Role of Serum ADA in Patients of Extra-Pulmonary Tuberculosis in a Tertiary Care Hospital of Bangladesh

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ABSTRACT

Objective: In this study our main goal is to evaluate the sensitivity and specificity of serum ADA in Extra-pulmonary tuberculosis patient.

Method: This cross-sectional descriptive type study was carried out at Medicine departments of Sir Salimullah Medical College & Mitford Hospital, Dhaka from 19th December 2016 to 18th June 2017. A total 100 patients were included in the study where detailed history was taken then thorough clinical examinations.

Results: More than one third of the patients (36.0%) had tubercular pleural effusion and 28.0% of the patients had tubercular ascites while 18.0% had tubercular meningitis, 10.0% patients had tubercular lymphadenopathy and 8.0% patients had pott's disease. Elevated serum ADA level was highest in Tubercular pleural effusion (94.4%) and lowest in tubercular lymphadenopathy (40.0%) while normal ADA level was highest in tubercular lymphadenopathy (60.0%) and lowest in Tubercular pleural effusion (5.6%). Chi-square test revealed that difference of serum ADA level and different extra-pulmonary TB was significant (p= 0.025). Also, elevated ADA level was highest in the age group 20 years and below (80.0%) and lowest among the age group above 40 years of age while normal ADA level was highest in the age group above 40 years and lowest among the age group 20 and below. Chi-square test revealed that difference of serum ADA level and age of the patients were significant (p= 0.049).

Conclusion: We can conclude that, ADA level were significantly higher among extrapulmonary TB cases specially in Tubercular pleural effusion, tubercular meningitis, tubercular ascites, pott's disease and tubercular lymphadenopathy. Serum ADA can be easily performed as the routine test in diagnosis of tuberculosis which is relatively easy, cheap, specific and sensitive biomarker in establishment of disease diagnosis.

INTRODUCTION

Tuberculosis is caused by infection with mycobacterium tuberculosis which is a part of complex organism including mycobacterium bevies and mycobacterium africanum.[1]Although TB can be fully cured with the use of appropriate drugs, the major hurdle to treatment for TB lies in the late diagnosis of the disease due to the lack of simple and cost-effective diagnostic procedures.

Although the isolation of tuberculous bacilli from clinical specimens is the gold standard for diagnosis, this is not achieved in every single patient. Chest X ray, identification of bacilli, and the histopathological detection of granulomatous lesions in addition to clinical findings generally lead to true diagnosis. Therefore, in recent years, there has been a great demand for finding new

microbiological, genetic, immunological, and biomedical diagnostic methods to diagnosis TB quickly and accurately. Measuring of adenosine deaminase activity (ADA) is a biomedical method.[2-3] It seems ADA is an index for cellular immunity[2] and previous studies have proved its value in TB diagnosis, even for assessing TB effusions.[4-5] Activity of this enzyme increases in TB patients.[5]

In this study our main goal is to evaluate the sensitivity and specificity of serum ADA in Extra-pulmonary tuberculosis patient.

OBJECTIVE

General Objective: To assess the sensitivity and specificity of serum ADA in Extra-pulmonary tuberculosis patient.

Specific Objective

- To detect serum ADA level in the patients.
- To evaluate the relationship between serum ADA level and extra- pulmonary Tuberculosis

METHODOLOGY

Study Type: This was a cross-sectional descriptive type study.

Place of the Study and Period of the Study: The study was carried out at Medicine departments of Sir Salimullah Medical College & Mitford Hospital, Dhaka from 19th December 2016 to 18th June 2017.

Study Population and Sample Size: A total 100 patients included in the study, from Medicine departments of Sir Salimullah Medical College & Mitford Hospital, hospitalized for investigation for pyrexia of unknown origin and clinically suspected TB patients. Adenosine deaminase level was measured during diagnosis of PUO.

Sampling Method: Sample of the study was selected by purposive method.

Inclusion Criteria

- Patients age more than 12 years.
- Patients with pyrexia of unknown origin (PUO) whom were suspected for extra-pulmonary tuberculosis.
- Diagnosed case of extra-pulmonary tuberculosis.
- Given informed written consent.

Procedure of Data Collection: Detailed history was taken then thorough clinical examinations were done. In all patient serum ADA, tuberculin skin test and other test on the basis of site of involvement such as for pulmonary sputum for AFB, CXR, Histopathological examination (FNAC/Biopsy), X-ray Spine, Bone, Joints, Cytological examination of effusions, ascitis, CSF, CT scan/MRI of brain (with contrast if needed), molecular test e.g. Gene Xpert was done. All these data were collected by using preformed data sheet.

Data Analysis: Data entry, quality control and data cleaning had been done following standard method. All data forms and questionnaires had been checked for errors and necessary correction had been made before data entry. Data had been entered using data entry program with built in range and consistency checks (SPSS). The prevalence rate had been determined by simple percentages. Chi-square test was used to assess comparison between different groups. A p-value <0.05 was considered statistically significant. All statistical analysis was done using SPSS software version 20.

RESULTS

In figure-1 shows age distributions of the patients where most of the patients belong to 20-40 years age group 56%, followed by 30% in 20 and below age group ,14% in above 40 age group.

In figure-2 shows gender distribution of the patients where 48% were male and 52% were female.

In figure-3 shows distribution of the respondents by Gene xpert test. More than two-third (69.0%) of the patients had Gene xpert detected tuberculosis.

In table-1 shows distribution of respondents by serum ADA level. Two-third of the patients had high level of serum ADA with mean 26.6±17.5 and range was from 5 to 80.

In table-2 shows distribution of respondents by diagnosis. More than one third of the patients (36.0%) had tubercular pleural effusion and 28.0% of the patients had tubercular ascites while 18.0% had tubercular meningitis, 10.0% patients had tubercular lymphadenopathy and 8.0% patients had pott's disease.
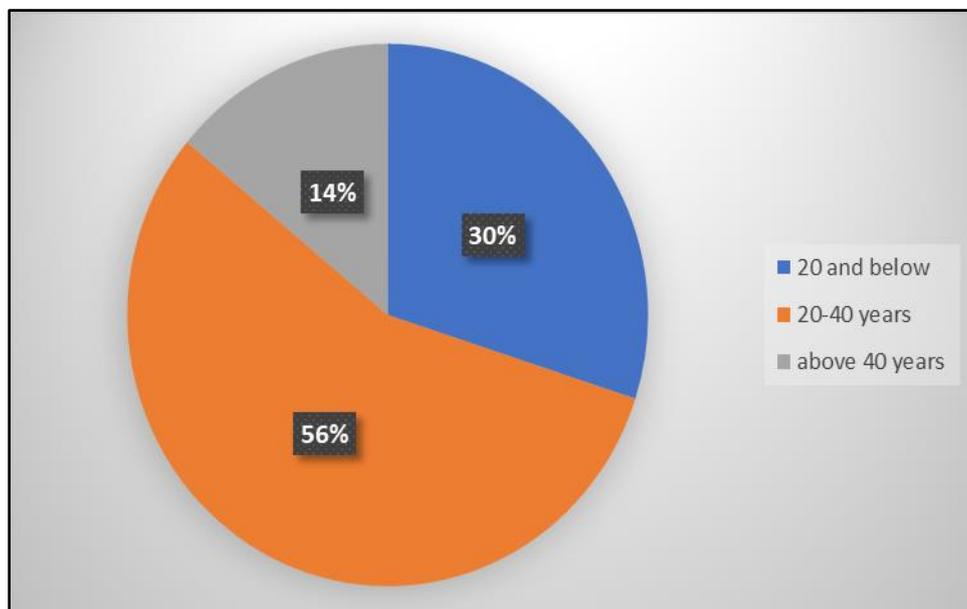

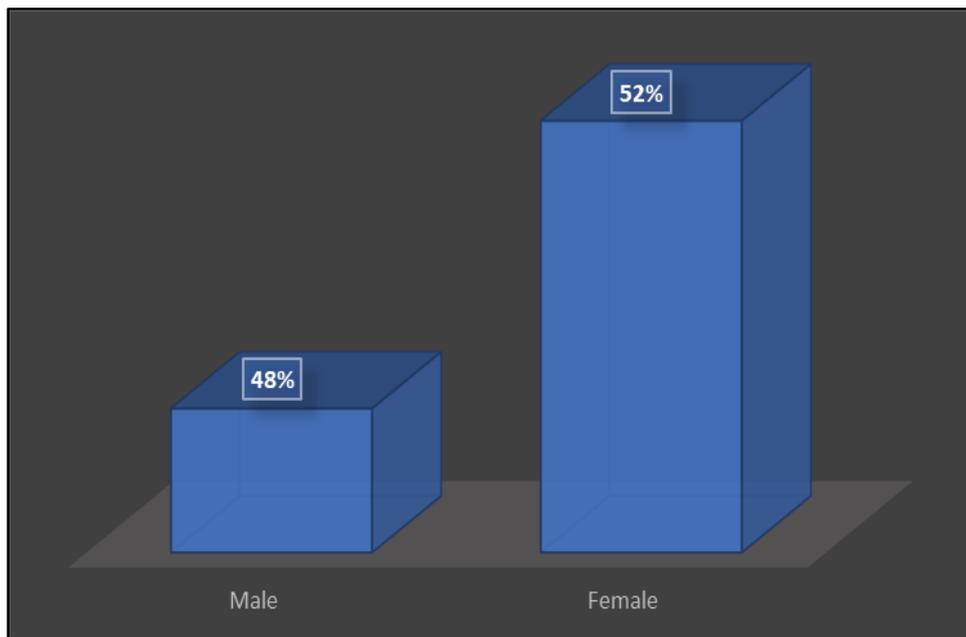**Figure 1: Age distributions of the patients.**

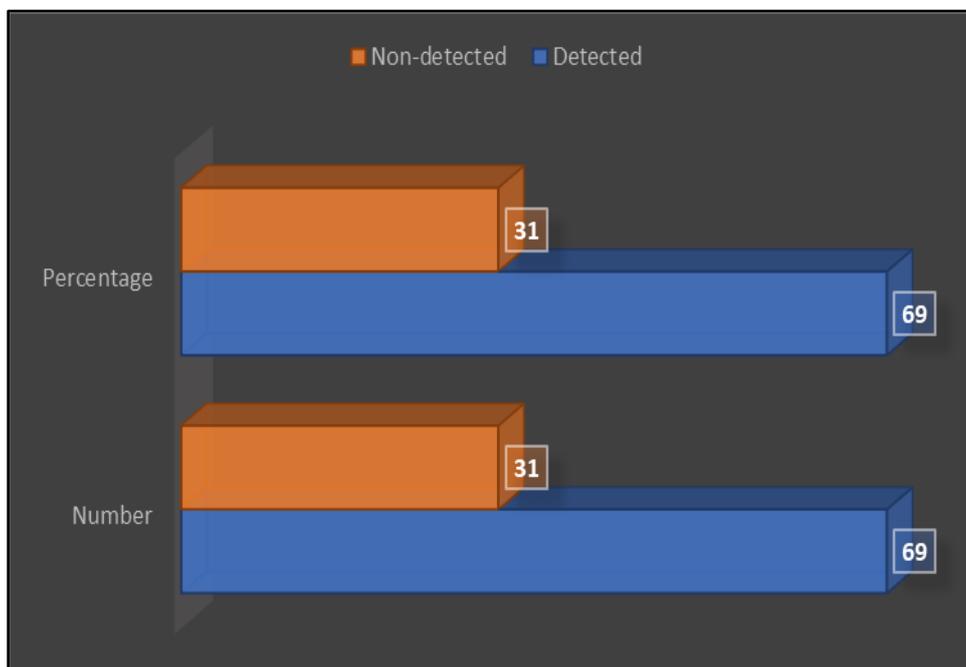**Figure 2: Gender distribution of the patients.**

Figure 3: Distribution of respondent by Gene xpert test.

In table-3 shows relationship between serum ADA level and extra-pulmonary Tuberculosis. Elevated serum ADA level was highest in Tubercular pleural effusion (94.4%) and lowest in tubercular lymphadenopathy (40.0%) while normal ADA level was highest in tubercular lymphadenopathy (60.0%) and lowest in Tubercular pleural effusion (5.6%). Chi-square test revealed that difference of serum ADA level and different extra- pulmonary TB was significant (p= 0.025).

In table-4 shows relationship between ADA level and age of the patients. Elevated ADA level was highest in the age group 20 years and below (80.0%) and lowest among the age group above 40 years of age while normal ADA level was highest in the age group above 40 years and lowest among the age group 20 and below. Chi-square test revealed that difference of serum ADA level and age of the patients were significant (p= 0.049).

In table-5 shows relationship between ADA level and gender of the patients. Above normal ADA level was higher in male (75.0%) than female (65.4%) while normal ADA level was higher in female (34.6%) than male (25.0%). Chi-square test revealed that this difference of ADA level and age of the patients were not significant (p= 0.459).

In table-6 shows relationship between ADA level and Gene Xpert of the patients. Above normal ADA level was higher in Gene xpert detected cases (94.2%) than Gene xpart negative cases (16.1%) while normal ADA level was higher in Gene xpart negative cases (83.9%) than Gene xpert detected cases (5.8%). Chi-square test revealed that this difference of ADA level and Gene xpert detection were significant (p= <0.001).

Table 1: Distribution of respondent by ADA level

Serum ADA level	n	%
Normal	30	30.0
High	70	70.0
Mean		26.6±17.5
Total	100	100.0

Table 2: Distribution of respondent by diagnosis

Diagnosis of the patient	n	%
Tubercular pleural effusion	36	36.0
Tubercular ascites	28	28.0
Tubercular meningitis	18	18.0
Tubercular lymphadenopathy	10	10.0
Pott's Disease	8	8.0
Total	100	100.0

Table 3: Relationship between serum ADA level and extra- pulmonary Tuberculosis

Diagnosis	ADA level				P value
	Normal		Elevated		
	No	%	No	%	
Tubercular pleural effusion	2	5.6	34	94.4	
Pott's Disease	4	50.0	4	50.0	
Tubercular meningitis	6	33.3	12	66.7	0.025
Tubercular ascites	12	42.9	16	57.1	
Tubercular lymphadenopathy	6	60.0	4	40.0	
Total	30	30.0	70	70.0	

Table 4: Relationship between serum ADA level and age of the patients

Age in Years	ADA level				P value
	Normal		Elevated		
	No	%	No	%	
≤ 20	6	20.0	24	80.0	
21-40	14	25.0	42	75.0	0.049
>40	10	71.4	4	28.6	
Total	30	30.0	70	70.0	

Table 5: Relationship between ADA level and gender of the patients

Gender	ADA level				P value
	Normal		Above normal		
	No	%	No	%	
Male	12	25.0	36	75.0	0.459
Female	18	34.6	34	65.4	
Total	30	30.0	70	70.0	

Table 6: Relationship between ADA level and Gene Xpert of the patients

Gene Xpert for MTB	ADA level				P value
	Normal		Above normal		
	No	%	No	%	
Detected	4	5.8	65	94.2	<0.001
Not detected	26	83.9	5	16.1	
Total	30	30.0	70	70.0	

DISCUSSION

In our study two-third of the patients (70%) had high level of ADA with mean 26.6±17.5 and range was from 5 to 80. One study first to report that high ADA in tubercular pleural effusion.[6] Meta-analysis of studies conducted between 1966 and 1999 concluded that the test performance was reasonably good (sensitivity range 47.1 - 100%, and specificity 0 - 100%) in diagnosing tuberculosis etiology in pleural effusion.[7] In a study the mean level (SD) of ADA was 83.5 ± 50.3 U/L in TPE (tubercular pleural effusion) and 28.7±23.6 U/L in MPE (Malignant pleural effusion). ADA level of the pleural fluid was significantly higher in TPE (P < 0.001).[8] Findings were not similar in a study in Gujrat where mean pleural fluid ADA levels of 54.97±23.51 U/L in TB group were statistically highly significant in comparison with NTB group as a whole as well as cardiac, hepatic, renal subgroups (p<.001).[9] In our study above normal ADA level was highest in Tubercular pleural effusion (94.4%) and lowest in tubercular lymphadenopathy (40.0%). Fisher's exact test revealed that this difference of ADA level and different extra- pulmonary TB was significant (p= 0.025).

Similar outcome was found in different studies. In a study there was significant difference in the mean rank of the level of serum ADA among the TB patients to control group. The PTB had higher mean rank (116.52) followed by EPTB (99.48) and Normal Control had significantly less mean rank (40.16) with p value 0.001.[10]

Above normal ADA level was higher in male (75.0%) than female (65.4%) while normal ADA level was higher in female (34.6%) than male (25.0%). Chi-square test revealed that this difference of ADA level and sex of the patients were not significant (p= 0.459) compared to other study similar outcome was found. The Mean Rank Serum ADA level was found higher in male of 41.82 U/L than in female of 30.81 U/L with p value of 0.037. The variation of Mean Rank Serum ADA level among male and female was not found statistically significant.[10]

Above normal ADA level was higher in Gene xpert detected cases (94.2%) than Gene xpert negative cases (16.1%) and this difference of ADA level and Gene x-pert detection were significant (p= <0.001). In one study reported that in extra-pulmonary disease, overall sensitivity was found to be 94.29%, specificity 92.16%, positive predictive value 89.00% and negative predictive value 95.92%; and in pulmonary disease, sensitivity was found to be 92.80%, specificity 90.00%, positive predictive value 92.86 % and negative predictive value 90.00% and significantly associated.[11]A serum ADA cut-off value of 15 was determined to differentiate between TBM and non-TBM, with a sensitivity of 84% and a specificity of 82%. A serum ADA value greater than the mean value of 30.28 IU/L in TBM was observed in only one case (less than 1%) out of 148 patients with BM.[12]Another study have reported a serum ADA cut-off value of 31.23 U/L associated with a sensitivity of 96% and specificity of 83% for the diagnosis of TBM from other meningitis.[13]

CONCLUSION

We can conclude that, ADA level were significantly higher among extrapulmonary TB cases specially in Tubercular pleural effusion, tubercular meningitis, tubercular ascites, pott's disease and tubercular lymphadenopathy. Serum ADA can be easily performed as the routine test in diagnosis of tuberculosis which is relatively easy, cheap, specific and sensitive biomarker in establishment of disease diagnosis.

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