein=5.0 g/dL
    Base Risk (ADA 48) = 37%
    Age adjustment (35-45 years) = 0%
    Protein adjustment (4.5-5.0 g/dL) = -4%
    FINAL TB RISK = 37% - 4% = 33% (INTERMEDIATE → workup needed)
```

Note: Nomogram provides probabilistic estimate. Clinical judgment, imaging, and microbiological confirmation remain essential.

Figure 5. Nomogram table for TB risk stratification. Nomogram-style table providing base TB risk by ADA level and adjustment factors for age and pleural protein to estimate final TB probability in patients with intermediate ADA values.