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Diagnostic value of serum ADA level in extra pulmonary tuberculosis cases in a tertiary care hospital, Bihar

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Abstract--Travelling through time, space and history if there is one disease which always comes to our mind is tuberculosis (TB). Still on many occasions it remains undiagnosed and hence not treated appropriately. In many instances patient is not able to give proper sputum sample or in a way it should be. On the top of it in resource poor countries availability of health care professionals is an issue to examine the sputum. Furthermore, when extra pulmonary TB is the case invasive diagnostic procedures such as biopsy becomes important which is a challenging thing to perform in many of our setups in our state. So, the aim of this study was to investigate the diagnostic value of ADA in extra pulmonary TB. Methods: It is an analytical study in which serum ADA values in EPTB cases were compared with controls. 100 patients matched for age and sex were included. Data analysis was done using SPSS version 27. Results: Our data analysis showed mean ADA levels in EPTB patients was 43.6 which was significantly higher than control group (p value <0.001). Conclusion: According to our analysis serum ADA can be a valuable

addition in the diagnosis of EPTB cases. Its diagnostic specificity would increase if the cut off value increases.

Keywords---Extrapulmonary tuberculosis, Serum Adenosine deaminase, Diagnosis

Introduction

Background

Tuberculosis is caused by *Mycobacterium tuberculosis*. In our fight with TB the world has confronted the pain of their own unspeakable loss. Every year about 10 million people fall ill with tuberculosis (TB). One of the hardest things that we health care professionals face is that although it is a preventable and curable disease, 1.5 million people die from TB each year as it overwhelms the poorest of the souls in developing countries. This makes tuberculosis world's topmost infectious disease killer. An estimated 9.9 million people confronted TB worldwide in 2020.[1]

Most of the victims of tuberculosis can be traced to 8 developing nations: India, Bangladesh, Pakistan, Nigeria, Indonesia, Philippines South Africa and China[2]. TB has always been an important public health challenge in India.

When TB is bacteriologically confirmed or clinically diagnosed in other parts of the body other than the lung such as the peritoneum, , genitourinary tract, joints, bones, meninges, lymph nodes and skin it is classified as extrapulmonary tuberculosis (EPTB). The prevalence of EPTB among new and relapse TB cases globally in 2016 was 15%. [3] Adenosine Deaminase(ADA) is an enzyme of purine nucleotide metabolism.It deaminates adenine to inosine. It has been shown that mycobacterial antigen stimulates production of ADA in lymphocytes and monocytes. ADA is required for differentiation as well as proliferation of these cells.Limited studies are available for the utility of ADA estimation in serum for the diagnosis of EPTB [4,5].

ADA is a significant indicator of active cellular immunity. It increases in biological fluids in the course of infectious disease characterized by micro-organisms infecting the macrophages.

The method to diagnose EPTB has always been an invasive strategy as it either involves taking out serositis fluid for examination and or doing biopsy of the involved part followed by cytopathology. Furthermore most of the previous researches on ADA estimation were mostly done on serositis fluid and not in serum. Data involving estimation of ADA in serum, its sensitivity and specificity have been conflicting in earlier researches. So, the need of the hour is to do further comprehensive research on this topic and arrive at a consensus regarding the usefulness and value of ADA in serum in cases of extrapulmonary TB.

Objectives

The aim of this study is to investigate the diagnostic value of serum ADA level in extra pulmonary TB.

Study Design

This prospective cross-sectional study was carried out in IGIMS, PATNA in the immunology and tuberculosis lab of IGIMS, Patna in between June 2020 to May 2021. A total of 100 patients with pathology, smear, culture or Xene Expert-based diagnosis of extra pulmonary TB were enrolled in this study. Exclusion criteria included:

Patients who had lung cancer in addition to TB, those with other respiratory tract infections, or immunocompromised patients.

In this study, other group (100 healthy controls), matched for age and sex, were also included. After obtaining informed consent, 3 mL of blood sample were collected in aseptic conditions from each participant and immediately sent to the laboratory to separate the serum. In the laboratory ADA levels were determined using Biogenix Adenosine Deaminase assay kit (BIOGENIX Inc. Pvt. Ltd., India) by enzymatic kinetic method on Semi-automated clinical chemistry analyzer with flow-through cell *Photometer 5010 v5+*

Ethics Considerations

Prior ethical approval was taken from the Institutional Ethics Committee (IEC), Indra Gandhi Institute of Medical Sciences (IGIMS), Patna vide letter no.1609 /IEC/IGIMS/2020 dated 17/06/2020.

Statistical Analysis

In this study, SPSS software version 27 was used for data analysis. Chi-square test was used for qualitative variables. To determine the diagnostic value of serum ADA activity, the ROC (receiver operator characteristic) curve method was used. ANOVA was also used to compare the groups for quantitative variables. In this test, the *P-value* greater than 0.05 contributes to normal distribution of data. The homogeneity of the data was tested using homogeneity of variances or the Levine's test. In this test, the *P* value greater than 0.05 indicates the homogeneity of data.

Results

In the TB group 60 males and 40 females and in the control group 59 males and 41 females participated. Age groups are shown in Figures 1.

The distribution of data was normal in all the study groups (*P* value was 0.2, 0.221, for the control and TB groups, respectively) (Table 1). Homogeneity of variances test showed that the data were not homogeneous ($P < 0.001$). ANOVA test showed a significant difference between the groups ($P < 0.001$). ANOVA results are shown in Table 2.

Pearson correlation coefficient was applied between the age and the ADA levels in each group. The results are shown in Table 3. As shown in Table 3, no significant correlation was found between age and the ADA level in the groups. The sensitivity and specificity of statistical analysis was tested using ROC curve method . (Results are shown in Table 3 and Figure 3). According to the curve coordinates, If ADA cut off point was equal to 14, 97% sensitivity and 88% specificity could be observed, and if it was equal to 21, the sensitivity and specificity would be 57% and 100%, respectively.

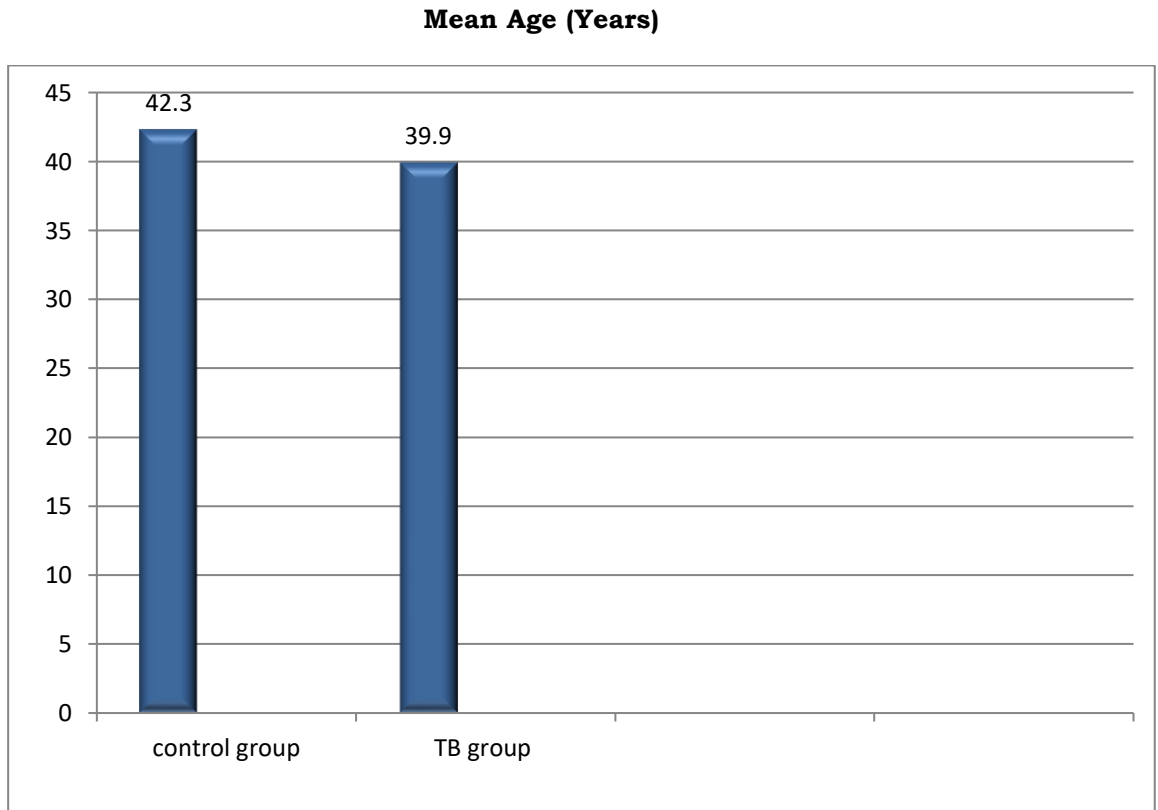
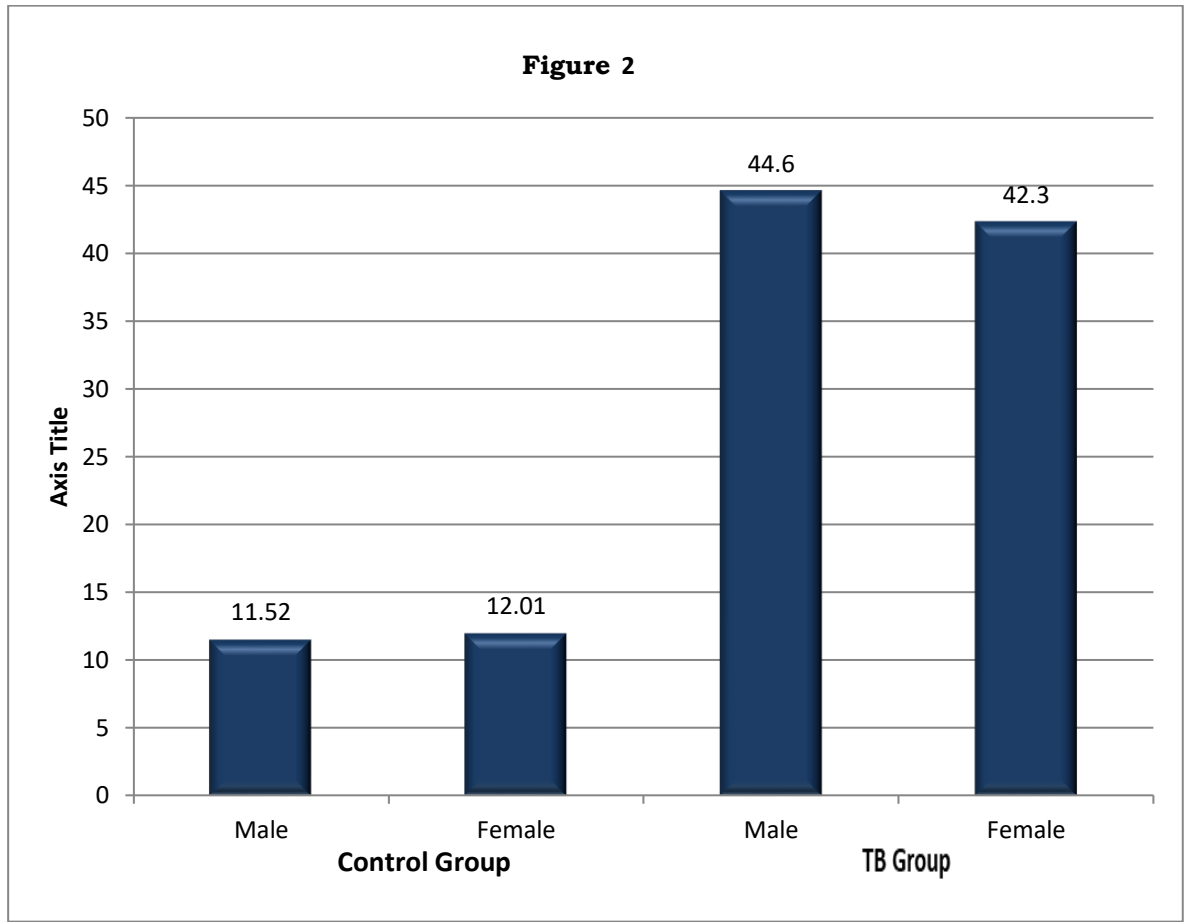


Figure- 1. Mean Age Of The Patients in control and TB groups



Mean serum ADA Levels in the study. Groups shown based on Sex

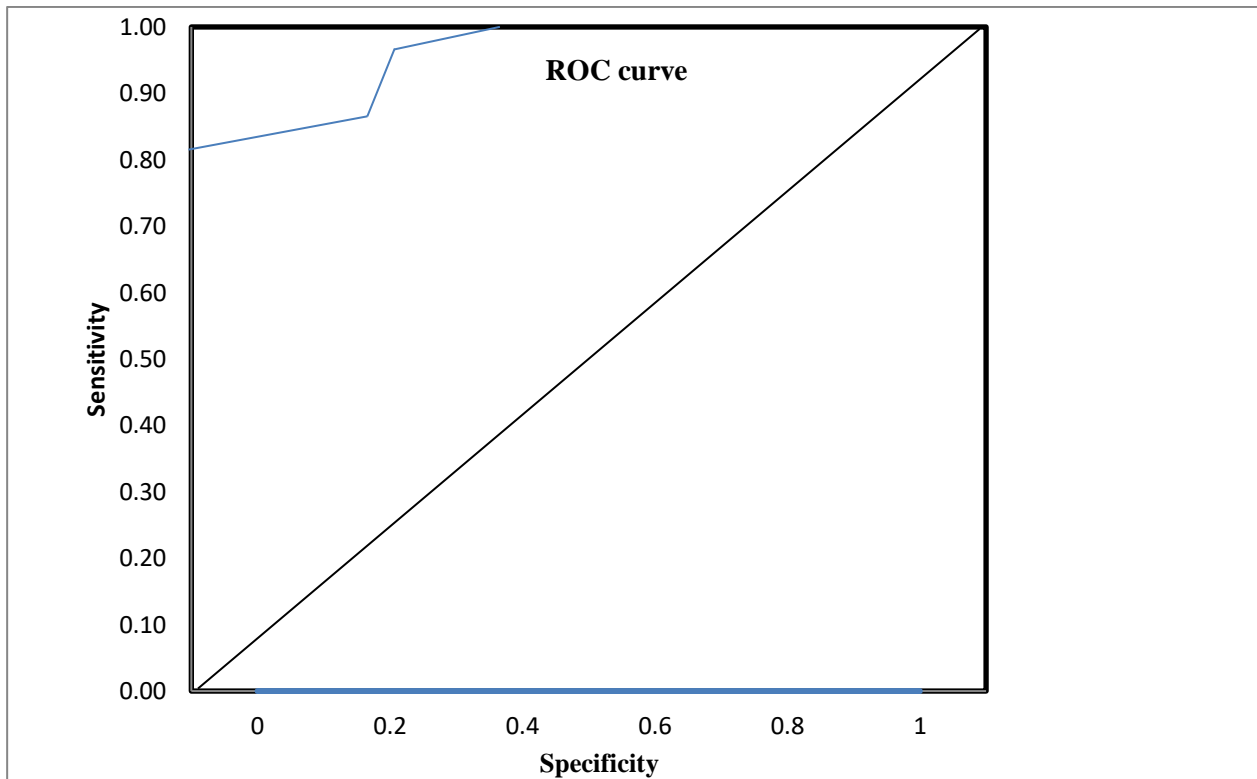


Figure 03.Sensitivity and specificity of ADA in the Diagnosis of Extra pulmonary TB

Table- 1
Comparison of Mean Serum Levels of ADA among the Study Groups

Groups	Descriptive				
	Mean	Variance	SD	Min	Max
Control	11.76	8.6	2.8	5	14
T.B	43.60	101.19	9.9	12	52

Table-2
ANOVA test among the study groups

ANOVA	Changes	Df	Mean square	Test	P Value
Intergroups	3610.72	2	1780.88		
Within groups	7301.46	118	66.04	29.97	0.000
Total	11833.08	120	-		

Table-3
The Correlation Coefficient Between Age and the ADA level Among the Study Groups

Age	Correlation	P Value
Control Groups	0.075	0.664
TB Groups	0.07	0.814

Discussion

There have been conflicting results about the usefulness of ADA in the diagnosis of extra pulmonary TB [2-11]. Our study has been successful to a great extent in establishing the usefulness of ADA in this regard and in arriving at a consensus regarding the value and sensitivity and specificity of ADA in diagnosing extra pulmonary TB. In our study the value of ADA in cases of Extra pulmonary TB was much higher than the control group. There are very few literatures about the usefulness and value of serum ADA in extra pulmonary TB and most are on serositis fluids like pleural, peritoneal and CSF [references].

In a study by KK Mathura and *etal* on serositis fluids it was opined that ADA levels in inflammatory fluids is a useful index in the diagnosis of TB serositis with a sensitivity of 96.4% and specificity of 100%. [6]

KhanFY and *et al*, conducted a prospective study in the year 2009-2010, to determine the value of ADA and IFN- γ in pleural fluid for the diagnosis of Tubercular pleural effusion. They concluded that IFN- γ and ADA could be used as valuable parameters for the differentiation of TB from nontuberculous effusion and that IFN- γ was more sensitive and specific than ADA for TB effusion. The results for IFN- γ versus ADA were: sensitivity, 100% versus 86%, respectively; specificity, 100% versus 74%, respectively; positive predictive value, 100% versus 88.5%, respectively; and negative predictive value, 100% versus 69.7%, respectively. [7] In a retrospective study for the utility of serum ADA estimation in the diagnosis of extrapulmonary tuberculosis by Prashant Chikkahonnaiah and *etal* in the year 2017, the mean serum ADA levels in patients of TB showed significantly higher values than disease controls (other respiratory illnesses). Although, the levels of mean ADA were higher in extrapulmonary TB group (group B) as compared to pulmonary TB group (group A), it was not statistically significant. ROC showed sensitivities of 73.7% and 89.5% for group A and group B respectively at the cut-off of 17.5 and a high AUC of 0.814 and 0.945 for group A and group B respectively when compared to disease controls (group C). [8]

In an analytical study conducted by Shokrollah Salmanzadeh and *etal* in the year 2018 titled "Diagnostic Value of Serum Adenosine Deaminase Level in Extrapulmonary Tuberculosis", pulmonary tuberculosis patients were compared with two other groups of patients including lung cancer patients and healthy controls, based on national tuberculosis protocol. Based on the data analyzed in this study, the mean ADA level in the patients with extra pulmonary tuberculosis was 23.8 IU/L which was significantly higher than that in the other groups

$P < 0.001$). Mean ADA levels in lung cancer patients and in healthy subjects were 15.8 IU/L and 10.7 IU/L, respectively.[9]

However, these observations are in contrast with an earlier study by AliasgarhFarazi in the year 2013 that showed low sensitivity of serum ADA assay for differentiating TB from other respiratory illnesses and thus disapproved its utility for TB diagnosis [10]. Agarwal et al and Anil Chander in their study showed significantly higher serum ADA levels in sputum smear negative pulmonary TB patients than other lung diseases like pneumonia, pulmonary abscess, lung cancer etc.[11,12]

In a study by Imtiaz Ahmed and *etal*, in the year 2020 they concluded that, ADA level were significantly higher among extrapulmonary TB cases specially in Tubercular pleural effusion, tubercular meningitis, tubercular ascites, pott's spine and tubercular lymphadenopathy.[13]

Conclusion

Based upon the findings of this study measured levels of ADA is very useful in the diagnosis of extrapulmonary TB. Its level was significantly higher in extrapulmonary TB cases (Tubercular pleural effusion, tubercular meningitis, tubercular ascites, pott's spine tubercular lymphadenitis). Serum ADA estimation can be easily done in labs in resource poor countries like India as it is relatively easier to perform and cheap. Besides its sensitivity and specificity is comparable to other biomarkers used for other diseases.

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