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## **To study the diagnostic yield of pleural fluid adenosine deaminase (ADA) combined with Lymphocytic/Neutrophil (L/N) ratio in tubercular pleural effusion at a tertiary care center**

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**Abstract**--Introduction: Tuberculosis is one of the leading causes of death worldwide and tubercular pleural effusion is the second most common form of extrapulmonary tuberculosis after lymph node tuberculosis. The most commonly used method to diagnose exudative pleural effusion is by the help of Light's Criteria. The goal of our study was to search for another diagnostic tool that may have a better diagnostic yield for diagnosing pleural effusion than the present methods. Material and Methods: A prospective observational study was conducted in the pulmonary medicine department of a tertiary care center over a period of 18 months, where patients with pleural effusion were enrolled in the study after proper informed consent. These effusion cases were differentiated among tubercular and non-

tubercular groups by recognized methods. Among these cases, the non-tubercular patients were taken as controls. Results: A total of 45 cases were taken after considering the inclusion and exclusion criteria, with 30 tubercular effusion cases and 15 controls. The sensitivity and specificity of combined ADA & LNR were calculated to be 94.4% with a test accuracy of 89.29%. Conclusion: Our study concludes, that tubercular pleural effusion contributes substantially to the burden of disease in the world including in India. ADA combined with LNR can be a more precise diagnostic modality for tubercular pleural effusion in comparison to other diagnostic methods.

**Keywords**---Pleural fluid, tuberculosis, adenosine deaminase.

## Introduction

Tuberculosis (TB) is one of the most prevalent infectious bacterial diseases with a death toll approx 1.3 million in the year 2020, making it a leading cause of death among infectious diseases.<sup>1</sup> In 2021, India has the highest burden of TB worldwide with approx 20 lakhs cases documented.<sup>2</sup> Pulmonary Tuberculosis (PTB) is its most common manifestation but it affects other organs also, categorizing it as Extrapulmonary Tuberculosis (EPTB). It has been seen that HIV-positive patients are more prone to this infection accounting for 45% of cases while only 20% of the non-HIV patients suffer from TB.<sup>3</sup>

The most frequent presentation of EPTB in India is lymph node tuberculosis (LNTB) i.e. 35% of EPTB cases and the second most common presentation of EPTB is pleural tuberculosis or tubercular pleural effusion (TPE).<sup>3</sup> Pleural effusion (PE) is classified into transudative and exudative types, both are generally differentiated with help of Light's Criteria.<sup>4,5</sup> Three most prevalent condition in exudative effusion are tuberculous pleural effusion (TPE), malignant pleural effusion (MPE) and parapneumonic pleural effusion.<sup>6</sup> Pleural tissue biopsy and pleural fluid examination are two main methods for confirming the diagnosis of TPE. While Mycobacterium tuberculosis (MTB) culture of pleural fluid is controversial in the diagnosis of TPE due to its low success rate i.e. 36%.<sup>7</sup> However, it is difficult to distinguish between TPE and MPE due to their non-distinct clinical characteristics and negative laboratory findings.<sup>8</sup> As there are contradictory results on sensitivity and specificity of MTB culture of pleural fluid and pleural biopsy, there is a need to develop a reliable molecular marker for precise diagnosis.<sup>9</sup>

Adenosine Deaminase (ADA) is an enzyme present in lymphocytes that are notably raised in tubercular pleuritis patients. It has a specificity of 90% and sensitivity of 92% for ADA threshold values ranging from 44.0 & 38.0 IU/L respectively, as mentioned in the meta-analysis of 63 studies.<sup>10</sup> Cut-off value of 40 IU/L ADA had an acceptable diagnostic accuracy<sup>11</sup>, except in cases where it can be false positive like in rheumatoid pleurisy, malignancy and empyema. Therefore, the importance of image-guided pleural biopsies increases in the false-positive ADA scenario.<sup>12</sup> The differential cell count of pleural fluid is

predominantly lymphocytic. The profound appearance of lymphocytes may contribute to lymphomas being misdiagnosed. The appearance of neutrophils in the pleural fluid in exudative effusion is indicative of acute pleural inflammation. In conditions like pneumonia, pulmonary embolism, early tuberculosis, and pancreatitis, neutrophils that are present in the effusion are in increased amounts. For the differentials of effusion, the lymphocyte neutrophil ratio (LNR) is low-cost, reproducible, and helps in the easy calculation of the hematological parameter.<sup>13</sup> The ADA activity in the tubercular group was considerably higher than in any other group (p-value <0.05) as stated by Burges LJ et al in their study.<sup>14</sup> The sensitivity and specificity of the ADA at a level of 50 U/L were evaluated to be 91% and 81% respectively, for recognizing TB respectively. The sensitivity and specificity, negative predictive value and positive predictive value, and the ability to detect TB were tested at 88.0 %, 95.0 %, 88.0 %, 95.0 %, 92.0 % respectively when the additional condition of LNR was more than or equal to 0.75 was included. The authors concluded that ADA is a competent tool for diagnosing tuberculous pleural effusion in conjunction with differential cell counts and LNR. Another study done by Behera BK and Satish KTN also concluded that ADA in conjunction with LNR is more competent in diagnosing tuberculous pleuritis than ADA alone.<sup>15</sup> Hence the goal of this study was, therefore, to decide whether the use of ADA levels in pleural fluid in conjunction with LNR would be more sensitive and specific in diagnosing tubercular pleural effusion than ADA alone.

### **Material and Methods**

This prospective observational study was conducted on patients hospitalized to the department of pulmonary medicine, Teerthankar Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh for a duration of 18 months. The institutional ethical committee was informed and approval was taken before initiating research. A documented consent was taken from the patients who satisfy the inclusion requirements. An information sheet was given to all the participating patients. The inclusion and exclusion criteria for the present study in mention below:

Inclusion Criteria:-

- Cases of tubercular pleural effusion.
- Age  $\geq$  18 years.
- Patient willing to participate in the study by giving a written consent

Exclusion Criteria: -

- Cases of non-tubercular pleural effusion.
- Age < 18 years

### **Methodology**

Patients of pleural effusion after admission from the emergency or outpatient department were recruited for the study. Detailed history taking and clinical examination were performed. A routine investigation like: two samples of sputum examination for Acid Fast Bacilli (early morning & spot), chest X-ray PAV and pleural fluid examination for Routine microscopy, ADA (ERBA Mannheim adenosine deaminase assay kit), ZN staining, Mycobacteria culture, CBNAAT, pleural biopsy (USG guided or via thoracoscopy) were done. Effusion was

classified as either exudative or transudative by Light's criteria. Ultrasound-guided diagnostic thoracentesis was done under local anesthesia. Tubercular pleural effusion was diagnosed after the identification of tubercular bacilli in pleural fluid, culture, histopathological confirmation and polymerase chain reaction (PCR). Pleural fluid adenosine deaminase levels of  $> 40\text{U/L}$  were taken as tubercule pleural effusion. Pleural fluid LNR  $> 0.75$  indicate pleural effusion<sup>15</sup>. The non-tubercular patients were taken as controls. Ultrasonography of thorax, computed tomography thorax and semi-rigid thoracoscopy were also performed as per need.

## Observation and Results

Table 1: Demographic details

Variables	Tubercular Group (n=30)			Non-Tubercular Group (n=15)		
	Mean	S.D.	Range	Mean	S.D.	Range
Age (n=30)	39.56	16.48	18-70	46.20	15.19	20-70
Sex	n	%		N	%	
Male	14	46.7		10	66.7	
Female	16	53.3		5	33.3	

The tubercular group included 30 subjects who were abiding by the inclusion requirements and 15 subjects were taken as controls – non- tubercular participants. The age range in our study was 18-70 years with the tubercular group showing an average age of  $39.56 \pm 16.48$ . 14 (46.7%) subjects were males and 16 (53.3%) subjects were females. The non-tubercular participants exhibited an age range of 20-70 years showing an average age of  $46.20 \pm 15.19$ . There were 5 (33.3%) females and 10 (66.7%) male subjects in the control group.

Table 2: Distribution of patients according to the previous history of TB or ATT intake, effusion side, sputum AFB, pleural fluid AFB, pleural fluid CBNAAT, pleural fluid MTB culture, pleural biopsy, diabetes mellitus

PATIENT DISTRIBUTION		TUBERCULAR GROUP (n=30)		NON-TUBERCULAR GROUP (n=15)		x <sup>2</sup> , p
		N	PERCENTAGE	N	PERCENTAGE	
HISTORY OF TB OR ATT INTAKE	YES	4	13.3	0	0	x <sup>2</sup> =2.190 p=0.138
	NO	26	86.7	15	100	
EFFUSION SIDE	BILATERAL	1	3.3	0	0	x <sup>2</sup> =1.008 p=0.581
	LEFT	12	40	8	53.3	
	RIGHT	17	56.7	7	46.7	
SPUTUM AFB	POSITIVE	3	10	0	0	x <sup>2</sup> =45 p=<0.001
	NEGATIVE	27	90	15	100	

PLEURAL FLUID AFB	POSITIVE	2	6.7	0	0	$\chi^2=6.429$ $p = <0.001$
	NEGATIVE	28	93.3	15	100	
PLEURAL FLUID CBNAAT	POSITIVE	10	33.3	0	0	$\chi^2=6.429$ $p=0.011$
	NEGATIVE	20	66.7	15	100	
PLEURAL FLUID MTB CULTURE	DETECTED	3	10	0	0	$\chi^2=1.607$ $p = 0.205$
	STERILE	27	90	15	100	
PLEURAL BIOPSY REPORT	TUBERCULAR	11	36.7	0	0	$\chi^2=45$ $p = < 0.001$
	NEGATIVE	0	0	15	100	
	NOT DONE	19	63.3	0	0	
DIABETES MELLITUS	PRESENT	5	16.7	6	40	$\chi^2=2.947$ $p = 0.085$
	ABSENT	25	83.3	9	60	

Table 2 shows distribution of patients according to the previous history of tuberculosis or anti tubercular therapy (ATT) intake, effusion side on chest x ray, sputum AFB, pleural fluid AFB, pleural fluid CBNAAT, pleural fluid culture, pleural biopsy report and diabetes mellitus. There were 4(13.3%) patients with previous history of TB or ATT intake and none in non-tubercular group. There was 1 (3.3%) patient with bilateral pleural effusion, 12 (40%) With left and 17 (56.7%) with right side pleural effusion in tubercular group. In non-tubercular group, there were 8 (53.3%) with left and rest 7 (46.7%) with right sided pleural effusion. Only 3 patients in sputum & 2 patient in pleural fluid were found to be AFB positive in tubercular group and rest were negative in both the groups. Mycobacteria (MTB) was detected by CBNAAT only in 10 patients from tubercular group, rest were negative in both tubercular and non-tubercular group. Pleural fluid was sterile in majority of cases except in 3 cases who were from tubercular group. Pleural biopsy suggestive of TB in only 11 cases of tubercular group and with no results in 15 cases of non-tubercular group, and in remaining 19 cases of TB group biopsy was not performed. There was 5 (16.7%) patients with diabetes mellitus in tubercular group and 6 (40%) patient in the non-tubercular group.

Table 3: Comparison of mean P/F glucose between the two groups

P/F Parameters	Groups	N	Mean	S.D.	S.E.	M.D.	95% C.I.	t-value	p-value <sup>#</sup>
Glucose	Test	30	69.8	74.42	13.58	-7.80	-49.94-34.33	-0.374	0.711
	Control	15	77.66	44.00	11.36				
Protein	Test	30	4.66	1.39	0.25	0.41	-0.55-1.39	0.866	0.391
	control	15	4.25	1.76	0.45				
ADA	Test	30	52.63	28.36	5.17	21.80	6.29 - 37.30	2.836	0.007 <sup>†</sup>
	Control	15	30.83	12.20	3.15				
L/N ratio	Test	30	1.35	0.92	0.16	0.55	0.01-1.10	2.053	0.046 <sup>†</sup>
	Control	15	0.80	0.69	0.17				

<sup>#</sup>P-value derived from independent sample t-test; <sup>†</sup>significant at  $p < 0.05$

In table 3, the mean P/F glucose, protein, ADA, and LNR were compared between the two groups. The study showed NO statistically substantial difference in mean of P/F glucose ( $p=0.711$ ), and protein ( $p=0.391$ ) between the tubercular group and non-tubercular group. A statistically substantial difference was found in mean pleural fluid ADA ( $p=0.007$ ) and LNR ( $p=0.046$ ) between the tubercular group and non-tubercular group. The mean P/F ADA ( $52.63 \pm 28.36$ ) of tubercular participants was considerably elevated compared to controls ( $30.83 \pm 12.20$ ) and similarly, the mean P/F LNR ( $1.35 \pm 0.92$ ) of tubercular participants was Considerably elevated compared to controls ( $0.80 \pm 0.69$ ).

Table 4: Distribution of patients as per symptoms

SYMPTOMS	PRESENT / ABSENT	TUBERCULAR GROUP (n=30)		NON-TUBERCULAR GROUP (n=15)		$\chi^2$ , p
		N	PERCENTAGE	N	PERCENTAGE	
FEVER	PRESENT	16	53.3	9	60	$\chi^2 = 0.180$ $p = 0.0671$
	ABSENT	14	46.7	6	40	
COUGH	PRESENT	21	70	5	33.3	$\chi^2 = 5.511$ $p = 0.019$
	ABSENT	9	30	10	66.7	
CHEST PAIN	PRESENT	20	66.7	7	46.7	$\chi^2 = 1.667$ $p = 0.197$
	ABSENT	10	33.3	8	53.3	
DYSPNEA	PRESENT	13	53.3	7	46.7	$\chi^2 = 46.7$ $p = 53.3$
	ABSENT	17	46.7	8	53.3	

The distribution of patients according to symptoms can be seen in Table 3. The main symptoms at the time of presentation were fever, cough, chest pain, and dyspnea. There were 16 (53.3%) patient who were having fever in the tubercular group and 9 (60%) from the non-tubercular group. Cough was present in 21 (70%) patients in the tubercular group and 5 (33.3%) in the non-tubercular group. Chest pain was present in 20 (66.7%) patients in the tubercular group and 7 (46.7%) in the non-tubercular group. Dyspnea was also seen in 13 (53.3%) cases in the tubercular group and 7 (46.7%) in the non-tubercular group.

The sensitivity was 80% (CI: 61.43% to 92.29%) & specificity was 73.3% (CI: 44.90% to 92.21%) of pleural fluid ADA for detecting TPE and the accuracy of the test came out to be 77.78%. The sensitivity was determined as 73.33% (CI: 54.11% to 87.72%) & specificity was 60.00% (CI: 32.29% to 83.66%) of pleural fluid LNR for detecting TPE and the accuracy of the test came out to be 68.89%. The sensitivity & specificity of combined pleural fluid ADA & L/N ratio for detecting TPE was calculated to be 94.44% (CI: 72.71% to 99.86%) & 80.00% (CI: 44.39% to 97.48%) and the accuracy of the test came out to be 89.29%.

## Discussion

This hospital-based observational research was carried out in the Department of Respiratory Medicine, TMMC & RC, Moradabad, Uttar Pradesh. There were 45 patients included in the study out of which 30 cases were tubercular and 15 in

the control group. The goal of the analysis was to evaluate the diagnostic yield of Adenosine Deaminase (ADA) in pleural fluid in conjunction with LNR in tubercular pleural effusion. Tubercular pleurisy is the most common manifestation of TB, affecting 30% of the population annually causing 1.7 million deaths.<sup>16-18</sup> But contrary to its global load, the diagnosis of TP poses difficulties. A newer approach to diagnosis is required to establish with the help of chest X-ray, ultrasonography, and diagnostic pleural aspiration.<sup>19</sup> Furthermore if needed, additional tests like culture, biochemical analysis & pleural biopsy can be included.

In the present study with a cut-off value of 40 U/L, the sensitivity and specificity of ADA for detecting TPE were calculated to be 80% (CI: 61.43% to 92.29%) and 73.3% (CI: 44.90% to 92.21%). The accuracy of the test was 77.78%. ADA has been found to be extremely sensitive biomarkers with reasonable diagnostic value for TPE.<sup>19-20</sup> The main concern is to determine the cutoff value of ADA which defines its usefulness in predicting TPE. Cutoff values can differ, the range of threshold values can be from 27 to 77 U/L. Research from southwest England and the research is done in Egypt for the diagnosis of TPE recorded similar diagnostic accuracy and sensitivity which were approx. 83.3% and 85% with a threshold value of 35U/L. While 35-40 U/L is the generally agreed cut-off for ADA, there are some studies that have indicated that pleural fluid ADA decreases with age. So, in order to minimize the number of false-positive outcomes, it is also proposed that a lower cut-off should be considered in elderly patients.<sup>21-22</sup>

In concordance with our results, the findings of the meta-analysis conducted by Liang QL et al<sup>10</sup> have shown that the average sensitivity and specificity of ADA were 92% and 90% respectively. The highest combined specificity & sensitivity was 91 percent, while the area under the curve was 0.96, suggesting high accuracy. Another meta-analysis was done by Goto M et al<sup>23</sup> for threshold levels of tuberculous pleural effusions ADA. The research showed that the summary of test characteristics' measure calculated demonstrated sensitivity equal to specificity which was 92.2 percent. Greco S et al<sup>24</sup> did a meta-analysis of 31 trials involving 4738 patients and included ample data to evaluate the ADA sensitivity and specificity in TPE diagnosis. The SROC curve yielded 93 percent of overall maximum joint sensitivity and specificity. An Indian study conducted by Dharampal AS<sup>25</sup> found a sensitivity of 87% and specificity of 85.7% of ADA in the diagnosis of TPE. This study also found high NPV – of 91.3% and PPV – of 79.4%. The levels of ADA were reported above 36 IU/L in the study conducted by Verma SK et al<sup>26</sup> in Allahabad, India in tubercular effusion subjects. They concluded that with the ADA threshold of 36 IU/L, the sensitivity and specificity were high - 100% and 77.7% respectively. The value above 100 IU/L was particularly observed in cases of tubercular effusion.

In the present study, the sensitivity and specificity of LNR of more than 0.75 in detecting TPE were calculated to be 73.33% (CI: 54.11% to 87.72%) and 60.00% (CI: 32.29% to 83.66%). The accuracy of the test came out to be 68.89%. When the criteria of ADA >40U/L was combined with an L/N ratio >0.75, it yielded higher sensitivity and specificity for detecting TPE. The sensitivity and specificity of the combined ADA and L/N ratio were calculated to be 94.44% (CI: 72.71% to 99.86%) and 80.00% (CI: 44.39% to 97.48%). The accuracy of the test was

89.29%.

In concordance with the present study, Antin SS et al<sup>27</sup> concluded that conjoint use of both parameters serves as a useful modality. The sensitivity was 61%, specificity was 71%, positive predictive value was 83 percent, NPV was 45% and efficiency for identification of TB was 64% at 50 U/L. The sensitivity and PPV raise to 100%, and 93% respectively when an additional parameter of L/N ratio of 0.75 or greater was incorporated. While the specificity and NPV showed an elevation of 83%, and 100% respectively. A recent hospital-based observational study by Behera BK et al<sup>15</sup> showed that all cases of TB effusion had ADA levels above 40 units per liter. These effusions were primarily lymphocytes rich along with LNR above 0.75. The LNR was below 0.75 in pleurisy of non-tubercular origin. The lymphocyte/neutrophil ratio was greater than 0.75 in 97 TPE patients and none of the non-tuberculous effusions. Valdes L et al<sup>28</sup> by using ADA as well as lymphocytes accurately diagnosed tubercular origin in two hundred sixteen out of two hundred eighteen effusion samples. A study done by Suresh R, Prem Kumar VT<sup>29</sup> showed ADA in conjunction with LNR to be more diagnostic for TPE rather than isolated use of ADA. When ADA is taken more than 40 U/L, the utility of ADA in the interpretation of tubercular pleural effusion is very noteworthy. The sensitivity and specificity were further improved when the L/N ratio of 0.75 or higher was incorporated. In nutshell, for the analysis of pleural tuberculosis, ADA (>40) in conjunction with L/N proportion (>0.75) can serve as a vital biomarker. This can be helpful in clinical observations and conventional measurements together with biopsy of pleura and microbial investigation.

In comparison to culture, a disadvantage in the analysis of adenosine deaminase enzyme levels is the nonavailability of data on drug susceptibility normally found after culture examination. There are patients who are not willing to endure the invasive procedures. So, the deaminase enzyme levels tend to be high enough to avoid pleural biopsy. The enzyme levels are also helpful for effusions presenting primarily with a lymphocytic picture in areas with a prevalence of non-resistant tuberculosis.<sup>17</sup>

There is a need to establish a definitive diagnosis of tubercular pleural effusion. The diagnosis can be established only when tubercular bacteria can be detected in either biopsy, fluid analysis, or sputum. As previously mentioned, the yield of pleural fluid microscopy is less than 5 %. In 20 to 40% of cases, histological analysis of pleurisy through biopsy is not definitive.<sup>30-31</sup> So if a biopsy is negative or inconclusive, the tubercular bacteria can be grown in pleural specimens in fewer than ten percent of cases.<sup>30</sup> This normally takes at least 3 weeks. In cases of difficulty in establishing a definitive diagnosis, the role of pleural fluid biomarkers like adenosine deaminase, and interferon-gamma is useful. Hence, the adenosine deaminase enzyme levels should be frequently monitored and a standard threshold value should be made for the diagnosis of tubercular effusion.

## **Conclusion**

Adenosine deaminase is a classical and highly sensitive biomarker for the diagnosis of tubercular pleurisy. It can be effectively used to distinguish tubercular pleurisy from non-tubercular pleurisy. This hospital-based observational study was conducted with 30 TPE cases and 15 controls. The goal



of the research was to evaluate the diagnostic yield of Adenosine Deaminase (ADA) in pleural fluid in conjunction with Lymphocytic/Neutrophil Ratio (LNR) in tubercular pleural effusion. The sensitivity and specificity of ADA for detecting TPE were calculated to be 80% (CI: 61.43% to 92.29%) and 73.3% (CI: 44.90% to 92.21%). The accuracy of the test came out to be 77.78%. When the criteria of LNR above 0.75 was paired with ADA above 40U/L, yielded higher sensitivity and specificity for detecting TPE. The sensitivity and specificity of combined ADA & LNR were calculated to be 94.44% (CI: 72.71% to 99.86%) and 80.00% (CI: 44.39% to 97.48%). The accuracy of the test was 89.29%.

The measurement of adenosine deaminase has shown high sensitivity and specificity in TPE. It is especially very useful in the areas of high prevalence. The adenosine deaminase enzyme levels can be used as a dependable marker in the detection of tubercular effusion. It is due to the quick, cheap, and easy-to-carry nature of the test. In conclusion, with the results of the present study, we can come to an agreement that values of ADA with L/N ratio are a more precise diagnostic modality for tubercular pleural effusion as compared to ADA alone.

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