

**Original article:**

## **Combined efficacy of pleural fluid lymphocyte neutrophil ratio and pleural fluid adenosine deaminase for the diagnosis of tubercular pleural effusion**

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**Abstract:**

Increased pleural fluid adenosine deaminase (ADA) activity is classically associated with tuberculous pleuritis. However, increased activity can also occur in a number of other diseases and this may negatively affect diagnostic utility of ADA measurements and decrease its specificity for the diagnosis of tuberculosis. The presence of ADA in pleural fluid reflects cellular immune response in pleural cavity and in particular, the activation of T lymphocytes. Different disease entities are typically associated with the presence of particular type of leucocytes. The Objectives of the study was to determine whether the combined use of ADA activity and lymphocyte neutrophil ratio would provide a more efficient means for diagnosing tuberculous pleurisy than the use of ADA levels alone. Biochemistry, cytology and microbiology studies were performed on 90 consecutive pleural fluids. ADA and differential counts were determined on all exudative effusions. ADA activity in tuberculous effusions was significantly higher than in any other diagnostic group. At a level of 50U/L, the sensitivity, specificity, positive predictive value, NPV, and efficiency for identification of TB calculated at 61%, 71%, 83%, 45%, and 64% respectively. When the additional requirement of a lymphocyte neutrophil ratio of 0.75 or greater was included, the sensitivity, specificity, PPV, NPV, and efficiency for identification of TB were calculated at 100%, 83%, 93%, 100% and 95% respectively. ADA when combined with lymphocyte neutrophil ratio remains a useful test in the diagnosis of tuberculous pleuritis.

**Keywords:** Adenosine deaminase, lymphocyte neutrophil ratio, tuberculous pleuritis.

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### **INTRODUCTION**

Pulmonary tuberculosis is the most frequent cause of death by an infectious agent worldwide. Among the extrapulmonary presentations after tuberculous lymphadenitis, pleural tuberculosis is the second most frequent, failure to diagnose and treat pleural tuberculosis can result in progressive disease with the involvement of other organs in as many as 65% of patients [1]. Conventional methods have proven to be insufficient for diagnosis of pleural tuberculosis. Many studies have demonstrated the diagnostic significance of increased adenosine deaminase

(ADA) in tuberculous pleurisy, other studies have shown that ADA is of limited value [2], as raised levels are also associated with a number of other diseases including malignancies (especially those of haematological origin), bacterial infections (Q fever, brucellosis), empyema's, and other collagen vascular diseases including SLE and rheumatoid arthritis [3].

### **MATERIALS AND METHODS**

The present study was conducted at Navodaya Medical College, Raichur during the period between January 2015 and December 2015. 90 consecutive pleural fluid specimens from patients admitted to

medical and pulmonary wards were analysed. All exudative pleural effusion cases were included. Patients with transudative pleural effusion, malignant pleural effusion, immunodeficient states like HIV/AIDS, those on chemotherapy were excluded. Patients having hemothorax or empyema's too turbid for analysis were excluded.

Besides a detailed history and clinical examination, the following investigations were carried out:

- a) Blood investigations: Haemoglobin, total leucocyte count, differential leucocyte count, erythrocyte sedimentation rate, total protein, serum albumin, serum LDH
- a) Random blood sugar, blood urea, serum creatinine;
- b) Urine examination – albumin, sugar and microscopic examination.
- c) Sputum examination – for acid fast bacilli by ZeilNeilson(ZN) stain, gram's stain
- d) mantoux's test
- e) Chest radiography – postero-lateral and lateral views in selected areas
- f) Pleural fluid analysis – colour protein by biuret method, sugar by folinwu method, cell type and count – total and differential count ; smear for acid fast bacilli –ZN stain, Gram's stain, LDH activity using an enzymatic ultraviolet optimized method; malignant cells, ada estimation
- g) Pleural biopsy The hospital records of all patients have exudative effusions were reviewed and a diagnosis made according to the following predetermined criteria.

**Tuberculosis pleuritis was diagnosed on the basis of**

- a) Identification of the bacillus in the pleural fluid or biopsy specimen by stain or by culture, or the presence of granuloma in the pleural biopsy of tissue

b) Clinical and radiological evidence for TB in the absence of any other obvious cause associated with pleural effusions and associated with a positive response to

antituberculous therapy .

Infective effusions included the following: pneumonic effusions associated with acute febrile illness, pulmonary pneumonic infiltrates, purulent sputum and responsiveness to antibiotic treatment and identification of the organism in the pleural fluid; septicaemia, characterised by radiological evidence of pulmonary infiltrates and multisystem involvement in the presence of positive blood cultures; and other positive infective conditions in the absence of any other case associated with pleural effusions. Empyematous effusions, characterised by the finding of frank pus in the pleural cavity, were included provided the specimen's turbidity did not interfere with the relevant investigations.

Neoplastic effusions were diagnosed when one of the following criteria was met:

- a) The presence of cytological or histologic evidence of a malignant pleural effusion
  - or
  - b) Cases of pleural effusion with a known malignancy at other sites
  - c) Histopathology confirmation with exclusion of any other known cause to be associated with pleural effusion
- Other exudates were defined by effusions that were clearly caused by pancreatitis, Dressler's syndrome, collagen vascular disease, pulmonary embolus or infarction, and various other rare but well documented causes of exudative pleural effusions. In all cases there was an absence of malignancy, pulmonary infiltrates, and disease causing transudates

Patients having multiple superimposed diseases or effusion of unknown origin were classified as “undiagnosed”. In all patients with exudative pleural effusion, the diagnosis was confirmed by pleural fluid culture and/or pleural biopsy and these patients were treated with antitubercular treatment were followed up

**Statistical analysis**

Mean and standard deviation for continuous variables and proportions for categorical variables are reported. Ada alone, L/N alone and ADA values were the combined with various L/N ratios by calculating sensitivity, specificity, PPV, NPV and efficiency. An interactive dot diagram was used for cut-off points

and plot versus criteria values graph used. SPSS version 16.0 was used for statistical analysis.

**RESULTS**

Although 90 samples were used for analysis. The remaining 90 patients consisted of 62 men and 28 women. The age of the study population ranged from 18 years to 70 years Out of the total 90 patients, 18 patients were nontubercular of which 10 patients were HIV positive, 2 patients had malignant pleural effusion, 2 patients had connective tissue disorder, 2 patients had empyema which was not grossly turbid. We could not diagnose the cause in the remaining 2 patients with exudative pleural effusion.

**Table 1: Of the 90 patients with exudative pleural effusion, 38 patients had ADA >50U/L and they were confirmed to be of tubercular origin and improved with treatment. 8 patients which were non-tubercular but had ADA >50U/L. 24 patients with ADA <50U/L were confirmed to be tubercular in origin and improved. 20 patients with ADA levels <50U/L were non-tubercular.**

ADA alone (U/L)	In Tuberculous Pleural Effusion	Non-Tuberculous Pleural Effusion	Total
>50	38	8	46
<50	24	20	44
Total	62	28	90

**Table 2: Of the 70 patients whose L/N ratio >0.75, 62 were of tubercular in origin and improved with treatment and 8 patients were non-tubercular in origin**

L/N ratio	In Tuberculous Pleural Effusion	Non-Tuberculous Pleural Effusion	Total
>0.75	62	8	70
< 0.75	0	20	20
Total	62	28	90

**Table 3: This table shows, 38 patients had ADA >50U/L and L/N ratio >0.75 were of tubercular origin and improved with treatment. 3 patients who had both ADA >50U/L and L/N ratio >0.75 were non- tubercular origin. 15 patients had ADA <50U/L and L/N ratio <0.75 were of non-tubercular origin.**

ADA and L/Nratio	Tuberculous Pleural Effusion	Non-tuberculous PleuralEffusion	Total
>50U/L And>0.75	38	3	41
<50U/L. And<0.75	0	15	15
Total	38	18	56

**Table 4: Comparison of ADA activity alone, L/N ratio alone, and ADA activity combined with L/N ratio as a means for diagnosing TB pleuritis**

Criteria used to diagnose TB						
ADA level	L/N ratio	Sensitivity%	Specificity %	PPV%	NPV%	Efficiency%
>50U/L	-	61	71	83	45	64
>50U/L	>0.75	100	83	93	100	95
-	>0.75	100	71.4	88.6	100	91.1

According to table 4, sensitivity, specificity, positive predictive value, negative predictive value and efficiency of combined ADA and L/N ratio were much higher than ADA alone arm.

## DISCUSSION

Increased ADA activity in pleural effusion is classically associated with tuberculosis[4]. However it may occur due to a number of causes and this may negatively affect the diagnostic utility of ADA measurements and decrease its specificity in the diagnosis of TB. Our results show that, at a cutoff level are 50U/L, ADA has a sensitivity, specificity, PPV, NPV and efficiency of 61%, 71%, 83%, 45%, and 64% respectively. When the L/N ratio's was considered together with ADA activity, the results

improved considerably for the diagnosis of tuberculosis pleuritis. Pleural fluid lymphocytes is also found in malignant conditions, collagen vascular disease, rheumaticpleuritis, sarcoidosis and up to one third of all transudates. Parapneumonic and empyematouseffusions are characterised by neutrophil-predominant, exudative effusions [5,6]. In the cases and tuberculosis pleurisy, a predominant lymphocyte count was usually found, resulting in a L/N ratio of 0.75 or greater, whereas in other

conditions of exudative pleural effusion, L/N ratio was found to be less than 0.75[8].

TB pleurisy is traditionally diagnosed by either identification of M tuberculosis in pleural fluid and/or biopsy specimen cultures or from the presence granulomas in the pleural biopsy tissue. Pleural fluid cultures have sensitivity of 20-30%, pleural biopsy specimen 50-80%, depending upon the clinician's proficiency[9]. Because of the long culture periods required, clinical and therapeutic decisions are often

made before the lab results become available. Polymerase chain reaction, having a sensitivity of 78% for active disease, has not been found to be an efficient alternative[10].

### CONCLUSION

In conclusion, it is suggested that the combined use of adenosine deaminase activity along with lymphocyte neutrophil ratio would provide a more efficient means for diagnosing tuberculosis pleuritis than the use of ADA alone.

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