International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2025: 7.089

Diagnostic Utility of Combined Pleural Fluid Adenosine Deaminase Activity and Lymphocyte Proportion in Tuberculous Pleural Effusion: A Prospective Observational Study

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Abstract: ***Background: Tuberculous pleural effusion (TPE) is a common form of extrapulmonary tuberculosis. Although pleural fluid adenosine deaminase (ADA) is widely used for diagnosis, combining ADA with lymphocyte predominance may improve diagnostic accuracy. This study evaluated the diagnostic utility of combined pleural fluid ADA activity and lymphocyte proportion in TPE. Methods: This prospective observational study included 117 patients with pleural effusion. Pleural fluid ADA levels and differential leukocyte counts were analyzed. Tuberculous and non-tuberculous pleural effusions were compared, and diagnostic performance was assessed using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Results: Eighty-two patients (70.1%) had tuberculous pleural effusion. ADA >40 IU/L showed 92.68% sensitivity and 80.00% specificity. Lymphocyte proportion >50% demonstrated 91.46% sensitivity and 82.86% specificity. The combined use of both parameters increased specificity to 97.14% and PPV to 98.61%, thereby improving diagnostic confidence. Conclusion: Combined pleural fluid ADA activity and lymphocyte predominance provide a simple, inexpensive, and highly specific diagnostic approach for tuberculous pleural effusion, particularly in resource-limited settings.***

Keywords: Tuberculous pleural effusion, Adenosine deaminase, Pleural fluid, Lymphocyte proportion, Extrapulmonary tuberculosis, Diagnostic accuracy.

1. Introduction

Tuberculosis (TB) remains a major global public health problem despite significant advances in its diagnosis and treatment. According to the World Health Organization (WHO), TB continues to be one of the leading infectious causes of morbidity and mortality worldwide, with India contributing the highest burden of disease. Extrapulmonary tuberculosis accounts for approximately 15–20% of all TB cases, among which tuberculous pleural effusion (TPE) is one of the most common manifestations. Early diagnosis of TPE is essential for prompt initiation of antitubercular therapy and prevention of complications.

Tuberculous pleural effusion results from a delayed hypersensitivity reaction to *Mycobacterium tuberculosis* antigens within the pleural space, leading to an exudative, predominantly lymphocytic effusion. Although several diagnostic modalities are available, establishing a definitive diagnosis remains challenging because pleural fluid is usually paucibacillary. Conventional methods such as Ziehl–Neelsen staining have poor sensitivity, while mycobacterial culture requires several weeks to yield results. Pleural biopsy, although considered the reference standard in many cases, is invasive, expensive, and not always feasible, particularly in resource-limited settings.

Pleural fluid adenosine deaminase (ADA) has emerged as one of the most widely used biomarkers for the diagnosis of tuberculous pleural effusion. ADA is a key enzyme involved in purine metabolism and is released in increased amounts by activated T lymphocytes during cell-mediated immune responses. Numerous studies have demonstrated high sensitivity and specificity of pleural fluid ADA in differentiating tuberculous from non-tuberculous pleural effusions, making it an inexpensive and rapid diagnostic tool. Similarly, tuberculous pleural effusions characteristically demonstrate lymphocyte predominance, reflecting the underlying immunological response. However, elevated ADA levels and lymphocyte-rich pleural effusions may also be observed in certain non-tuberculous conditions, limiting the diagnostic accuracy of either parameter when used alone.

Recent evidence suggests that combining pleural fluid ADA activity with lymphocyte predominance may improve diagnostic performance by increasing specificity and positive predictive value without significantly compromising sensitivity. Such an approach is particularly valuable in high TB burden countries where rapid, reliable, and cost-effective diagnostic methods are essential for clinical decision-making.

The present prospective observational study was undertaken to evaluate the diagnostic utility of combined pleural fluid adenosine deaminase activity and lymphocyte proportion in differentiating tuberculous from non-tuberculous pleural effusions. The study also aimed to determine the sensitivity, specificity, positive predictive value, and negative predictive value of these parameters individually and in combination, thereby assessing their usefulness as practical diagnostic markers in routine clinical practice.

2. Materials and Methods

Study Design and Setting

This prospective observational study was conducted in the Department of Pathology, Government Medical College, Jhalawar, Rajasthan, in collaboration with the Department of Respiratory Medicine, over a period of one year from December 2024 to December 2025.

Study Population

A total of 117 consecutive patients presenting with pleural effusion and undergoing diagnostic pleural fluid aspiration were enrolled in the study after obtaining informed written consent. Patients were classified into tuberculous pleural effusion (TPE) and non-tuberculous pleural effusion (Non-TPE) groups based on clinical findings, radiological investigations, microbiological evidence, biochemical parameters, cytological examination, and final clinical diagnosis.

Inclusion Criteria

- Patients aged ≥18 years presenting with pleural effusion.
- Patients who underwent diagnostic thoracocentesis.
- Patients providing informed written consent for participation.

Exclusion Criteria

- Patients already receiving antitubercular therapy.
- Patients with inadequate pleural fluid samples for analysis.
- Patients unwilling to participate in the study.

Sample Collection and Laboratory Analysis

Pleural fluid was collected under strict aseptic precautions by diagnostic thoracocentesis. Routine biochemical, microbiological, and cytological investigations were performed according to standard laboratory protocols.

Pleural fluid adenosine deaminase (ADA) activity was estimated by the standard enzymatic method in NABL-accredited diagnostic laboratories. Differential leukocyte count was performed on cytocentrifuged and stained pleural fluid smears, and the percentage of lymphocytes was recorded for each sample.

An ADA level >40 IU/L and lymphocyte proportion >50% were considered positive for the diagnosis of tuberculous pleural effusion based on established diagnostic criteria.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Differences between groups were analyzed using the independent Student's *t*-test for continuous variables and the Chi-square test for categorical variables. A *p*-value <0.05 was considered statistically significant**.**

The diagnostic performance of pleural fluid ADA, lymphocyte proportion, and their combined use was assessed by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy.

3. Results

A total of **117 patients** were included in the study. The majority of patients were older than 50 years (34.2%), and males constituted 66.7% of the study population. Tuberculous pleural effusion (TPE) was diagnosed in 82 (70.1%) patients, while 35 (29.9%) had non-tuberculous pleural effusion (Non-TPE).

Table 1: Baseline demographic and clinical characteristics of the study population

Variable	Number (%)
Total patients	117
Age <20 years	5 (4.3)
Age 21–30 years	30 (25.6)
Age 31–40 years	19 (16.2)
Age 41–50 years	23 (19.7)
Age >50 years	40 (34.2)
Male	78 (66.7)
Female	39 (33.3)
TPE	82 (70.1)
Non-TPE	35 (29.9)

Chest pain (56.4%) was the most common presenting symptom, followed by breathlessness (53.8%), fever (52.1%), cough (44.4%), and weight loss (40.2%). Right-sided pleural effusion was the predominant radiological finding (47.0%), followed by left-sided (38.5%) and bilateral involvement (14.5%).

Table 2: Clinical presentation and radiological distribution

Variable	Number (%)
Clinical presentation	
Chest pain	66 (56.4)
Breathlessness	63 (53.8)
Fever	61 (52.1)
Cough	52 (44.4)
Weight loss	47 (40.2)
Radiological distribution	
Right	55 (47.0)
Left	45 (38.5)
Bilateral	17 (14.5)

Patients with TPE had significantly higher mean pleural fluid ADA levels (56.2 ± 11.9 IU/L) and lymphocyte proportions (66.1 ± 10.8%) than patients with Non-TPE (31.8 ± 6.8 IU/L and 37.2 ± 12.4%, respectively; p <0.001). The duration of illness was significantly shorter in patients with TPE than in those with Non-TPE (5.70 ± 2.88 vs. 9.83 ± 2.66 weeks; p <0.001).

Table 3: Comparison of laboratory parameters between TPE and Non-TPE

Parameter	TPE	Non-TPE	p-value
Mean duration (weeks)	5.70 ± 2.88	9.83 ± 2.66	<0.001
ADA (IU/L)	56.2 ± 11.9	31.8 ± 6.8	<0.001
Lymphocyte (%)	66.1 ± 10.8	37.2 ± 12.4	<0.001

Using a cut-off value of ADA >40 IU/L, sensitivity, specificity, PPV, and NPV were 92.68%, 80.00%, 91.57%, and 82.35%, respectively. A lymphocyte proportion >50%

demonstrated a sensitivity of 91.46%, specificity of 82.86%, PPV of 92.59%, and NPV of 80.56%. When both parameters were combined, specificity increased to 97.14% and PPV to 98.61%, while sensitivity remained 86.59%, indicating superior rule-in performance.

Table 4: Diagnostic performance of ADA, lymphocyte percentage and combined criteria

Parameter	ADA >40 IU/L	Lymphocyte >50%	Combined criteria
Sensitivity (%)	92.68	91.46	86.59
Specificity (%)	80	82.86	97.14
PPV (%)	91.57	92.59	98.61
NPV (%)	82.35	80.56	75.56

ADA levels and lymphocyte percentage showed a moderate positive correlation in the overall study population (r = 0.62), whereas only weak positive correlations were observed within the TPE and Non-TPE groups individually.

Table 5: Correlation between ADA levels and lymphocyte percentage

Group	Correlation coefficient (r)	Interpretation
TPE	0.18	Weak positive
Non-TPE	0.29	Weak positive
Overall	0.62	Moderate positive

4. Discussion

Principal Findings

The present prospective observational study evaluated the diagnostic utility of pleural fluid adenosine deaminase (ADA) activity and lymphocyte predominance, individually and in combination, for the diagnosis of tuberculous pleural effusion (TPE). The study demonstrated that both ADA and lymphocyte percentage were significantly higher in patients with TPE than in those with non-tuberculous pleural effusion. While ADA alone showed excellent sensitivity (92.68%), combining ADA (>40 IU/L) with lymphocyte predominance (>50%) substantially improved specificity (97.14%) and positive predictive value (98.61%), thereby reducing false-positive diagnoses. These findings support the combined use of biochemical and cytological parameters as a simple, rapid, and cost-effective diagnostic strategy for TPE, particularly in tuberculosis-endemic regions.

Demographic Profile

Tuberculous pleural effusion accounted for 70.1% of all pleural effusions in the present study, reaffirming tuberculosis as the predominant cause of exudative pleural effusion in India. This observation is consistent with reports from TB-endemic countries, where tuberculosis remains a major contributor to pleural disease, unlike Western populations where malignancy predominates. The male predominance (66.7%) observed in our cohort is comparable with previous studies by Sharma et al., Aggarwal et al., and Light, who attributed this trend to greater occupational exposure, smoking, environmental factors, and differences in healthcare-seeking behaviour. Although patients across all age groups were affected, the highest proportion belonged to the age group above 50 years, suggesting that tuberculous pleural effusion is increasingly encountered among older adults, possibly because of age-related immune decline and a higher burden of comorbidities. This differs from earlier Indian studies that reported a predominance among younger adults, reflecting changing epidemiological trends in tuberculosis.

Clinical Profile

Chest pain, breathlessness, and fever were the most common presenting symptoms in our study, consistent with the classical clinical presentation of tuberculous pleural effusion. Most patients also demonstrated unilateral pleural effusion, with a slight right-sided predominance, a finding that has been consistently reported in previous studies. Interestingly, patients with non-tuberculous pleural effusion had a significantly longer duration of symptoms than those with tuberculous pleural effusion. This observation may reflect the heterogeneous nature of non-tuberculous pleural diseases, including malignant and chronic inflammatory conditions, which often have a more insidious clinical course than tuberculous pleuritis. Therefore, although symptom duration may provide useful clinical context, it should be interpreted alongside biochemical and cytological findings rather than as an isolated diagnostic indicator.

Pleural Fluid ADA Activity

Pleural fluid ADA has been extensively investigated as a diagnostic biomarker for tuberculous pleural effusion because it reflects T-lymphocyte activation and cell-mediated immune responses induced by *Mycobacterium tuberculosis*. In the present study, patients with TPE had significantly higher pleural fluid ADA levels than those with non-tuberculous pleural effusion (55.35 ± 11.43 IU/L vs. 31.74 ± 6.97 IU/L, **$p < 0.001$**). Furthermore, using a diagnostic cut-off of **40 IU/L**, ADA demonstrated a sensitivity of **92.68%** and specificity of **80.00%**, confirming its excellent ability to identify patients with tuberculous pleural effusion.

These findings are consistent with those reported by **Burgess et al.**, who demonstrated high diagnostic accuracy of pleural fluid ADA in tuberculosis, and by **Greco et al.**, whose meta-analysis established ADA as one of the most reliable biochemical markers for TPE. Similar observations have also been reported from India by **Aggarwal et al.**, **Sharma et al.**, and **Dhooria et al.**, supporting the continued utility of ADA in tuberculosis-endemic regions.

Despite its excellent sensitivity, ADA is not entirely disease-specific. Elevated ADA levels may also occur in empyema, rheumatoid pleuritis, lymphoma, and occasionally malignant pleural effusions because these conditions also involve activation of cellular immunity. Therefore, although ADA serves as an excellent screening and initial diagnostic test, interpretation in conjunction with clinical, radiological, and cytological findings is essential to minimize false-positive diagnoses.

Pleural Fluid Lymphocyte Predominance

The present study also demonstrated a significantly higher pleural fluid lymphocyte percentage in patients with tuberculous pleural effusion than in those with non-tuberculous pleural effusion (65.70 ± 10.51% vs. 36.34 ± 12.26%, **$p < 0.001$**). Using a threshold of **>50% lymphocytes**, lymphocyte predominance showed a sensitivity of **91.46%** and specificity of **82.86%**, indicating

that pleural fluid cytology remains an important adjunctive investigation in the diagnosis of TPE.

The lymphocyte-rich nature of tuberculous pleural effusion reflects the delayed type IV hypersensitivity response triggered by mycobacterial antigens within the pleural cavity. Recruitment and activation of CD4+ T lymphocytes result in cytokine-mediated inflammation and granulomatous immune responses, producing the characteristic lymphocytic exudate observed in TPE. This immunopathogenesis explains the consistently high lymphocyte proportion reported in tuberculous pleural effusions.

Our findings are in agreement with previous studies by **Light**, **Porcel**, **Dhooria et al.**, and **Aggarwal et al.**, all of whom identified lymphocyte predominance as a characteristic cytological feature of tuberculous pleuritis. However, lymphocyte predominance alone is insufficient for establishing the diagnosis because chronic malignant pleural effusions and certain inflammatory disorders may also demonstrate lymphocyte-rich exudates. Consequently, pleural fluid cytology should be interpreted alongside biochemical markers such as ADA to improve diagnostic confidence.

Combined ADA and Lymphocyte Predominance

This is the principal finding of the present study. Although ADA alone demonstrated excellent sensitivity, combining **ADA >40 IU/L** with **lymphocyte predominance >50%** substantially improved diagnostic specificity from **80.00%** to **97.14%**, while increasing the positive predictive value to **98.61%**. These findings indicate that patients fulfilling both criteria are highly likely to have tuberculous pleural effusion, making the combined approach an excellent **rule-in diagnostic strategy**.

The improved diagnostic performance can be explained by the complementary nature of the two markers. ADA reflects the intensity of T-cell-mediated immune activation, whereas lymphocyte predominance represents the characteristic cellular response within the pleural cavity. When interpreted together, these parameters reduce the likelihood of false-positive diagnoses that may occur when ADA is elevated because of non-tuberculous inflammatory conditions.

Our findings are consistent with observations by **Porcel**, **Burgess**, and **Dhooria et al.**, who reported that combining biochemical and cytological parameters improves the diagnostic accuracy of pleural fluid analysis. In resource-limited settings where advanced molecular diagnostics or pleural biopsy may not be readily available, this combined approach offers a rapid, inexpensive, and minimally invasive alternative for supporting the diagnosis of tuberculous pleural effusion and facilitating early initiation of anti-tubercular therapy.

Importantly, while the combined strategy modestly reduced sensitivity (**86.59%**), the marked gain in specificity and positive predictive value makes it particularly valuable when clinicians wish to confirm rather than merely suspect tuberculous pleural effusion. In high tuberculosis burden countries such as India, this balance between sensitivity and specificity has considerable clinical relevance and may reduce unnecessary invasive investigations while improving diagnostic confidence.

Taken together, these findings suggest that the combined interpretation of pleural fluid ADA activity and lymphocyte predominance provides greater diagnostic confidence than either parameter alone and may serve as a practical first-line diagnostic strategy for tuberculous pleural effusion in tuberculosis-endemic settings.

Correlation Between ADA Activity and Lymphocyte Percentage

A moderate positive correlation ($r = 0.62$) was observed between pleural fluid ADA activity and lymphocyte percentage in the overall study population, indicating that increasing ADA levels were generally associated with greater lymphocytic predominance. However, the correlation within the individual TPE and non-TPE groups was relatively weak, suggesting that although both parameters are related to the host immune response, they reflect different aspects of the inflammatory process.

This finding is biologically plausible because ADA is an intracellular enzyme released predominantly from activated T lymphocytes during cell-mediated immune responses, whereas lymphocyte percentage represents the proportion of inflammatory cells within the pleural fluid. Therefore, although both markers increase in tuberculous pleural effusion, they are influenced by additional factors such as disease stage, immune status, and the intensity of pleural inflammation. Similar observations have been reported by Greco et al. and other investigators, who concluded that ADA and lymphocyte predominance should be regarded as complementary rather than interchangeable diagnostic markers.

5. Strengths of the Study

The present study has several strengths. First, it was a prospective observational study in which all patients underwent a standardized clinical, biochemical, cytological, and radiological evaluation. Second, both ADA activity and pleural fluid lymphocyte percentage were assessed simultaneously in the same patient cohort, allowing direct comparison of their individual and combined diagnostic performance. Third, the study was conducted in a tuberculosis-endemic region, making the findings highly relevant to routine clinical practice in similar healthcare settings. Finally, by evaluating the combined diagnostic utility of ADA and lymphocyte predominance, the study provides a practical and inexpensive approach that can be readily implemented in resource-constrained institutions.

6. Limitations of the Study

The present study has certain limitations. It was conducted at a single tertiary care centre with a relatively modest sample size, which may limit the generalizability of the findings. ADA estimation was performed through NABL-accredited private diagnostic laboratories, and although standardized analytical methods were used, minor inter-laboratory variation cannot be excluded. In addition, the study evaluated only two routinely available diagnostic markers and did not

compare their performance with newer biomarkers such as interferon-γ, interleukin-27, or nucleic acid amplification tests. Future multicentric studies involving larger populations and incorporating advanced diagnostic modalities would help validate and expand upon these findings.

7. Conclusion

The present study demonstrates that pleural fluid adenosine deaminase activity and lymphocyte predominance are valuable diagnostic markers for tuberculous pleural effusion. While each parameter individually showed high diagnostic accuracy, their combined interpretation significantly improved diagnostic specificity and positive predictive value, thereby enhancing diagnostic confidence. The combined use of pleural fluid ADA (>40 IU/L) and lymphocyte predominance (>50%) represents a simple, rapid, minimally invasive, and cost-effective diagnostic approach, particularly in tuberculosis-endemic settings where access to advanced diagnostic techniques may be limited. Incorporating these routinely available investigations into the initial evaluation of patients with pleural effusion may facilitate earlier diagnosis, reduce unnecessary invasive procedures, and support timely initiation of anti-tubercular therapy. Further multicentric studies with larger sample sizes are warranted to validate these findings and establish standardized diagnostic algorithms.

Acknowledgements
The author expresses sincere gratitude to the Department of Pathology, Government Medical College, Jhalawar, Rajasthan, for providing the facilities and academic support required to conduct this study. The author is especially grateful to the guide, faculty members, laboratory staff, and all the patients who willingly participated in this research.

Declarations

Ethical Approval
The study was approved by the Institutional Ethics Committee of Government Medical College, Jhalawar, Rajasthan (Approval No. 101, dated 24 July 2024).

Informed Consent
Written informed consent was obtained from all participants prior to enrolment in the study.

Funding
The authors received no financial support for the conduct of this study.

Conflict of Interest
The authors declare that there are no conflicts of interest.

Author Contributions

Dr. Utkarsha Gera: Conceptualization, methodology, data collection, laboratory work, data analysis, interpretation of results, manuscript drafting, and final manuscript preparation.

Dr. Chetna Jain: Study supervision, methodology, critical review of the manuscript, and overall guidance.

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