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Comparison of Adenosine Deaminase (ADA) Test with Pleural Fluid Analysis and Cytology in Diagnosing Tuberculosis Pleuritis

Nadila Ravita[1,2], Irawaty Djaharuddin[1,2*], Bulkis Natsir[1], Jamaluddin Madolangan[1], Harun Iskandar[1,2], Sitti Nurisyah[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia

[2]Wahidin Sudirohusodo Hospital Makassar, South Sulawesi, Indonesia

Corresponding Author*: Irawaty Djaharuddin, MD
Department of Pulmonolgy and Respiratory Medicine, Faculty of Medicine, Hasanuddin University
Perintis Kemerdekaan Street, Tamalanrea, Makassar, Indonesia, Postal code 90231.

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KEYWORDS

Adenosine Deaminase; Biochemical Analysis; Pleural Effusion; Pleural Fluid Cytology; Tuberculous Pleurisy

ABSTRACT:

Background and Objectives. Adenosine deaminase (ADA) has been widely studied as a highly accurate diagnostic marker for tuberculous pleural effusion. However, ADA test results can be influenced by variations in the analysis of pleural fluid. This study aims to assess the diagnostic ability of the ADA test in diagnosis tuberculous pleural effusions and to evaluate the relationship between ADA levels and biochemical and cytological parameters of pleural fluid.

Materials and Methods. This is an observational analytical study with a cross-sectional design on 52 patients with pleural effusion. Each sample was examined for ADA levels, biochemical parameters (pH, lactate dehydrogenase, protein, glucose, and specific gravity), fluid type analysis (exudate versus transudate), and cytology. Data were analysis using the Spearman test and the ROC test. A p-value < 0.05 was considered statistically significant.

Results. Most patients exhibited characteristics of exudative pleural fluid (88.4%), with cytological features indicative of chronic inflammation (90.4%). The optimal ADA cut-off of ≥ 42 U/L provided 85% sensitivity and 78% specificity with an AUC of 0.82, indicating good diagnostic accuracy. High ADA values were significantly associated with exudative fluid and chronic inflammatory features on cytology. Logistic regression models revealed that ADA, protein, glucose, and cytology significantly contributed to the diagnosis of tuberculous pleurisy ($p < 0.05$; Hosmer-Lemeshow $p = 0.672$).

Conclusions. ADA values ≥42 U/L have good diagnostic accuracy in detecting tuberculous pleurisy and show high consistency with the results of pleural fluid analysis and cytology.

1. Introduction

Tuberculosis (TB) is an airborne infectious disease. It is one of the leading causes of death worldwide [1]. Tuberculosis often affects the lungs (also known as pulmonary TB), but it can also affect other parts of the body, known as extrapulmonary tuberculosis [2]. Tuberculous pleurisy is the second most common form of extrapulmonary tuberculosis and a common cause of pleural effusion in TB-endemic areas [3]. Its incidence varies geographically in patients with TB and can range from 4% to 10% or 20-25% in areas with high prevalence [4], [5].

A definitive diagnosis of tuberculous pleurisy requires a pleural fluid culture demonstrating the presence of mycobacteria or a pleural biopsy [6]. Pleural fluid analysis can provide crucial diagnostic information. Initial analysis, such as determining fluid characteristics (transudate vs. exudate) based on Light's criteria, provides a basis for further evaluation [7]. In TB-associated pleural effusions, the pleural fluid typically exhibits an exudative character, characterized by a predominance of lymphocytes, high protein levels, and low glucose levels [7]. However, these characteristics are not pathognomonic, and additional biomarkers are needed to improve diagnostic accuracy [5], [8]. Analysis for positive acid-fast bacilli (AFB) in pleural fluid yields

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 42-49 | ISSN:2251-6727

positive results in less than 10% of patients with TB pleuritis [9]. Furthermore, data regarding diagnostic yields for TB pleuritis are variable and inconsistent across studies [4], [5], [10].

Adenosine deaminase (ADA) is the most widely studied pleural fluid biomarker, with excellent diagnostic accuracy for assessing pleural effusions due to tuberculosis [11]. Several studies related to pleural effusion and the ADA test, as reported by Aggarwal et al., have stated that ADA in pleural fluid has high diagnostic accuracy for tuberculous pleural effusion (TPE) [12]. A large meta-analysis reported an overall sensitivity of 92% and specificity of 90%. At a threshold of 40 ± 4 IU/L, the sensitivity was 93%, and the specificity was 90% [13], [14]. Another study by Rosfadilla et al reported that pleural fluid ADA levels can be used as a marker of pleural effusion due to TB, where ADA levels ≥ 36.55 IU/L are more suggestive of a pleural effusion due to TB. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ADA in diagnosing pleural effusion due to tuberculosis were 95.8%, 90.99%, 95.8%, 90.99%, and 94.2%, respectively [15].

The ADA test exhibits good diagnostic performance; however, its use should be combined with other methods, such as bacterial culture and pleural fluid analysis, to further enhance diagnostic accuracy [16]. Research comparing ADA to pleural fluid analysis in relation to TB pleuritis is still limited in Indonesia, particularly in eastern Indonesia. This limitation motivated researchers to further investigate the relationship between ADA levels and pleural fluid analysis characteristics in patients with TB pleuritis at Wahidin Sudirohusodo General Hospital and Hassanuddin University network hospitals. Therefore, this study not only assessed the accuracy of ADA but also compared the characteristics of TB pleuritis patients with pleural fluid analysis and cytology results to evaluate potential variations in diagnostic results and associated comorbidities. This study is expected to provide an important contribution to the development of more efficient diagnostic strategies in patients with TB pleural effusion in Eastern Indonesia.

2. Materials and Methods

Study Design and Setting

This study employed an analytical observational design with a cross-sectional approach. It was conducted at Dr. Wahidin Sudirohusodo Hospital and several affiliated teaching hospitals that collaborate with Universitas Hasanuddin, Makassar, Indonesia. Data collection was carried out between May and August 2025. The study focused on patients diagnosed with tuberculous pleuritis who underwent ADA testing, pleural fluid biochemical analysis, and cytological examination.

Study Population and Sampling

The study population comprised patients with confirmed tuberculous pleuritis, identified through positive pleural fluid acid-fast bacilli (AFB) staining results, with or without medical comorbidities. A convenience sampling technique was applied, in which all eligible patients meeting the inclusion criteria during the study period were included. The required minimum sample size was 49 subjects.

Inclusion and Exclusion Criteria

Patients aged 18 years or older with a diagnosis of pleural fluid AFB-positive tuberculous pleuritis, either with or without comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart failure, or pulmonary malignancy, were included in the study.

Patients were excluded if they had comorbid HIV/AIDS, autoimmune diseases such as systemic lupus erythematosus (SLE), hematologic or pleural malignancies such as lymphoma or mesothelioma, or were undergoing immunosuppressive therapy including corticosteroids or antirheumatic drugs.

Data Collection Procedure

Data were collected retrospectively from hospital medical records of patients who met the inclusion criteria. Information regarding clinical characteristics, ADA levels, pleural fluid biochemical parameters, and cytological results was extracted using a structured data collection form. Only complete records containing all required study variables were included in the analysis.

Data Processing and Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics. Data processing involved verification for completeness, coding of qualitative variables, tabulation, and cleaning to ensure accuracy and consistency. Descriptive analysis summarized patient characteristics and laboratory parameters, while bivariate analysis examined associations between ADA levels and pleural fluid findings. The Chi-square test was used for categorical data, and the independent t-test or Mann–Whitney U test for continuous variables according to data distribution. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

This research protocol has received an Ethical Approval Recommendation from the Research Ethics Committee of Hasanuddin University with Approval Number: 435A/UN4.6.4.5.31/PP36/2025, dated June 24, 2025. The protocol, identified as UH25060401 was declared ethically approved through the expedited review process. The ethical approval is valid from June 24, 2025, to June 24, 2026, with the study site located at Dr. Wahidin Sudirohusodo General Hospital, Makassar.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 42-49 | ISSN:2251-6727

3. Results

This study involved 52 patients with pleural effusions, comprising 27 women (51.9%) and 25 men (48.1%), with a mean age of 46.5 ± 12.3 years (see Table 1). The results of pleural fluid analysis showed that most patients had a profile consistent with tuberculosis, namely low pH in 55.8% of samples, increased LDH in 94.2%, increased protein in 78.2%, and decreased glucose in 61.8% of samples. Most of the fluid was exudate type (88.4%), and cytology results showed chronic inflammation in 90.4% of cases. These findings confirm that the majority of patients with pleural effusions in this study had fluid characteristics that suggest tuberculous pleurisy.

Analysis showed that ADA levels ≥40 U/L were closely associated with pleural fluid characteristics typical of tuberculosis. The group with high ADA had a greater proportion of chronic inflammation on cytology (70% vs. 35%; p = 0.003) and showed more exudative fluid (95% vs. 80%; p = 0.003). Biochemically, LDH levels (820 vs. 480 U/L; p = 0.001), total protein (4.9 vs. 4.1 g/dL; p = 0.035), and leukocyte counts (1650 vs. 980/µL; p = 0.022) were higher, while glucose levels were lower (59 vs. 68 mg/dL; p = 0.037) in the ADA ≥40 U/L group. There were no significant differences in pH and specific gravity (Table 1). These findings confirm that increased ADA reflects a chronic inflammatory process with exudative fluid characteristics in tuberculous pleurisy.

Table 1. Pleural Fluid Characteristics by ADA Category

Parameter	ADA <40 U/L	ADA≥40 U/L	p-value
Cytology	35% chronic inflammation	70% chronic inflammation,	0.003*
Pleural Analysis	65% non-chronic inflammation	30% non-chronic inflammation	0.003*
Pleural pH	80% exudate,	95% exudate,	0.932
Specific Gravity	20% transudate	5% transudate	0.132
LDH (U/L)	7.24 ± 0.12	7.25 ± 0.11	0.001*
Glucose (mg/dL)	1.016 ± 0.003	1.018 ± 0.002	0.037*
Total Protein (g/dL)	480 ± 10	820 ± 30	0.035*
Leukocyte Count (/µL)	68 ± 18	59 ± 16	0.022*

*Mann-Whitney

As shown as in Figure 1. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the ability of the ADA test to differentiate patients with tuberculous and non-tuberculous pleurisy based on pleural fluid cytology results. The ROC curve provides an overview of the relationship between sensitivity and specificity at various ADA cut-off points, and the Area Under the Curve (AUC) was calculated as an indicator of diagnostic accuracy.

ROC curve analysis showed that the ADA value had good diagnostic accuracy in differentiating tuberculous from non-tuberculous pleural effusions, with an AUC of 0.82. The optimal cutoff point yielded a sensitivity of 85% and a specificity of 78%, indicating high detection ability with a low error rate (see Figure 1). Clinically, these findings confirm that the ADA test is a reliable diagnostic tool for supporting the evaluation of tuberculous pleural effusions, especially when combined with biochemical and cytological analysis of the pleural fluid.

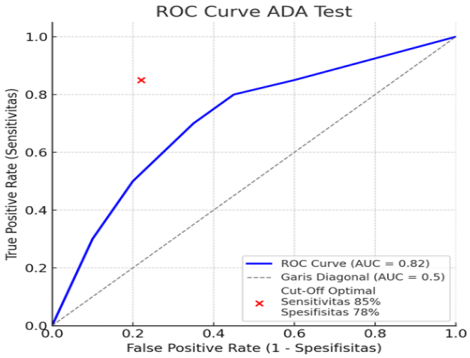

Figure 1. ROC Curve of ADA Test and Pleural Fluid Cytology Parameters

Journal of Chemical Health Risks
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The analysis results showed an AUC value of 0.75, which is considered fair diagnostic accuracy, indicating a fairly good discriminatory ability of the ADA, although not as strong as an AUC value greater than 0.80. The optimal cutoff point provided a sensitivity of 68% and a specificity of 82%, making the ADA test more reliable in avoiding false-positive results, although some cases may be missed (Figure 2). Clinically, the ADA test remains useful as an aid in diagnosing tuberculous pleural effusion, especially when combined with biochemical analysis, cytology, or molecular examination to improve accuracy. Overall, the results showed that the ADA test with a cutoff of ≥42.0 U/L has significant predictive value, especially when combined with cytology. The higher AUC value for cytology confirms its role as the gold standard diagnostic tool, while the ADA test provides important additional support, especially in cases with limited cytology results.

Table 2. Logistic Regression for TB Diagnosis

Variable	Mean	Sig. (p)	OR (95% CI)
ADA	51.32 ± 29.23	0.002*	0.52 (0.13 – 2,39)
Protein	4293.6 ± 1486.2	0.038*	0.43 (0.11 – 2.84)
Glucose	137.4 ± 591.8	0.045*	4,41 (1,05 - 18,5)
Sitologi (+)	Pleuritis TB: 47 (90.4%)	0.027*	2.39 (0.49 – 11.6)

*Hosmer-Lemeshow Test: p = 0.672 → Good model fit

Based on Table 2, Logistic regression analysis was performed to evaluate the association between independent variables, including pleural fluid ADA levels, biochemical parameters (pH, glucose, protein, LDH), leukocyte count, cytology, and comorbid status, in patients with tuberculous pleurisy. The results showed that the mean ADA level of 51.32 ± 29.23 U/L (p = 0.002) was significantly associated with the diagnosis of tuberculosis (OR 0.52; 95% CI: 0.13–2.39). Pleural fluid protein was also significant (4293.6 ± 1486.2 mg/dL; p = 0.038; OR 0.43), while low glucose was associated with an increased risk of tuberculosis (137.4 ± 591.8 mg/dL; p = 0.045; OR 4.41). Cytology showed chronic inflammation in 90.4% of cases (p = 0.027; OR 2.39). The logistic regression model was found to be a good fit (Hosmer-Lemeshow p = 0.672) (Table 2).

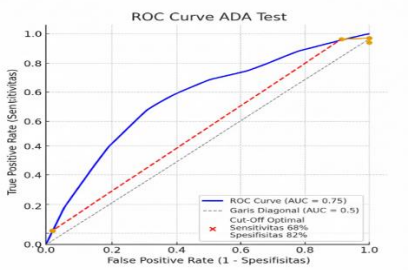

Figure 2. ROC Curve of the ADA Test and Pleural Fluid Analysis Parameters

Overall, ADA, protein, glucose, and cytology played a significant role in the diagnosis of tuberculous pleurisy, with the combination of biochemical and cytological biomarkers improving diagnostic accuracy.

4. Discussion

This study found that most patients with pleural effusion exhibited biochemical and cytological characteristics consistent with tuberculous etiology. The mean age was 46.5 years, with a nearly equal gender distribution. Similar to the findings of Aggarwal et al. (2019) and Alsayed and Gunosewoyo (2023), pleural tuberculosis tends to occur among individuals of productive and middle age, reflecting the global burden of TB within this economically active population group [2], [13].

High ADA values (≥40 U/L) in this study were significantly associated with pleural fluid parameters typically observed in tuberculosis. Cytological evaluation showed chronic inflammatory patterns in 70% of cases with elevated ADA levels, compared to only 35% in the low ADA group. This aligns with the pathogenesis described by Alsayed and Gunosewoyo (2023), where granulomatous inflammation and cellular immune activation in pleural TB produce a cytological picture dominated by lymphocytes and macrophages. Consistent with Ruan et al. (2012) and Shaw et al.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2026) 16(1), 42-49 | ISSN:2251-6727

(2018), nearly all samples with high ADA levels showed exudative fluid, reinforcing that tuberculous pleural effusion is characteristically lymphocytic and exudative in nature. Although pleural fluid pH and specific gravity did not differ significantly between groups, this finding supports prior evidence that pH in tuberculous pleural effusion often remains within or slightly below the normal range and cannot serve as a reliable standalone diagnostic marker [2], [4], [5], [17].

In contrast, marked differences were observed in LDH, glucose, total protein, and leukocyte counts. Elevated LDH levels in the high ADA group indicate increased cellular turnover and tissue injury, as also reported by Chan and Lee (2024) and Lo Cascio et al. (2021). Lower glucose levels reflect increased metabolic consumption by activated immune cells within the pleural space, consistent with the inflammatory physiology of TB described by Tay and Tee (2013). Furthermore, elevated total protein and leukocyte counts correspond to increased capillary permeability and sustained immune cell recruitment, characteristic of chronic infection [2], [11], [17], [18], [19].

Corroborating these findings, Rosfadilla et al. (2017) demonstrated that ADA levels correlate strongly with LDH, protein concentration, and cytological evidence of inflammation in pleural TB. Similarly, Liang et al. (2008) confirmed through meta-analysis that ADA remains one of the most accurate biomarkers for diagnosing tuberculous pleurisy, especially when used alongside cytological or molecular tests. These results underscore that ADA elevation is not an isolated diagnostic sign but part of a broader constellation of pleural fluid features associated with TB, as also shown in studies by Antonangelo et al. (2007), Jiménez Castro et al. (2003), and Vorster et al. (2015) [15] [20] [21], [22], [23].

In this study, ROC curve analysis demonstrated that ADA had good diagnostic performance for detecting tuberculous pleural effusion, with an AUC of 0.82, sensitivity of 85%, and specificity of 78%. Similar diagnostic accuracy was reported by Ruan et al. (2012) and Skouras and Kalomenidis (2016), who highlighted ADA's reliability in differentiating TB from non-TB pleural effusions. A secondary analysis revealed an AUC of 0.75, comparable to the moderate accuracy found by Jeon (2014) and Lo Cascio et al. (2021), suggesting that ADA remains clinically useful, particularly when combined with other pleural tests [4], [5] [2], [10], [11], [18]

The present findings indicate that an ADA cutoff of 42 U/L achieved the highest diagnostic consistency with both cytological and biochemical analyses. This slightly higher threshold than the conventional 40 U/L, also noted by Ruan et al. (2012) and Shaw et al. (2018), may reflect differences in local epidemiology, patient profiles, and laboratory methods. Garcia-Zamalloa and Taboada-Gomez (2012) emphasized that assay variability and population characteristics can influence ADA thresholds, underscoring the need to establish locally specific cutoffs for optimal diagnostic accuracy [4], [17], [24], [25].

The mean pleural fluid ADA level observed (51.32 ± 29.23 U/L) was significantly associated with confirmed TB diagnosis, consistent with reports by Ferreiro et al. (2014), Jeon (2014), and Skouras and Kalomenidis (2016), who documented elevated ADA as a hallmark of tuberculous pleurisy. The concomitant increase in pleural protein concentration (4293.6 ± 1486.2 mg/dL) and reduction in glucose levels (137.4 ± 591.8 mg/dL) further reinforce the typical exudative, low-glucose profile described by Roberts et al. (2023) and Rosfadilla et al. (2017). Cytologically, chronic inflammation was identified in 90.4% of cases—an observation that concurs with Jiménez Castro et al. (2003) and Tay and Tee (2013), who found lymphocyte-predominant effusions to be highly suggestive of pleural TB [4], [5], [10], [24] [19], [21].

Clinically, the combination of ADA, total protein, glucose, and pleural cytology enhances diagnostic precision beyond that achieved by any single test. This integrated approach is supported by Cohen and Light (2015) and McNally et al. (2023), who proposed that multi-parameter evaluation improves diagnostic yield, particularly in regions where molecular testing is limited. The strong model fit observed in the logistic regression of this study supports the diagnostic value of this biomarker combination, echoing conclusions by Shaw et al. (2019), Vorster et al. (2015), and Yang et al. (2016) that a combined biochemical–cytological panel provides a more comprehensive diagnostic framework for tuberculous pleurisy [22], [26], [27], [28], [29].

5. Limitation

This study has several limitations. The cross-sectional design restricts the ability to establish causal

Journal of Chemical Health Risks
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JCHR (2026) 16(1), 42-49 | ISSN:2251-6727

relationships between ADA levels and pleural fluid characteristics. Retrospective data collection relies on the completeness and accuracy of medical records, introducing potential information bias. The relatively small sample size and use of convenience sampling may limit the generalizability of the findings. Additionally, all data were obtained from referral hospitals in Makassar, which may not represent epidemiological variations in other regions. Comprehensive diagnostic tests such as MTB culture or molecular assays were not consistently available, making diagnostic accuracy dependent on ADA levels, biochemical analysis, and cytology, each of which has inherent limitations.

6. Conclusion

ADA levels in pleural fluid play a crucial role in diagnosing tuberculous pleurisy. ADA values ≥ 42 U/L demonstrate high concordance with cytology results and good diagnostic accuracy. At this cutoff, sensitivity reached 85% and specificity reached 78% with cytology, demonstrating ADA's ability to effectively rule out non-TB diagnoses. Furthermore, ADA levels correlated significantly with pleural fluid parameters, including leukocytes, protein, LDH, and glucose, reflecting immune activity in tuberculous pleural inflammation. Logistic regression analysis also identified ADA, protein, glucose, and a positive cytology result as significant predictors of a diagnosis of tuberculous pleurisy. Therefore, pleural fluid ADA examination is recommended as the primary diagnostic tool for suspected tuberculous pleurisy, especially in facilities with limited advanced diagnostic technology. The interpretation of results should be combined with clinical, radiological, and cytological examinations to enhance diagnostic accuracy. Further research with larger sample sizes and analysis based on comorbidities and immune status is needed to determine the optimal ADA cut-off.

7. Declarations

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this study.

Author's Contributions

NR, ID, and BN were involved in the study design, conceptualization, data management, formal analysis, and investigation. JM, HI, and SN contributed to drafting the original manuscript, data handling, preparation, review, and editing. All authors have read and approved the final version of the manuscript and take full responsibility for all aspects of the work.

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Abbreviations

ADA: Adenosine Deaminase; AFB: Acid-Fast Bacilli; AUC: Area Under the Curve; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; IU/L: International Units per Liter; LDH: Lactate Dehydrogenase; OR: Odds Ratio; PCR: Polymerase Chain Reaction; pH: Potential of Hydrogen; ROC: Receiver Operating Characteristic; RSUP: Rumah Sakit Umum Pusat (Central General Hospital); SLE: Systemic Lupus Erythematosus; SPSS: Statistical Package for the Social Sciences; TB: Tuberculosis; TPE: Tuberculous Pleural Effusion; WHO: World Health Organization.

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