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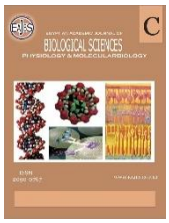
**Citation**: *Egypt.Acad.J.Biolog.Sci. ( C.Physiology and Molecular biology ) Vol. 17(2) pp255-263 (2025)*
**DOI: 10.21608/EAJBSC.2025.462732**

Egypt. Acad. J. Biolog. Sci., 17(2):255-263 (2025)

Egyptian Academic Journal of Biological Sciences
C. Physiology & Molecular Biology
ISSN 2090-0767
www.eajbsc.journals.ekb.eg



# Pleural Fluid Adenosine Deaminase as a Biochemical Indicator in Diagnosing Tuberculous Pleural Effusion in Patients from Sudan

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**ARTICLE INFO**

**Article History**
Received: 22/9/2025
Accepted: 29/10/2025
Available: 3/11/2025

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***Keywords***:
Adenosine deaminase, tuberculous pleural effusion, biochemical marker, Sudan.

**ABSTRACT**

**Background**: The determination of optimal adenosine deaminase (ADA) levels for diagnosing TPE has been extensively researched. The study aimed to establish local diagnostic cutoff values for ADA in pleural fluid (pfADA) to evaluate TPE and enhance its utility. **Methods**: A cross-sectional study was conducted involving 60 patients with TPE who were referred to the Tropical Diseases Teaching Hospital in Khartoum State from December 2021 to March 2022. Demographic and clinical data were gathered. The pfADA was estimated using spectrophotometric methods, in conjunction with a pleural biopsy performed at the same site. The cutoff value of pfADA was established through the analysis of the receiver operating characteristic (ROC) curve. **Results**: Of 60 patients enrolled, 42 (70%) tested positive for pfADA; within this group, 34 (81%) exhibited positive tuberculosis granuloma in the biopsy. The optimal pfADA diagnostic cutoff value was **29 U/L**, with sensitivity, specificity, positive predictive value (PPV), negative predictive value, and area under the curve (AUC) reported as 94.4%, 66.7%, 78.1%, 92.3%, and 0.806, respectively. Compared to pfADA-negative patients, pfADA-positive patients showed significantly elevated levels of albumin >3.5 g/dl (88.1% vs. 11.1%; p = 0.033), LDH >1000 U/L (42.6% vs. 22.2%; p = 0.001), lymphocytosis (80% vs. 50%; p = 0.042), and neutropenia (20% vs. 50%; p = 0.049). **Conclusion**: This is the first study to establish a local pfADA cut-off of 29.0 U/L for identifying TPE within the studied population.

## INTRODUCTION

Tuberculosis (TB) remains a significant cause of morbidity and mortality globally, with an estimated 1.25 million deaths occurring in 2023 (Global Tuberculosis Report, 2024).

Extrapulmonary tuberculosis presents diagnostic challenges and constitutes approximately 15% of the global TB burden (Global Tuberculosis Report, 2024). Tuberculous pleural effusion (TPE) represents a prevalent manifestation of extrapulmonary tuberculosis and is the primary etiology of pleural effusion in developing nations (Baumann *et al.,* 2007; Udwadia & Sen, 2010).

Adenosine deaminase (ADA) is an enzyme involved in purine metabolism, in converting adenosine and deoxyadenosine to inosine and deoxyinosine, respectively, produced by lymphocytes, and is essential for the development and maintenance of the immune system (Chang *et al.,* 2018).

Extensive research has been conducted on the utility of pleural fluid ADA (pfADA) as a biochemical marker for diagnosing tuberculous pleurisy (TPE) (Arnold *et al.,* 2015; Arpinar Yigitbas *et al.,* 2021; Blakiston *et al.,* 2018; Chang *et al.,* 2018; Fei *et al.,* 2023; Li *et al.,* 2015; Mortazavi-Moghaddam *et al.,* 2016; Ren Tay & Tee, 2013; Salam *et al.,* 2022). pfADA is a straightforward, rapid, cost-effective, and minimally invasive procedure compared to pleural biopsy. It demonstrates high sensitivity and specificity and is feasible in the majority of laboratories (Baba *et al.,* 2008; Chen *et al.,* 2004; Jiménez Castro *et al.,* 2003; Lee S. J. *et al.,* 2014; Lee Y. C. G. *et al.,* 2001).

In a high prevalence setting, an ADA cutoff value exceeding 40 U/L was sometimes linked to a strong positive predictive value (PPV) (Shaw *et al.,* 2018). While in a low prevalence setting, low ADA levels, along with a high negative predictive value (NPV), may be utilized to rule out TPE (Sivakumar *et al.,* 2017).

Sudan exhibits a reduction in tuberculosis (TB) incidence, with an estimated 26,000 cases annually and a pooled prevalence of 30.7% (Badawi *et al.,* 2024). The presumptive diagnosis of TPE with a pfADA level exceeding 40 U/L is not recognized in Sudan's TB guidelines, particularly in low-prevalence settings, as per WHO recommendations. Furthermore, there is a lack of local data providing a diagnostic pfADA cut-off value for TPE. This study represents the first effort to establish a local diagnostic cut-off value for pfADA to identify TPE within our study population

## MATERIALS AND METHODS

### Study Design and Subjects:

A descriptive cross-sectional hospital-based study was conducted on 60 patients with TPE referred to the Tropical Diseases Teaching Hospital in Khartoum State in the period from December 2021 to March 2022. The TPE was considered positive in the presence of the following: confirmed acid-fast bacilli in pleural fluid; tuberculosis granuloma in pleural biopsy histology; and positive pleural fluid and biopsy cultures for Mycobacterium tuberculosis (*M. tuberculosis*). The TPE clinical diagnosis was set based on the clinical pictures, radiographic features, and consequently the positive response to anti-tuberculosis therapy. Patients who did not meet the aforementioned diagnostic criteria, those diagnosed with transudative or malignant pleural effusions, or those on anti-tuberculous treatment were excluded. All study subjects signed written informed consent after knowing the study purpose and data confidentiality.

### Data Collection and Sampling:

A well-structured questionnaire was designed to include demographic (age, gender, residence, occupation, education, and marital status), clinical (sweating, fever, cough, shortness of breath [SOB], and chest pain), and pleural fluid data (ADA, lactate dehydrogenase [LDH], albumin, chest X-ray [CXR], and lymphocyte/neutrophil differential).

Twenty milliliters (20 ml) of pleural fluid were collected through thoracentesis, accompanied by a pleural biopsy undertaken from the same location. Pleural fluid underwent centrifugation at 3,000 g for 15 minutes at 4°C to assess levels of pfADA, albumin, and LDH. The activity of pfADA

was assessed using the spectrophotometric method outlined by Guisti and Galanti (Giusti G & Galanti B, 1984). Following sample centrifugation, 25 mL of the pleural fluid supernatant was transferred into a test tube, accompanied by 500 mL of an adenosine solution. The mixture underwent heating for one hour at 37°C, after which the reaction was halted by the addition of phenol nitroprusside and hypochlorite solutions. The mixture underwent heating for 30 minutes at a temperature of 37°C. The amount of ammonia released due to ADA activity was quantified using a spectrophotometer at a wavelength of 600 nm. pfADA levels were quantified and expressed in units per liter (U/L). A distinct fluid sample was obtained to measure albumin and LDH levels using an automated analyzer. Lymphocytes and neutrophils were counted as well. An effusion is classified as lymphocyte- or neutrophil-predominant when the counts of these cells in pleural fluid exceed 0.5 of the total fluid count.

**Statistical Analysis:**

Data analysis was conducted utilizing the Statistical Package for Social Sciences (SPSS, V. 21.0, IBM; Chicago, USA). Categorical variables were expressed as numbers and percentages and compared using the chi-square ($x^2$) test. The multiple receiver operating characteristic curve (ROC) was employed to determine the best cutoff value of the pfADA level for diagnosing TPE.

The sensitivity, specificity, PPV, and NPV were also calculated to measure diagnostic accuracy. A P value of less than 0.05 was deemed significant.

## RESULTS

***In Vivo* Study:**

The study included 60 patients diagnosed with tuberculous pleural effusion (TPE), with a male predominance of 75% compared to 25% females. Additionally, 35% of the participants were aged between 18 and 30 years. Most patients exhibited chest pain (95%), followed by shortness of breath (91.7%) and coughing (80%) (Table 1).

Chest x-ray findings revealed that a significant proportion of patients exhibited massive pleural effusion, with 26 individuals (43.3%) affected. Additionally, high albumin levels (≥3.5 g/dl) were observed in 42 patients (70%), while elevated LDH levels (>1000 U/L) were noted in 22 patients (36.7%), as detailed in Table 2.

The ROC curve analysis established a diagnostic cutoff value for pfADA at 29 U/L, yielding a sensitivity of 94.4%, a specificity of 66.7%, a PPV of 78.1%, an NPV of 92.3%, and an area under the curve (AUC) of 0.806 (95% CI, 0.680-0.931, $P$ = 0.000) (Fig. 1). Demonstrating significant validity of pfADA in diagnosing TBE, exhibiting high sensitivity and satisfactory specificity.

The pfADA analysis indicated positive outcomes in 42 patients (70%), with 34 of these patients (81%) exhibiting a positive tuberculosis granuloma in the biopsy. Patients testing positive for pfADA exhibited significantly elevated levels of albumin >3.5 g/dl (88.1% vs. 11.1%; $P$ = 0.033), LDH levels >1000 U/L (42.6% vs. 22.2%; $P$ = 0.001), lymphocytosis (80% vs. 50%; $P$ = 0.042), and neutropenia (20% vs. 50%; $P$ = 0.049) in comparison to those testing negative for pfADA (Table 3).

**Table 1.** The demographic and clinical characteristics of patients with TPE (N = 60).

| | ***Characteristics*** | ***N*** | ***%*** |
|---|---|---|---|
| ***Gender*** | *Male* | *45* | *75.0* |
| | *Female* | *15* | *25.0* |
| ***Age (Yrs.)*** | *<18* | *6* | *10.0* |
| | *18-30* | *21* | *35.0* |
| | *31-45* | *8* | *13.3* |
| | *46-60* | *19* | *31.7* |
| | *>60* | *6* | *10.0* |
| ***Residence*** | *Urban* | *36* | *60.0* |
| | *Rural* | *24* | *40.0* |
| ***Occupation*** | *Worker* | *20* | *33.3* |
| | *Farmer* | *13* | *21.7* |
| | *Employee* | *13* | *21.7* |
| | *Student* | *8* | *13.3* |
| | *Retired* | *6* | *10.0* |
| ***Education*** | *Illiterate* | *12* | *20.0* |
| | *Primary* | *17* | *28.3* |
| | *Secondary* | *25* | *41.7* |
| | *University* | *6* | *10.0* |
| ***Marital status*** | *Married* | *34* | *56.7* |
| | *Single* | *26* | *43.3* |
| ***Symptoms*** | *Chest pain* | *57* | *95.0* |
| | *Short of breath* | *55* | *91.7* |
| | *Cough* | *48* | *80.0* |
| | *Fever* | *39* | *65.0* |
| | *Weight loss* | *28* | *46.7* |
| | *Sweating* | *20* | *33.3* |
| ***Symptoms duration (month)*** | *< 1* | *8* | *13.0* |
| | *1 - 3* | *28* | *47.0* |
| | *> 3* | *24* | *40.0* |

**Table 2.** The pleural effusion levels in CXR and pleural fluid analysis in patients with TPE (N = 60).

| | **Parameters** | **N (%)** | **%** |
|---|---|---|---|
| **Pleural effusion in CXR** | Mild | 9 | 15.0 |
| | Moderate | 25 | 41.7 |
| | Massive | 26 | 43.3 |
| **Albumin (g/dl)** | <3.5 | 18 | 30.0 |
| | ≥3.5 | 42 | 70.0 |
| **LDH (U/L)** | <320 | 14 | 23.3 |
| | 320 - 1000 | 24 | 40.0 |
| | >1000 | 22 | 36.7 |
| **Lymphocyte effusion diff. (%); Median** | | 70 | |
| **Neutrophil effusion diff. (%); Median** | | 30 | |

CXR, chest X-ray; diff, differential.

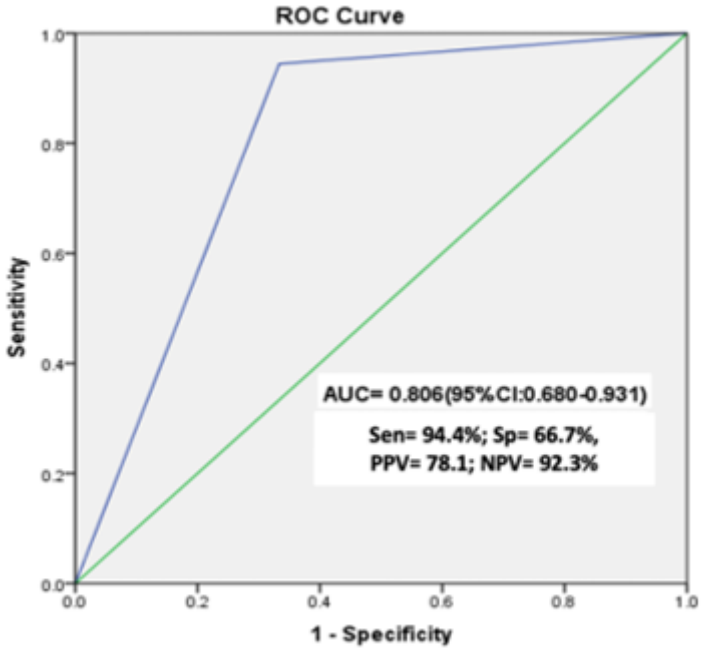


**Fig. 1.** The receiver operating characteristic curve (ROC) to evaluate the validity of ADA in detecting TP

**Table 3.** The association of pfADA levels with albumin, LDH, lymphocytes, and neutrophil values.

| Parameters | | pfADA <29 U/L (n = 18) | pfADA ≥29 U/L (n = 42) | *P.* value |
|---|---|---|---|---|
| | | n (%) | n (%) | |
| **Pleural biopsy** | | 8 (19.0%) | 34 (81.0) | 0.002 |
| **Albumin (g/dl)** | <3.5 | 16 (88.9%) | 5 (11.9%) | 0.033 |
| | ≥3.5 | 2 (11.1%) | 37 (88.1%) | |
| **LDH (U/L)** | <320 | 10 (55.6%) | 4 (9.5%) | 0.001 |
| | 320-1000 | 4 (22.27%) | 20 (47.6%) | |
| | >1000 | 4 (22.2%) | 18 (42.6%) | |
| **Lymphocytes diff (%); Median** | | 50 | 80 | 0.042 |
| **Neutrophils diff (%); Median** | | 50 | 20 | 0.049 |

LDH, lactate dehydrogenase; diff, differential

## DISCUSSION

Tuberculous pleural effusion (TPE) ranks as the second most prevalent form of extrapulmonary tuberculosis. Pleural effusions frequently occur in regions where tuberculosis is prevalent. The study indicated that the majority of patients were male (M:F = 3:1) and aged between 18 and 45 years (48.3%). This finding aligns with an epidemiological analysis performed by Baumann et al., which reported an overall male-to-female ratio of 2:1, with TPE being significantly more prevalent in individuals under 45 years of age (Baumann *et al.,* 2007), and with a systematic review that indicated that TPE predominantly affects younger individuals (mean age = 34 years) residing in areas with a higher prevalence of tuberculosis (Zhai *et al.,* 2016). Chest pain, shortness of breath, cough, and fever were the primary complaints in over fifty percent of the patients, as anticipated. The findings of Zhai et al. corroborate this assertion, where the most prevalent symptoms of TPE include a dry cough and pleuritic chest pain (Zhai *et al.,* 2016). When both symptoms are present, pain typically precedes the cough. The assessment of ADA levels has been examined globally,

with most authors endorsing it as a valuable diagnostic tool for investigating TPE, particularly in regions with a high prevalence of tuberculosis (Zhai *et al.,* 2016).

The use of pfADA as a biochemical marker for diagnosing TPE is supported by its cost-effectiveness, simplicity, safety, and speed in facilitating decision-making during diagnosis. This study identified a pfADA cutoff value of 29 U/L, which demonstrated a sensitivity of 94.4%, a specificity of 66.7%, a PPV of 78.1%, an NPV of 92.3%, and an AUC of 0.806. Indicating that pfADA serves as a valid diagnostic method for TPE by demonstrating excellent sensitivity and high specificity. In line with what we found, Huan et al. established a local pfADA cutoff of 29.6 U/L for TPE, demonstrating a sensitivity of 97.6% and a specificity of 90.4% (Huan *et al.,* 2021). Chang et al. determined a local diagnostic cutoff value of 26.5 U/L for pleural fluid adenosine deaminase, demonstrating a sensitivity of 87.3%, specificity of 93.2%, positive predictive value of 79.2%, negative predictive value of 96.1%, and an accuracy of 91.9% (Chang *et al.,* 2018). A pfADA cutoff value of ± 40 U/L has been widely utilized in numerous studies as the optimal diagnostic threshold; however, findings regarding sensitivity, specificity, PPV, NPV, and accuracy have been inconsistent (Ahmed *et al.,* 1970; Garcia-Zamalloa & Taboada-Gomez, 2012; Huan *et al.,* 2021; Ren Tay & Tee, 2013; Saifullah *et al.,* 2016). Additionally, various studies have determined distinct diagnostic cutoff values for pfADA, which range from 10.25 to 77 U/L (Arnold *et al.,* 2015; Arpinar Yigitbas *et al.,* 2021; Blakiston *et al.,* 2018; Fei *et al.,* 2023; Li *et al.,* 2015; Mortazavi-Moghaddam *et al.,* 2016; Ren Tay & Tee, 2013; Salam *et al.,* 2022).

Our findings align with the meta-analysis, which examined 2162 citations and reported a sensitivity of 0.92 and a specificity of 0.90 (Aggarwal *et al.,* 2019). Additionally, the Spanish meta-analysis by Rosa M et al. reviewed 60 studies, indicating that ADA exhibited 93% sensitivity, 92% specificity, and an area-under-the-curve of 0.968 for the identification of tuberculosis (Palma *et al.,* 2019).

The present study demonstrated a significant association between elevated albumin levels exceeding 3.5 g/dl, increased LDH levels above 320 U/L, lymphocytosis, and neutropenia with a diagnosis of TPE. The findings delineate the essential characteristics of pleural tuberculosis, indicating that pleural fluid is an exudate typically characterized by a predominance of lymphocytes (Zhai *et al.,* 2016), elevated albumin and LDH levels, and a low pH (Vorster *et al.,* 2015). Previous studies indicated a significant correlation between pfADA and LDH, as well as an absolute lymphocyte count (Ren Tay & Tee, 2013), whereas other research identified a weak correlation (Mortazavi-Moghaddam *et al.,* 2016). The ratio of pfADA to LDH demonstrated predictive capacity for diagnosing malignant pleural effusion (MPE) (Gao *et al.,* 2023), which is the preferred method for diagnosing tuberculous pleurisy (TBP) (Arpinar Yigitbas *et al.,* 2021), and has been identified as a valuable biomarker for differentiating TPE from non-TPE (Fei *et al.,* 2023).

Due to the ease, speed, accuracy, cost-effectiveness, and repeatability of measuring ADA, our study established a diagnostic cutoff value for pfADA applicable in testing for TPE. The study identified 29 U/L as an effective local diagnostic cutoff value for pfADA, recommending its use for diagnosing TPE over more invasive and time-consuming tests. Additional research with larger sample sizes is required to support these findings.

**Conclusion**

In conclusion, the locally established pfADA cutoff value for identifying TPE contributes to the rationale for accurately diagnosing TPE. pfADA positivity showed a significant association with lymphocytosis, neutropenia, elevated LDH activity, and higher albumin levels.

**Declarations:**

**Ethical Approval and Consent to Participate**: The Sudan Medical Specialization Board (SMSB) and the hospital authorities granted ethical approval. Data was anonymously used

to identify numbers instead of names to protect the patient's identity and kept securely in a separate file.

**Competing interests:** The authors declared no conflict of interest.

**Availability of Data and Materials:** All data generated or analyzed during this study are included in this published article.

**Authors' Contributions:** All authors contributed to data collection, manuscript writing and revision, and approved the publication.

**Funding:** The authors declared that this study received no financial support.

**Acknowledgments:** Grateful thanks to all patients who participated in this study.

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