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Original Research Article

Study to Evaluate Efficacy of Adenosine Deaminase (ADA) Levels as a Diagnostic Tool in Tuberculous Pleural Effusion

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Abstract

Background: Tuberculous pleural effusion (TPE) is a common type of extrapulmonary tuberculosis (TB) especially found in high burden countries such as India. The low sensitivity of conventional diagnosis techniques (smear microscopy, culture and nucleic acid amplification tests) and a paucibacillary nature of the pleural fluid makes the diagnosis difficult. Adenosine Deaminase (ADA) is an enzyme that plays a role in cell-mediated immunity and is released from activated T-lymphocytes, and it has been suggested that it may be a useful biomarker for TPE.

Materials and Methods: This was a 15 months hospital-based observational study which included total of 60 patients of pleural effusion, 30 cases each of TPE and Non tuberculous pleural effusion. Biochemical parameters and ADA levels in pleural fluid samples were assessed by the Giusti and Galanti colorimetric method. A statistical analysis were performed using SPSS; with $p < 0.05$ taken as significant.

Result: These results indicate that ADA level was significantly higher in the TPE group (68.5 ± 18.4 IU/L) than in the non-TPE group (21.7 ± 9.6 IU/L) ($p < 0.001$). ADA showed high sensitivity and specificity (90% and 86.7% respectively) at a cut-off value of 40 IU/L, with good interpretable diagnostic accuracy.

Conclusion: ADA estimation in pleural fluid is a simple, rapid,and cost-effective tool that is invaluable in diagnosing tuberculous pleural effusion particularly in resource-limited and TB-endemic settings.

Keywords: Adenosine Deaminase, Tuberculous Pleural Effusion, Pleural Fluid, Diagnostic Marker, Sensitivity.
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Introduction

Tuberculosis (TB) is a major source of morbidity and mortality globally ranking as one of the most effective infectious diseases after COVID-19 through the years [1, 2]. Globally, millions of new cases are diagnosed each year, with a large proportion in high-burden countries. India has one of the largest TB burdens in the world, a substantial share of the global total [3]. Extrapulmonary tuberculosis other than pulmonary tuberculosis includes a significant portion of cases; pleural tuberculosis is the second most common form of extrapulmonary tuberculosis after tuberculous lymphadenitis [4]. In TB-endemic regions, the high susceptibility nature of the disease highlights the important need for rapid and accurate diagnostics, particularly for extrapulmonary forms like TPE.

TPE arises mainly from rupture of a subpleural caseous focus of infection into the pleural space [5]. Mycobacterial antigens are deposited in the pleural space and a strong DTH reaction occurs, presumably because of sensitized T-lymphocytes [6]. This subsequent inflammatory cascade results in capillary leakiness as well as the collection of exudative fluid rich in protein in the pleural space. In contrast to pulmonary TB, pleural TB is often paucibacillary, and pleural fluid contains very few bacilli. As a result, this making any direct microbiological confirmation challenging. In clinical practice, patients may be symptomatic with fever, chest pain, dyspnea, night sweats and weight loss, however, these symptoms are non-specific and overlap with other causes of pleural effusion which makes the diagnosis difficult [7].

There are some diagnostic challenges concerning TPE. Traditional techniques like smear microscopy of pleural fluid for Acid-Fast Bacilli (AFB) have incredibly low sensitivity, with only a small fraction of cases yielding a positive result [8]. Pleural fluid mycobacterial culture, although more

sensitive than smear examination, shows positivity in none but 25% of patients and it takes weeks for us to get the results [9]. They have high specificity but only a moderate sensitivity, about 0.62, which makes them not enough to be used alone. Though pleural biopsy is the definite standard for diagnosis owing to the increased sensitivity of pleural biopsy and its ability to show evidence of granulomatous inflammation, the study suggest that pleural biopsy is invasive, technically difficult, and not available in all clinical settings. Such limitations emphasize the immediate need for accurate, rapid and low-invasive diagnostic alternatives.

In this context, the body of evidence surrounding ADA as a biomarker has been evolving. ADA is an enzyme essential for purine metabolism and acts as a key regulator of cell-mediated immunity. Primarily originating from activated T-lymphocytes during immune responses. The marked elevation of ADA concentrations in pleural fluid in TPE is due to a strong cellular immune response and is often characterized by strong lymphocytic pleural effusions. Multiple articles have shown that the ADA estimation is a cheap, easy, and rapid test with a high sensitivity and specificity for the diagnosis of TPE [10]. Due to high TB burden in countries like India and limitations of conventional diagnostic methods, evaluation of the effectiveness of ADA in differentiating between tuberculous and nontuberculous pleural effusion is of significant clinical relevance. This study seeks to evaluate the utility of pleural fluid ADA in distinguishing TPE from other causes of pleural effusion in a high-prevalence context.

Objectives of the Study

- To Measure of ADA levels in pleural fluid of patients with pleural effusion.
- To compare pleural fluid ADA levels in TPE and Non-TPE in order to find out a statistically significant difference between the two groups.
- To assess the diagnostic performance of ADA for TPE, including its role in distinguishing TPE from other causes of pleural effusion in a high TB burden setting.

Materials and Methods

Study Design: This was a hospital based observational study for assessing the diagnostic utility of pleural fluid ADA levels in patients with pleural effusion. The observational design is appropriate for assessing and comparing ADA levels among patients with TPE and Non-TPE in usual clinical practice without experimental interventions.

Study Setting: The study was conducted in Department of Medicine at Bhagwan Mahavir Institute of Medical Sciences (BMIMS) Pawapuri, Bihar. The duration of the study spanned from December 2023 to March 2025 (~15 months). Eligible patients seen in the department during this period with pleural effusion on chest imaging were screened for inclusion in the study.

Sample Size: The study recruited 60 patients with pleural effusion, Patients were classified either in to one of tuberculous pleural effusion (TPE so called +ve group) or in to non-tuberculous pleural effusion group (non-TPE so called -ve group), 30 patients per group in each arm of binder were random considered and included. Grouping was done using Clinico-radiological and laboratory criteria.

Inclusion Criteria: All patients in the age group of 14−65 years with clinical or radiological suspicion of pleural effusion. Clinical evaluation was involved for symptoms like fever, cough, chest pain, dyspne, and loss of weight, while radiological confirmation was obtained through chest X-ray indicating accumulation of pleural fluid.

Exclusion Criteria: To minimize confounding due to age-related comorbidities, patients older than 65 years were excluded from the study. Study participants also excluded individuals who did not consent with informed consent.

Study Groups

The study population was divided into two categories. Group I include cases diagnosed as tuberculous pleural effusion. Diagnosis of TPE was confirmed by a combination of clinical features, chest X-ray, pleural fluid analysis and microbiological confirmation. Laboratory work for pleural fluid included examination for AFB, CBNAAT as well as sputum examination for AFB, wherever applicable. Group 2 represents patients with non-tuberculous pleural effusion. To this group, they added malignant pleural effusion, transudative effusions (e.g. CCF, renal failure, liver cirrhosis), as well as synpneumonic (parapneumonic) effusions.

Pleural Fluid Analysis: Diagnostic thoracocentesis was performed on all patients with aseptic precautions. Macroscopic examination of the pleural fluid obtained was done to observe at the color and clarity The type of cells present was established by cytological analysis. Biochemical analysis was Protein, lactate dehydrogenase (LDH) & Sugar level. Exudative and transudative effusions were distinguished using Light's criteria. Based on the Giusti and Galanti colorimetric method (standardized & commonly used method), ADA levels in pleural fluid were estimated.

Statistical Analysis: The collected data were entered and analyzed by using SPSS. Continuous

variables were expressed as mean ±standard deviation (SD). A chi-square test was used to compare categorical variables, an independent t-test to compare quantitative variables, and an analysis of variance (ANOVA) was used to compare quantitative variables between groups. Statistical significance was represented by p-values<0.05.

Results

Demographic Profile: Out of a total of 60 patients presented with pleural effusion 30 were cases of TPE while 30 were cases of non-tuberculous pleural effusion (non-TPE). Patients in the TPE group were younger (mean age 34.8 ± 11.2 years) versus (mean age 47.6 ± 13.5 years) versus non-TPE group). Among younger patients it was more frequent tuberculous pleural effusion, as opposed to pleural effusions non-tuberculous that occurs more frequently in older patients. In gender distribution, the vast majority in both groups were male.

Among the 30 patients in the TPE group, there were 21 (70%) males 9 (30%) females. In the non-TPE group, a similar trend was observed where 18 (60%) were males and 12 (40%) were females.

The study showed that male predominance was observed among the patients with pleural effusion.

Table 1: Demographic Characteristics of Study Population

Parameter	TPE (n=30)	Non-TPE (n=30)
Mean Age (years)	34.8 ± 11.2	47.6 ± 13.5
Male	21 (70%)	18 (60%)
Female	9 (30%)	12 (40%)

ADA Levels: There is plenty evidence that pleural fluid ADA levels are much higher in patients with tuberculous rather than non-tuberculous pleural effusion. This difference in mean ADA between the TPE & Non-TPE group is statistically highly significant ($P < 0.001$) with a mean ADA level in the TPE group of 68.5 ± 18.4 IU/L as compared to 21.7 ± 9.6 IU/L in the Non-TPE group suggesting very strong association of elevated ADA level with tuberculous pleural effusion.

Table 2: Comparison of Mean ADA Levels

Parameter	TPE (n=30)	Non-TPE (n=30)	p-value
Mean ADA (IU/L)	68.5 ± 18.4	21.7 ± 9.6	<0.001

Sensitivity and Specificity: ADA-positive showed high diagnostic performance with a cut-off of 40 IU/L. Using this cut-off, 27/30(90%) of TPE patients and 26/30(86.6%) of non-TPE patients had ADA levels >40 IU/L and <40 IU/L respectively. At this cut-off, the calculated sensitivity and specificity of ADA were 90% and 86.7%, respectively. We showed a positive predictive value (PPV) of 87.1% and a negative predictive value (NPV) of 89.7%. The combined diagnostic accuracy of ADA for tuberculous pleural effusion was 88.3% overall.

Table 3: Diagnostic Performance of ADA at Cut-off 40 IU/L

Parameter	Value (%)
Sensitivity	90%
Specificity	86.7%
Positive Predictive Value	87.1%
Negative Predictive Value	89.7%
Diagnostic Accuracy	88.3%

Comparison with Other Parameters: Pleural fluid protein and LDH levels were higher in both groups on biochemical analysis but had a less discriminatory power than ADA. Mean pleural fluid protein levels were 4.8 ± 0.6 g/dL and 3.6 ± 0.8 g/dL in TPE and Non-TPE, respectively. TPE (412 ± 95 IU/L) also had higher LDH levels than non-TPE (298 ± 102 IU/L).Where calculated, the ADA/LDH ratio (AAR) was higher in TPE patients, and with a potential extra diagnostic value in TPE, although the single ADA discriminant capacity was better.

Table 4: Comparison of Biochemical Parameters

Parameter	TPE (n=30)	Non-TPE (n=30)	p-value
Protein (g/dL)	4.8 ± 0.6	3.6 ± 0.8	<0.01
LDH (IU/L)	412 ± 95	298 ± 102	<0.05
ADA/LDH Ratio	0.17 ± 0.05	0.07 ± 0.03	<0.001

Overall, ADA demonstrated superior diagnostic efficacy compared to conventional pleural fluid biochemical parameters in differentiating tuberculous from non-tuberculous pleural effusion.

Discussion

Our study showed that pleural fluid ADA levels were detected higher in active TPE patients than in patients with non-tuberculous pleural effusion. The mean is the value of ADA in TPE group level elevated markedly and statistically highly significant difference was found between two groups ($p < 0.001$). Thus, our results are similar with the hypothesis of the relevant role of ADA as an enzyme associated with T-lymphocyte activation and cell-mediated immunity in the immunopathogenesis of tuberculous pleuritis. This study highlights the diagnostic role of ADA between TPE and non-TPE causes of pleural effusion with very high statistical significance. They further corroborate the existence of a cut-off value that provided the best separation between tuberculous and non-tuberculous effusions in the population being studied (40 IU/L).

Comparison with Previous Studies: The study's findings are consistent with previous reported works. The study observed considerable sensitivity and specificity of ADA for TPE supporting its potential as a biomarker. [11] consequently, tuberculous and malignant effusions exhibit widely different ADA levels, while differing considerably from parapneumonic effusions. In multiple analyses, [12] found that ADA levels over 40 IU/L provided a high diagnostic accuracy, especially in areas of high TB prevalence. [13] were similar sensitivity and specificity, highlighting the clinical significance of ADA assessment. In addition, several meta-analyses have determined that ADA is a test for TPE with a very high sensitivity and specificity, often with pooled sensitivity and specificity greater than 85–90% [14, 15]. The diagnostic performance seen in the current study is similar to the results from previously published literature, thus providing additional indirect evidence that supports the role of ADA as a diagnostic marker.

Diagnostic Implications: This study outcomes emphasize the clinical relevance of using ADA as a cheap and quick screening method for tuberculous pleural effusion. For ADA estimation, only pleural fluid from a normal thoracocentesis is needed. This method is less invasive and technically difficult than pleural biopsy. The high sensitivity and negative predictive value seen in this study point to a unique feature of ADA, it can help rule out TPE when levels are below the established cut-off. This is particularly crucial in resource-limited settings where sophisticated diagnostic facilities may not be readily accessible. This routine estimation of pleural fluid ADA can help in early diagnosis of tubercular pleural effusion along with timely initiation of anti-tubercular therapy which will help in decreasing the morbidity and while preventing invasive procedures.

Strengths: A major strength of this study was that it provided clinical comparison of tuberculous with non-tuberculous pleural effusion groups under standard clinical conditions. A defined cut-off value for ADA provides reproducible results. A consistent method was used for both the statistical review and analysis of pleural fluid, which adds to the study's internal validity.

Limitations: However, there are a few limitations, the sample size was small (60 patients), limiting generalizability. As a single-center study, the findings may not be generalizable to wider populations. This study cannot exclude the possibility since isoenzyme analysis typically not performed here, especially ADA2 isoenzyme, which could offer additional specificity. When considering the overall treatment outcome, it has also an important limitation as it did not include patients who were followed up in the long-term.

Conclusion

The present study concludes that pleural fluid ADA levels are higher in patients with tuberculous pleural effusion compared to non-tuberculous causes. Lower cut-off values up to 40 IU/L showed significant sensitivity, specificity, and overall accuracy in differentiating TPE from other types of pleural effusion. These results reinforce the expected ADA as a useful, fast and non-invasive biomarker for diagnosis.

Due to its simplicity, inexpensive nature, and good diagnostic accuracy, ADA is able to impact the need for an invasive procedure, such as pleural biopsy in a large number of patients. This tool is especially useful in areas where tuberculosis is endemic and in under-resourced clinical environments where advanced diagnostic modalities may not be readily accessible.

The routine incorporation of ADA measurement into pleural fluid analysis protocols can contribute to the early diagnosis, timely initiation of treatment, and better clinical outcomes of patients suspected of tuberculous pleural effusion.

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