STUDY OF DIAGNOSTIC VALUE OF PLEURAL FLUID LYMPHOCYTE/NEUTROPHIL RATIO & ADA LEVELS IN PATIENTS WITH TUBERCULAR PLEURAL EFFUSION

Dr. Kalluru Harsha Vardhan Reddy (first and corresponding author), Assistant Professor, Department of General Medicine, PES INSTITUTE OF MEDICAL SCIENCES AND RESEARCH, KUPPAM

Dr. Janani V (second author), Assistant Professor, Department of Pathology, PES INSTITUTE OF MEDICAL SCIENCES AND RESEARCH, KUPPAM

Dr. K.Vishnu Vardhan Reddy (third author), Assistant Professor, M.D, D.M Gastroenterology, Tirupathi

Dr. Uma. M.A. (fourth author), Professor and Head of the Department. PES INSTITUTE OF MEDICAL SCIENCES AND RESEARCH, KUPPAM.

ABSTRACT

Background: Tuberculous pleural effusion is traditionally linked to elevated adenosine deaminase (ADA) activity in the pleural fluid. Nonetheless, elevated activity can also transpire in several other ailments, which could potentially compromise the diagnostic efficacy of ADA assessments and reduce their specificity in tuberculosis (TB) diagnosis. The cellular immune response in the pleural cavity, and specifically the activation of T lymphocytes, is reflected in the presence of ADA in pleural fluids. Specific types of leukocytes are generally linked to different disease entities. The current study's goal is to assess how well the lymphocyte/neutrophil ratio and ADA activity work together to diagnose tuberculous pleural effusion.

Aim and Objectives: To study the diagnostic value of Lymphocyte/Neutrophil ratio and ADA levels in pleural fluid in patients with tubercular pleural effusion.

Materials and Methods: This is a prospective, observational study in which 150 patients with exudative pleural effusion were selected and their pleural fluid was collected for biochemical, cytological examination. ADA and differential cell counts were determined on all samples during the study period of December 2022 to November 2023

Results: At a level of $\geq$40 U/L, pleural fluid ADA has the following values: sensitivity = 94.6%, specificity = 94.8%, positive predictive value =96.6%, negative predictive value=91.7%, efficacy= 94.6%. At p-value (< 0.001), it was statistically significant. When the lymphocyte/neutrophil levels are included, they had a sensitivity=96.7%, specificity=100%, positive predictive value=100%, and negative predictive value=95.1% and efficacy=98%, with a ratio of $\geq$0.75.

Conclusion: When diagnosing tubercular pleural effusion, ADA is a very sensitive diagnostic marker. In patients with tubercular pleural effusion, the combination of pleural fluid ADA and lymphocyte/neutrophil ratio improves diagnostic accuracy more than pleural fluid ADA by itself.

Key-words: Adenosine deaminase, Pleural effusion, Tuberculosis, lymphocyte/neutrophil ratio

Corresponding author

Dr. Kalluru Harsha Vardhan Reddy

Email id: harshaallsmiles@gmail.com

INTRODUCTION:

A pleural effusion is an overabundance of fluid build-up inside the pleural space. Typically, each side of the pleural cavity holds roughly 10 ml of fluid [1]. The cause of pleural effusion is imbalance in the interval between the fluid's creation and resorption. It could be the beginning signs of any pulmonary or cardiac condition. Pleural effusion is not a separate disease entity; rather, it is a sign of an underlying disorder. When a pleural effusion is diagnosed, an attempt should be made to identify the underlying disorder. Pleural effusion can be broadly classified as transudative or exudative based on the standards outlined by Light [1]. Typically, transudative effusion is brought on by hypo-albuminemic condition or congestive heart failure. Exudative effusion can be brought on by pulmonary thromboembolism, local trauma, metastatic or localized cancer, pleuro-pulmonary infection, etc. Worldwide, tuberculosis is the most common infectious cause of death [2]. The most frequent extrapulmonary symptom of tuberculosis is pleural tuberculosis, which is only surpassed by tubercular lymphadenitis [3].

The ADA levels in pleural fluid is a reasonably priced chemical biomarker, making it a desirable screening method, especially in regions where tuberculosis is endemic. Elevated levels of ADA have also been linked to immunological disorders, pyogenic empyemas, and cancers.

There is a notable influx of inflammatory cells into the pleural space in cases of pleural effusion [5]. Different leucocytic predominance types are observed in various disease types as well as in various stages of the same disease [6]. Neutrophils are markedly elevated in parapneumonic and empyematous effusions [7]. Malignant and tubercular pleural effusions exhibit a lymphocytic predominance [7]. Purine catabolism involves the enzyme ADA. It converts deoxyadenosine to deoxyinosine and adenosine to inosine.

The final diagnosis of tubercular pleural effusion is made by presence of pleural granulomas or tubercle bacilli in pleural fluid, sputum, or a pleural biopsy specimen. Pleural biopsy is thought to be essential for a precise diagnosis whenever a tubercular pleural effusion is suspected due to the low concentration of tubercle bacilli in pleural fluid. However, a lot of work has gone into determining the markers of tubercular pleural effusion in pleural fluid because pleural biopsy is a challenging procedure and pleural fluid sampling is a simpler substitute.

AIM AND OBJECTIVES: To study the diagnostic value and accuracy of Lymphocyte/Neutrophil ratio and ADA levels in pleural fluid in patients with tubercular pleural effusion.

MATERIALS AND METHODS: This study was conducted at our tertiary care hospital in the Dept. of General Medicine in association with Dept. of Pathology. We included a total of 150 subjects, 92 were tubercular pleural effusion patients and 58 were non tubercular pleural effusion patients during the study period of December 2022 to November 2023.

Study design: Prospective, observational hospital-based study.

Sample size: 150

Inclusion Criteria: This study included tubercular and non-tubercular pleural effusion patients from our tertiary care hospital.

The presence of one or more of the following criteria were taken for the diagnosis of tubercular pleural effusion in the patient.[8]

1. Bacteriological confirmation (direct smear, culture, or histological finding) of Mycobacterium tuberculosis in pleural fluid or sputum
2. Tuberculosis cases confirmed by histopathology,
3. Radiological results that support tuberculosis,
4. A clinical presentation that rules out other clinical factors and is consistent with tuberculosis,
5. After receiving anti-tubercular therapy for six to eight weeks, there was a noticeable improvement in clinical and radiological outcomes.
6. Pleural fluid adenosine deaminase levels of greater than 40U/L; 7. Positive reaction (> 10 mm induration) to the 1 tuberculin unit (TU) purified protein derivative (PPD).
7. Pleural fluid adenosine deaminase levels of > 40U/L.

Exclusion Criteria: Patients with malignant pleural effusion, transudative pleural effusion and immunodeficient states like HIV.

RESULTS:

Of the 92 patients with tubercular pleural effusion, 22 (24%) were female and 70 (76%) were male. The age range of 92 patients with tubercular pleural effusion was 15 to 76 years, with a mean of 41.6 years and a standard deviation of ±14.9 years. Unilateral pleural effusion was present in all 92 tubercular pleural effusion patients. 50 patients (54.34%) were right-sided, and 38 patients (45.65%) were left-sided.

Table 1: Pleural fluid ADA levels in Tubercular & non-Tubercular pleural effusion.

ADA level	Tubercular pleural effusion	Non-Tubercular pleural effusion	Total
ADA≥ 40 IU	87	3	90
ADA≤40 IU	5	55	60
Total	92	58	150

Table 2: Pleural fluid lymphocyte-neutrophil ratio in tubercular & non-tubercular pleural effusion.

Lymphocytes to Neutrophils ratio	Tubercular pleural effusion	Non-Tubercular pleural effusion	Total
L/N≥75	89	0	89
L/N≤75	3	58	61
Total	92	58	150

For Table 1: Pleural fluid with an ADA ≥40 for tubercular pleural effusion diagnosis was found to have the following characteristics in 88 patients: sensitivity = 94.6%, specificity = 94.8%, positive predictive value =96.6%, negative predictive value=91.7%, efficacy= 94.6%.

For Table 2: In 92 patients with tubercular pleural effusion, a pleural fluid lymphocyte/neutrophil ratio of ≥0.75 was found to be diagnostically significant for tubercular pleural effusion. The results showed sensitivity=96.7%, specificity=100%, positive predictive value=100%, and negative predictive value=95.1% and efficacy=98%

Table 3: Combined pleural fluid ADA & Lymphocyte-Neutrophil ratio

ADA & L/N ratio	Tubercular pleural effusion	Non-Tubercular pleural effusion	Total
ADA≥40 and lymphocyte neutrophil ratio≥75	87	0	87
ADA<40 and/or lymphocyte neutrophil ratio<75	5	58	63
Total	92	58	150

For Table 3: Combining ADA levels of ≥40U/L with a pleural fluid lymphocyte/neutrophil ratio of ≥0.75 allowed for the diagnosis of tubercular pleural effusion in 92 patients, sensitivity=94.6%, specificity=100%, positive predictive value=100%, negative predictive value=92.1%, efficacy=96.7%

DISCUSSION & CONCLUSION:

Pleural effusions can be difficult to diagnose due to the wide range of differential diagnosis possibilities. Congestive heart failure (CHF), cancer, and pneumonia-related effusion are the most frequent causes.[9] Both single and combined diagnostic techniques were assessed in our study. We have looked at method combinations whose complementary qualities provide diagnostic choices that can be used to good effect in low-tech, high-prevalence countries.

In our study, 58 patients with non-tubercular pleural effusion and 92 patients with tubercular pleural effusion were among the 150 patients who had exudative pleural effusion. In our investigation, 87 patients with tubercular pleural effusion (34 with pleural effusion and

parenchymal lesion, 53 with pleural effusion only as determined by chest x-ray) had ADA ≥40 for pleural fluid, and 5 with ADA <40. ADA ≥40 was present in 3 out of 58 patients with non-tubercular pleural effusion, while ADA <40 was present in 55 patients. For the purpose of diagnosing tubercular pleural effusion in exudative pleural effusion cases, pleural fluid with an ADA of ≥40 had the following values: sensitivity = 94.6%, specificity = 94.8%, positive predictive value =96.6%, negative predictive value=91.7%, efficacy= 94.6%. According to Table 1, it was statistically significant (p value<0.001). Similar observations were studied by Bharat et al, Mehta AA et al, Bergess LJ et al. [10,12,13].

96 lymphocytic pleural fluid samples of patients with exudative pleural effusion were sequentially selected by Bharat et al. [10] and were then split into two groups: 56 tuberculous samples and 40 non-tuberculous samples. The ADA was found to have a 92.8% positive predictive value, a 90% negative predictive value, a 90% specificity, and a 92% sensitivity when the cut-off value for tubercular pleural effusion was 40. Similar observation was made in the study done by Berger et al[11],Mehta AA et al.'s study [12] in the assessment of 121 exudative pleural effusion cases, 49 of which were tubercular pleural effusion cases. According to their findings, the ADA had a sensitivity of 85.7%, specificity of 80.8%, positive predictive value of 75%, and negative predictive value of 89.5% when used as a cut-off value for the diagnosis of tubercular pleural effusion. In a retrospective analysis, Bergess LJ et al. [13] assessed 246 exudative pleural effusion cases, including 143 tubercular pleural effusion cases. They discovered that an ADA cut-off value of ≥50 yielded a 91% sensitivity, 81% specificity, 84% positive predictive value, and 89% negative predictive value when used to diagnose tubercular pleural effusion.

In our investigation, out of 92 patients with tubercular pleural effusion, 89 had a lymphocyte/neutrophil ratio in their pleural fluid that was less than 0.75, and 3 patients had a ratio less than 0.75. Of the 92 patients with tubercular pleural effusion, 87 had pleural fluid ADA levels ≥40U/L along with a pleural fluid lymphocyte/neutrophil ratio ≥0.75, while the remaining 5 patients had ADA levels <40U/L. The subsequent observation indicates that the diagnosis of tubercular pleural effusion is more specific and effective when the pleural fluid Lymphocyte/Neutrophil ratio ≥0.75 and ADA≥40 are combined. Comparable findings were reported in the Burgess LJ et al. study [13], which demonstrated that the combination of pleural fluid Lymphocyte/neutrophil ratio ≥0.75 and ADA ≥50 improved the specificity and efficacy for tubercular pleural effusion diagnosis.

In patients with tubercular pleural effusion, we attempted to assess and determine any correlation between pleural fluid ADA, pleural fluid lymphocyte/neutrophil ratio, and pleural biopsy findings. In our study, 21 patients with tubercular pleural effusion underwent pleural biopsy; of these, 15 had tuberculosis confirmed by histopathological examination, while the other five showed conflicting results.

ADA is an extremely sensitive diagnostic indicator for tubercular pleural effusion. When lymphocyte/neutrophil ratio and pleural fluid ADA are combined, diagnostic accuracy for tubercular pleural effusion patients is higher than when pleural fluid ADA is used alone.

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Conflicts of interest

There are no conflicts of interest

REFERENCES:

1. Raviglione MC, Luelmo F. Update on the global epidemiology of tuberculosis. Curr Issues Public Health. 1996 Aug;2(4):192–7.
2. Light RW, Macgregor MI, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972 Oct;77(4):507–13.
3. Mehta JB, Dutt A, Harvill L, Mathews KM. Epidemiology of extrapulmonary tuberculosis. A comparative analysis with pre-AIDS era. Chest. 1991 May;99(5):1134–8.
4. Antony VB, Godbey SW, Kunkel SL, Hott JW, Hartman DL, Burdick MD, et al. Recruitment of inflammatory cells to the pleural space. Chemotactic cytokines, IL-8, and monocyte chemotactic peptide-1 in human pleural fluids. J Immunol Baltim Md 1950. 1993 Dec 15;151(12):7216–23.

5. Light RW, Erozan YS, Ball WC. Cells in pleural fluid. Their value in differential diagnosis. Arch Intern Med. 1973 Dec;132(6):854–60.
6. Light RW, Erozan YS, Ball WC. Cells in pleural fluid. Their value in differential diagnosis. Arch Intern Med. 1973 Dec;132(6):854–60.
7. Chaudhary S PA. Role of pleural fluid adenosine deaminase (ADA) for the diagnosis of tuberculous pleural effusion. Calicut Med J. 2010;8:e4; 2010.

8. Porcel JM. Tuberculous pleural effusion. Lung. 2009 Oct;187(5):263–70.

9. Sahn SA. State of the art. The pleura. Am Rev Respir Dis. 1988 Jul;138(1):184–234.
10. Gupta BK, Bharat V, Bandyopadhyay D. Sensitivity, specificity, negative and positive predictive values of adenosine deaminase in patients of tubercular and nontubercular serosal effusion in India. J Clin Med Res. 2010 May 19;2(3):121–6.
11. Berger HW, Mejia E. Tuberculous pleurisy. Chest. 1973 Jan;63(1):88–92.
12. Mehta AA, Gupta AS, Ahmed S, Rajesh V. Diagnostic utility of adenosine deaminase in exudative pleural effusions. Lung India Off Organ Indian Chest Soc. 2014;31(2):142–4.
13. Burgess LJ, Maritz FJ, Le Roux I, Taljaard JJ. Combined use of pleural adenosine deaminase with lymphocyte/neutrophil ratio. Increased specificity for the diagnosis of tuberculous pleuritis. Chest. 1996 Feb;109(2):414–9.