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Research Article

DIAGNOSTIC YIELD OF ADA IN TUBERCULAR PLEURAL EFFUSION

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ABSTRACT

Objective: Tuberculosis (TB) is one of the most common causes of pleural effusion in developing countries like India encountered by medical professionals globally. The present study was carried out to evaluate the diagnostic yield of pleural fluid adenosine deaminase (ADA) in tubercular pleural effusion.

Methods: This descriptive study was conducted in the Department of Medicine and Pulmonary Medicine, Saheed Laxman Naik Medical College and Hospital from January 1, 2019, to March 31, 2020. All patients >15 years of age with lymphocytic exudative pleural effusion and pleural effusion associated with smear/CBNAAT-positive pulmonary TB patients, who attended the department during the study period, were included in the study. A case was taken as tuberculous employing defined criteria. Patients with transudative effusions, post-traumatic effusions, pregnant and lactating women, and persons on drugs that affect ADA activity like interferon alpha, deoxycoformycin, ribavirin, and viramidine were excluded from the study.

Results: The mean ADA value was 93.93±44.63 IU/L among the cases with tuberculous effusion and 56.36±62.81 IU/L in the non-tuberculous effusion group. At a cutoff value of 50.7 IU/L, pleural fluid ADA showed a sensitivity of 87% and a specificity of 74% in diagnosing TB etiology.

Conclusion: The mean ADA values were significantly higher in tuberculous pleural effusions when compared to the non-tuberculous group. When this was combined with pleural fluid lymphocyte dominancy, the specificity increased to 96%. Pleural fluid ADA values have a strong association with age. ADA estimation is a simple, cost-efficient, and diagnostically helpful investigation with high reliability.

Keywords: Tuberculosis, Exudative effusion, Adenosine deaminase, Specificity, Sensitivity.

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INTRODUCTION

Tuberculosis (TB) is one of the most common causes of pleural effusion in developing countries like India encountered by medical professionals globally. Pleural effusion in pulmonary TB can occur as the sequel to a primary infection of 6–12 weeks duration or as the reactivation of latent infection [1] Tuberculous pleural effusion (TPE) is the second most common extrapulmonary TB just behind lymph node TB [2]. Untreated TPE can develop into active TB [3]. Acute processes usually cause neutrophilic predominant exudative effusions, whereas lymphocytic effusions have a lot longer listing of differential diagnoses. Effusion with lymphocytic predominance may have several causes, the most common being pleural TB and metastatic neoplasia [4]. A few research papers propose that pleural fluid lymphocyte percentages of >85% are very suggestive of TB [5], while some series of patients with TPE indicate that only 10% of patients had <50% of lymphocytes in pleural fluid [6]. Malignancies, infectious diseases, pulmonary embolism, collagen vascular diseases, sarcoidosis, uremia, chylothorax, and post-coronary artery bypass graft pleural effusion are different causes of lymphocytic pleural effusions [7].

The pleural fluid in TPE is consistently an exudate with the pleural fluid protein concentration commonly exceeding 5 g/dL [8,9].

The diagnosis of TPE should be considered in any patient with an exudative pleural effusion.

For establishing the etiology of pleural effusion as TB, the yield of pleural fluid culture for mycobacteria is low down, at about 36% [10]. The combined sensitivity of biopsy and PF culture is as high as 90% [11]; however, closed pleural biopsy is an invasive procedure and involves a long waiting time for the culture results. Markers found in PF have therefore been extensively studied as a promising alternative to pleural biopsy [11]. Adenosine deaminase (ADA) level in pleural fluid is a cost-effective chemical biomarker and is routinely employed as a screening tool, in particular, in countries where TB is endemic [11].

Delayed hypersensitivity mediated by T–lymphocytes plays a large role in the pathogenesis of tubercular pleural effusion. ADA is a key T-lymphocyte enzyme, and its plasma activity is elevated in diseases in which cellular immunity is stimulated. ADA is the enzyme that catalyzes the conversion of adenosine to inosine in the purine salvage pathway. Demonstration of an elevated pleural fluid ADA level is useful in establishing the diagnosis of TPE. Other than TB, high pleural fluid ADA is associated with empyema, rheumatoid arthritis, and lymphoma. The former two diseases do not have pleural fluid lymphocytosis. Undeniably, if the diagnostic criteria used for TPE take into account a pleural fluid lymphocyte to neutrophil ratio of 0.75 or more, the specificity of the test is greater than before [12,13]. Some authors have utilized a range of cut-off levels for ADA in the pleural fluid between 30 and 70U/L for establishing the etiology of pleuritis as TB. The sensitivity, specificity, positive predictive value, and negative predictive value of pleural fluid ADA as a diagnostic test varies from 69.2 to 100, 66.6 to 97, 75 to 96, and 74 to 95, respectively, among studies conducted from the year 1999 to 2018 by different authors [2,3,14-27].

The present study was carried out to evaluate the diagnostic yield of pleural fluid ADA in tubercular pleural effusion.

METHODS

This descriptive study was conducted in the Department of Medicine and Pulmonary Medicine, SLN Medical College and Hospital from January 1, 2019 to March 31, 2020. Institutional Ethics Committee clearance [EC-4 (5)/2020] was obtained before the conduct of the study.

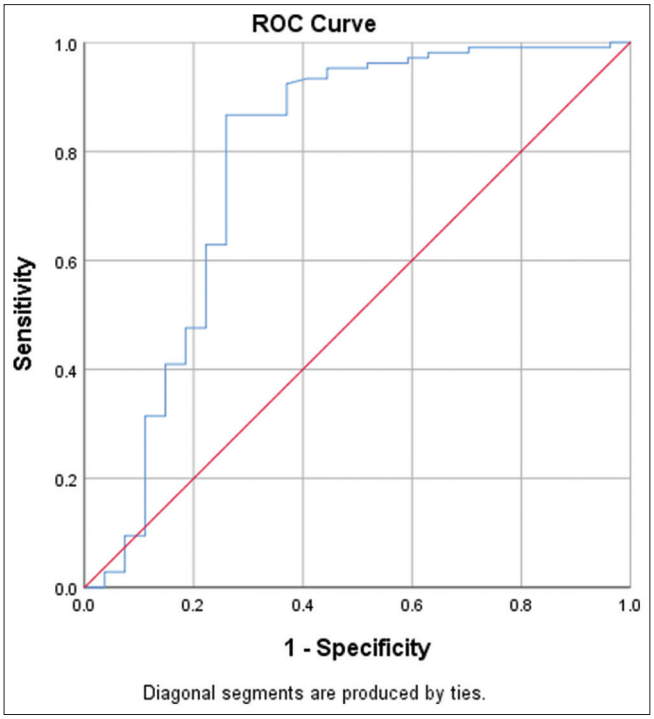

Fig. 1: ROC curve for pleural fluid ADA values

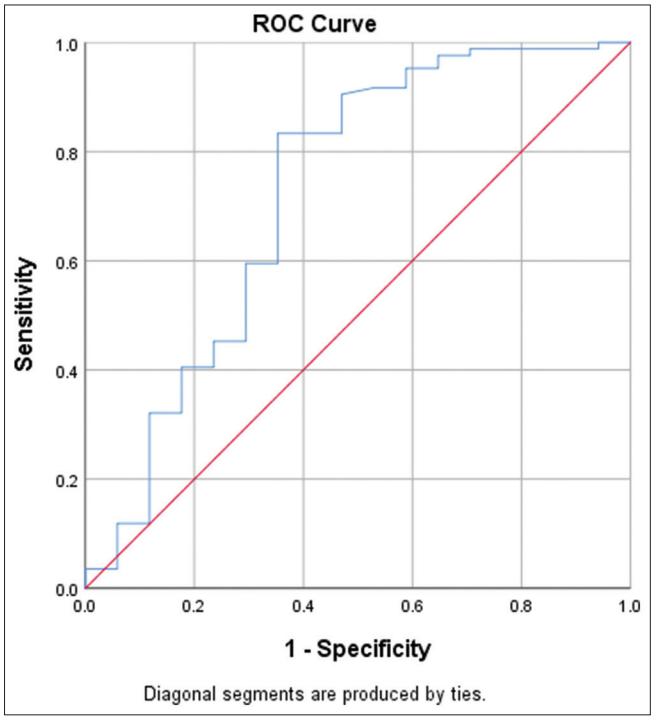

Fig. 2: ROC curve for ADA in age group ≤55 years (cutoff 50.6, Sn=83%, Sp=65%)

All patients >15 years of age with lymphocytic exudative pleural effusion (as per Light's criteria [28] – pleural fluid protein/serum protein >0.5; fluid LDH/serum LDH >0.6) and pleural effusion associated with smear/CBNAAT positive pulmonary TB patients, who attended the department during the study period were included in the study. A case was taken as tuberculous employing defined criteria. Patients with transudative effusions, post-traumatic effusions, pregnant and lactating women, and persons on drugs that affect ADA activity like interferon alpha, deoxycoformycin, ribavirin, and viramidine were excluded from the study.

After careful history taking and thorough clinical examination, radiological assessment with a chest X-ray (USG chest and CT chest only in selected cases) was done in all. Pleural fluid aspiration and analysis were done in all cases (biochemistry including ADA, cytology, and microbiology). The pleural fluid ADA test was done using Erba's ADA assay kit which is based on the kinetic Non-Guisti method in all patients to ensure uniformity in the results. Sputum for AFB/CBNAAT/cytology, lymph node aspiration cytology, etc. was done in indicated patients.

A case of TPE was diagnosed if any one of the following was present;

- Sputum for AFB/CBNAAT positive
- Pleural fluid AFB smear/culture positive
- Histopathological or cytological evidence of TB from lymph nodes or other sites
- If all were negative, a clinical and radiological picture suggestive of TB with a definite improvement in anti-TB treatment was taken as a diagnostic of TPE.

All the 132 cases of exudative pleural effusions who attended the department during the study period were taken for the study, which included 105 cases with tuberculous etiology.

Statistical analysis

Statistical analysis was done using SPSS version 26. The sensitivity and specificity of pleural fluid ADA in diagnosing TB were estimated. Quantitative variables were expressed as mean and standard deviation (Mean±SD). Categorical variables were expressed as proportions. $p<0.05$ was considered statistically significant and $p<0.001$ was considered statistically extremely significant. A ROC curve was plotted to find the optimum cut-off value of ADA to predict a diagnosis of TB. This was further verified using Youden's index.

RESULTS

Out of 132 cases included in our study, 105 cases were diagnosed as tuberculous effusion. Table 1 shows the baseline characteristics of the two groups, tuberculous and non-tuberculous. The male: female ratio was 2.5:1 among the tuberculous group and 2:1 among the non-tuberculous group. We found that those patients having TB effusion belonged to the 39.87±16.33 years age group compared to those with non- TPE 46.25±18.90 years.

The mean ADA value was 93.93±44.63 IU/L among the cases with tuberculous effusion and 56.36±62.81 IU/L in the non-tuberculous effusion group (p=0.0005** statistically extremely significant). The mean pleural fluid sugar of tubercular and non tubercular exudative pleural effusion is not associated with statistically significant. The mean pleural fluid protein of tubercular and non-tubercular exudative pleural effusion is associated with statistically significant (p=0.005*).

A ROC curve plotted for pleural fluid ADA values for TPEs showed an AUC of 0.782 [Figure 1]. At a cutoff value of 50.7 IU/L, pleural fluid ADA showed a sensitivity of 87% and a specificity of 74% in diagnosing TB etiology. This was further verified using Youden's index, which was maximum (0.61) at the above cutoff value (Table 2).

AUC	Standard error	p-value	95% CI
0.782	0.063	0.000	0.658-0.906

The sensitivity, specificity, positive predictive value, negative predictive, value, and diagnostic accuracy of pleural fluid ADA as a diagnostic test are shown in Table 3.

When this was combined with pleural fluid lymphocyte dominancy, the specificity increased to 96% (Table 4).

Table 1: Baseline characteristics of the patients of the two groups, tuberculous, and non-tuberculous pleural effusion

Demographic and biochemical parameters	Tuberculous effusion (n=105)	Non-tuberculous effusion (n=27)	p-value
Male: female	75:30=2.5:1	18:09=2:1	
Mean age±2SD	39.87±16.33	46.25±18.90	0.0821
Number of patients with age≤55 years, n (%)	84 (80)	17 (62.96)	
Number of patients with age>55 years, n (%)	21 (20)	10 (33.04)	
History of diabetes mellitus, n (%)	17 (16.19)	11 (40.74)	
History of smoking, n (%)	16 (15.24)	15 (55.56)	
Sputum for AFB, n (%)	0	0	
Sputum for CBNAAT, n (%)	4 (3.81)	0	
HIV, n (%)	1 (0.95)	0	
Mean pleural fluid ADA	93.93±44.63	56.36±62.81	0.0005**
Mean pleural fluid sugar	82.63±79.3	86.38±51.52	0.8161
Mean pleural fluid protein	5.95±1.46	4.89±2.59	0.0056*

p<0.05 was considered statistically significant and *P*<0.001 was considered statistically extremely significant. SD: Standard deviation, ADA: Adenosine deaminase, CBNAAT: Cartridge based nucleic acid amplification test, AFB: Acid –fast bacillus

Table 2: Youden's index

ADA value (IU/L)	Sensitivity	Specificity	Youden's index= (Sensitivity+Specificity)−1
12.1	100	4	0.04
20.9	98	37	0.35
30.1	95	48	0.43
40.8	91	63	0.54
50.7	87	74	0.61
59.8	76	74	0.5
70.5	69	74	0.44
80.5	55	78	0.33
90.1	48	81	0.29
100.1	38	85	0.23
110.5	30	89	0.19
120.6	26	89	0.14
130.5	20	89	0.09
141.4	14	89	0.03
159.6	10	93	0.02
164.4	9	93	0.01
282.1	0	100	0

Table 3: Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of pleural fluid ADA as a diagnostic test

Pleural fluid ADA (IU/L)	Tuberculous effusion (n=105)	Non-tuberculous effusion (n=27)	Total
≥50.7	91 (true positive)	7 (false positive)	98
<50.7	14 (false negative)	20 (true negative)	34

Sensitivity=91/105×100=86.6% Specificity=20/27×100=74% PPV=91/98×100=92.8% NPV=20/34×100=58.8% Diagnostic accuracy=(True positive+true negative)/total Cases×100=91+20/132×100=84% PPV: Positive predictive value, NPV: Negative predictive value, ADA: Adenosine deaminase

Sensitivity=68%

Specificity=96%

Positive predictive value=98%

Negative predictive value=43%

Diagnostic accuracy=(True positive+True Negative)/Total cases×100=73%

In the age group ≤55 years, an ADA cutoff value of 50.6 resulted in a sensitivity of 83% and specificity of 65% (Figure 2). Whereas, for patients aged ≥55 years, an ADA cutoff value of 58.2 IU/l resulted in a sensitivity of 100% and specificity of 90% (Figure 3).

Table 4: Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of pleural fluid adenosine deaminase and lymphocyte as a diagnostic test

Pleural fluid ADA (IU/L) and lymphocyte	Tuberculous effusion (n=105)	Non-tuberculous effusion (n=27)	Total
≥50.7 with lymphocyte dominant	71 (true positive)	1 (false positive)	72
<50.7±lymphocyte dominant	34 (false negative)	26 (true negative)	60

Sensitivity=68% Specificity=96% PPV=98% NPV=43% Diagnostic accuracy=(True positive+True negative)/total cases×100=73% ADA: Adenosine deaminase, PPV: Positive predictive value, NPV: Negative predictive value

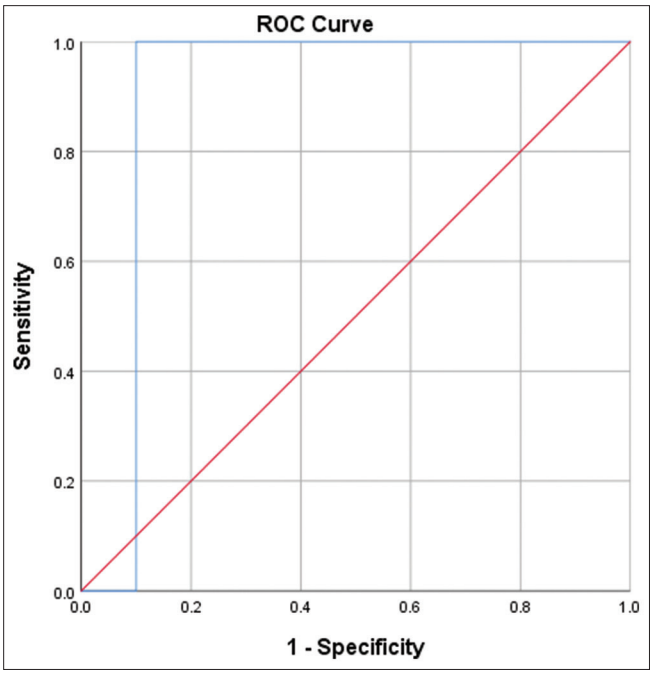

Fig. 3: ROC curve for ADA in the age group >55 years (cutoff 58.2, Sn=100%, SP=90%)

DISCUSSION

The mean ADA of TPE in our study was 93.93 (SD 44.63) IU/L. When a cutoff value of 50.7 IU/L of ADA was used, there was maximum sensitivity and specificity for the diagnosis of TB. A range of research articles has taken cut-off values ranging from 30 to 100 IU/L of

Table 5: Comparisons between the cutoff values taken for adenosine deaminase in some previous studies with ours, and mean adenosine deaminase values, the sensitivity, specificity, positive predictive value, and negative predictive value for each

Author (year)	Mean ADA value	ADA cut–off (U/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Sharngan *et al*. (2018) [2]	60.09±38.36	38.3	92.5	97	96	94
Mehta *et al*. (2014) [3]	64.11±32.33	40	85.7	80.8	75	89.5
Gupta *et al*. (2010) [14]	67.34±22.85	40	92.8	90	92.86	90
Verma *et al*. (2008) [15]	-	36	100	77	-	-
Dave *et al*. (2013) [16]	-	60	69.2	92	90	74
Sharma *et al*. (2001) [17]	95.8±57.5	35	83.3	66.6	-	-
		100	40	100		
Helmy *et al*. (2012) [18]	83.5±50.3	30	80	85	84.2	81
Chen *et al*. (2004) [19]		55.8	87.3	91.8	82.1	94.4
Nayak and Jayantibhai [20]	84.99±45.45	40	90	96.67	96.43	90.62
Riantawan *et al*. (1999) [21]	-	60	95	96	96	95
Yu *et al*. (2010) [22]	-	28.7	75.5	95.2	-	-
Goyal *et al*. (2016) [23]	94.5±41.8	65	83.3	72.2	80	76.5
Kate *et al*. (2015) [24]	107.7±31.95	40	93.3	90	93.3	90
Devkota *et al*. (2012) [25]	105.8±67.23	42.9	90.8	82.8		-
Bhushan *et al*. (2016) [26]	124.02±57.45	40	93.3	90	93.3	90
Present study	93.93±44.63	50.7	87	74	93	59

ADA: Adenosine deaminase, PPV: Positive predictive value, NPV: Negative predictive value

pleural fluid ADA in establishing the diagnosis of TB with changeable sensitivity and specificity [2]. The difference in the values may be due to the different methods used for ADA analysis, the prevalence of TB in different study groups, and also differences in study population characteristics. For ensuring equivalence in the outcome, we used the equal method for the examination of ADA in our study. A study completed by Tay and Tee. also observed similar finding to our study; the cutoff level of ADA for establishing the diagnosis of TPE was different in different age groups (72 IU/L in <55 years and 26 IU/L in >55 years age group [29]. In our study, the cutoff level of ADA was 50.6 IU/L in ≤55 years and 58.2 IU/L in ≥55 years. A similar study also analyzed other factors that can influence the pleural fluid ADA level. Although the strongest association was with age, additional factors such as pleural fluid protein, LDH, and fluid lymphocyte count also were seen to influence the level of ADA.

Most studies use a cutoff value of ADA of >40 IU/L for the diagnosis of TPEs. Our study revealed a cutoff value of 50.7 IU/L. Chen *et al*. study [19] had a cutoff of 55.8 IU/L for ADA, which is comparable to our value. When ADA values are combined with a pleural fluid lymphocyte ratio of more than 50%, the chances of making a diagnosis of TB are even higher. Pleural fluid ADA value >50 IU/L showed a sensitivity of 97.6% and a specificity of 87.5% in establishing the diagnosis of TPE in a study done by Rahman *et al*., Bihar, India. When this was pooled with a pleural fluid lymphocyte ratio >0.75, the sensitivity improved to 100% and specificity to 92.8% [30]. In our study, the specificity increased from 74% to 96% when pleural fluid lymphocyte dominancy is taken into consideration along with ADA.

Creating a definitive diagnosis with a gold standard is a lot more difficult in TPE. Although we had put forward the criteria for diagnosing TB, a gold standard diagnosis was available only in four cases. The majority of the cases had a clinical diagnosis. It is in these scenarios that ADA acts in a supportive role. Searching the literature, we observed that a lot of the other studies also have used diagnostic criteria similar to ours and were not based on gold standard diagnosis alone. The lack of thoracoscopy to take a pleural biopsy was a limitation of our study. In their study, Valdés *et al*. say again that with the high diagnostic yield of pleural fluid ADA in areas with a high prevalence of TB, it could be achievable to diagnose TPEs without pleural biopsy. Biopsy should be held in reserve for those patients with low pleural fluid ADA, negative fluid cytology, and high doubt of malignancy [31].

Table 5 compares the cutoff value taken for ADA in a few earlier studies with ours, and the sensitivity, specificity, positive predictive value, and negative predictive value for each. The mean ADA values for tuberculous effusions in these studies are also shown.

CONCLUSION

The mean ADA values were considerably higher in TPEs when compared to the non-tuberculous group. At the cutoff value of 50.7 U/L, ADA had a sensitivity of 87% and specificity of 74% in diagnosing TB. When this was combined with pleural fluid lymphocyte dominancy, the specificity increased to 96%. The low negative predictive value may be due to the high prevalence of the disease. Pleural fluid ADA values have a strong association with age in our study population. Assessment of ADA level in pleural fluid is exceedingly useful in establishing the cause of tubercular pleural effusion and excluding various other diagnoses, especially malignancy. ADA estimation is a simple, cost-efficient, and diagnostically helpful investigation with high reliability.

LIMITATION OF STUDY

The number of patients studied is small. A huge number of patients are necessary to validate our findings further and establish the definitive criteria.

AUTHOR'S CONTRIBUTIONS

All authors; Dr. Bibhu Prasad Behera, Dr. Manoranjan Dash, and Dr. Gopal Krushna Sahu contributed equally making the design of the study, data collection, statistical study, analysis of data, data interpretation, and manuscript writing. The corresponding author is Dr. Bibhu Prasad Behera.

CONFLICTS OF INTEREST

None.

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