Diagnostic value of pleural fluid adenosine deaminase among the patients with pleural tuberculosis

Fariborz Rousta
  Tabriz University of Medical Sciences

Mohsen Sokouti
  Tabriz University of Medical Sciences

Samad Beheshty Rouy
  Tabriz University of Medical Sciences

Sina Parsay (✉ sinaparsa91@gmail.com)
  Tabriz University of Medical Sciences   https://orcid.org/0000-0003-1013-200X

Research article

Abstract

Purpose Extra-pulmonary tuberculosis occurs in about 10-20% of patients most commonly as tuberculous lymphadenitis or pleural effusion. Pleural fluid Adenosine deaminase (ADA) activity considered as a useful biomarker for detecting pleural tuberculosis. The purpose of this study was to evaluate the diagnostic accuracy of pleural fluid adenosine deaminase level in patients with pleural tuberculosis. Methods In this cross-sectional study, 113 patients with exudative pleural effusion with unknown underlying diagnosis, were enrolled. Physical examination, chest CT, measurement of ADA level of pleural fluid, direct thoracoscopic examination, and biopsy of pleura were performed for all individuals. Results The diagnosis of tuberculous pleurisy was established in 40 individuals regarding the pathology report of biopsy samples. The mean ADA level of the TB and the non-TB group was 39.90±22.93 IU/L and 30.74±38.27 IU/L respectively, which was not statistically significant (P-value=0.167). Sensitivity, specificity, positive predictive value, and negative predictive value of ADA test were 35%, 86.30%, 58.33%, and 70.79%, respectively. Conclusion Based on low sensitivity and specificity of ADA test, in patients with unexplained exudative pleural effusion especially in those who were suspicious for tuberculous pleurisy, despite the low level of ADA, direct thoracoscopic pleural observation and multiple biopsies of pleura is highly recommended.

Background

Tuberculosis is a chronic bacterial infection caused by Mycobacterium tuberculosis. It remains as a disease with a high rate of mortality in the world especially in developing and low-income countries (1). Extra-pulmonary tuberculosis occurs in about 10% -20% of patients and the most common forms of involvement are tuberculous Lymphadenitis and tuberculous pleural effusion (2).

Pleural tuberculosis (TB) which is the topic of this study is characterized by symptoms such as chest pain, cough, and fever. Chest Radiography of these patients shows a small to moderate unilateral pleural effusion which is lymphocyte dominant in serologic evaluations. The condition also could be bilateral within the minority of cases (1, 3).

Based on epidemiologic studies in our region, the incidence of TB is differing from 16.7 to 95 cases per 100,000 with an average age of 38 years. The prevalence of tuberculosis among all patients with pleural effusion is between 4-22%, and pleura is involved in 3-23% of patients with tuberculosis. While in the developed areas, such as the United States, the overall incidence of tuberculosis is only 9.3 cases per 100,000 with a pleural involvement within less than 5% of patients (4, 5).

Different diagnostic methods have been used to diagnose pleural tuberculosis, including thoracentesis, measurement of serum and pleural fluid adenosine deaminase (ADA) level, pleural biopsy, and thoracoscopy assisted pleural examination and biopsy (3).

Measuring ADA activity in pleural fluid is an easy, inexpensive, fast and useful way for diagnosing TB in endemic areas, such as South Africa, Asia, Brazil, Spain, and Eastern Europe (6-8). Based on literature a

cut-off point of 40 U/L of ADA activity in a lymphocyte dominant pleural fluid is diagnostic for pleural TB. But the validity of the test is not generally accepted by consensus (9-11)

With the advancement in endoscopic techniques and video equipment, thoracoscopy has been suggested as a diagnostic and therapeutic modality in patients with pleural tuberculosis, and become more popular among the physicians. Thoracoscopic findings of these patients include caseous necrosis, miliary nodules, exudative pleural effusion, and pleural adhesion or fibrotic septa (12, 13).

Considering the important role of ADA in the diagnosis of pleural tuberculosis, evaluating the correlation between pleural ADA level and thoracoscopic findings of pleural tuberculosis seems necessary (14, 15).

This study aims to determine the correlation of the pleural fluid ADA activity and its diagnostic accuracy in histologically confirmed cases of pleural tuberculosis in order to reduce the use of thoracoscopy in patients with pleural effusion who represent a high ADA activity.

Methods

In this cross-sectional study, 113 patients who referred to cardiothoracic surgery department of Tabriz University of Medical Science with unexplained exudative pleural effusion throughout 18 months from March 2016 were enrolled.

The study population was measured by GPOWER software with a confidence interval of 95% and a test power of 80%.

All patients had a pleural effusion with unknown etiology and candidate for thoracoscopy and biopsy for diagnosing their underlying disorder.

The exclusion criteria were patients with transudative pleural effusion, post-traumatic effusion, known pulmonary disorders, history of pulmonary or pleural malignancies and a history of radiotherapy on the thoracic cavity.

All patients underwent a thoracoscopic study. Direct evaluation of the pleural cavity with obtaining multiple biopsies from pleura and a fluid sample for ADA analysis was performed. All specimens were analyzed by a certain pathologist and laboratory. The ADA level of pleural fluid was measured in all patients. The ADA level of greater than or equal to 40 U/L considered as diagnostic for TB.

Based on pathologic findings, patients were divided into two groups of pleural effusion due to TB and pleural effusion due to non-TB causes.

Data were analyzed by SPSS® version 22 using chi^2 and logistic regression analysis to determine the relationship between the level of pleural fluid ADA and pleural TB.

Ethical Consideration

The study was approved by the ethics committee of Tabriz University of Medical Science under the approval number of 5/d/8716-94/5-6/3. All diagnostic and therapeutic interventions were performed regarding the routine management of patients; no additional intervention or cost was imposed on participants in this study. Patients' data were recorded as encoded variables without mentioning the name of any participant. None of the patients' personal information was included in this research.

Informed consent was obtained from each participant; nevertheless, patients were excluded from the study in cases which the patient was not willing to participate in the study.

Results

From the total of 113 patients enrolled in this study, 73 (58.4%) were male, and 40 (32.0%) were female. Among them 42 (33.6%) individuals were smokers. The mean age of the patients was 49.77 ± 18.71 years. The mean ADA level was measured 33.98 ± 33.63 within the study population.

According to the histopathologic reports of the biopsy specimens, the diagnosis of TB was confirmed in 40 patients. These patients were evaluated as the case group (known as group A), and the other 73 with a diagnosis of non-tuberculous pleural effusion were considered as the control group (known as group B).

Dyspnea, Cough, and pleuritic chest pain with a frequency of 66.37%, 48.67% and 40.7% respectively, were the most dominant symptoms of patients at the time of admission following by fever and weight loss with a frequency of 30.97%, and 28.31%, respectively.

Table-1 demonstrates demographic data of individuals separately for each study groups.

Regarding the thoracoscopic examination, pleural effusion, plural adhesion bond, miliary nodules, and caseous necrosis were found in 100%, 67.5%, 70%, and 60%, of patients in group A respectively (Table-2).

Among the control group (group B), pleural effusions, thickening of pleura and miliary nodules were the dominant manifestations with a frequency of 100%, 46.57%, and 30.13% respectively (Table-2).

The underlying cause of pleural effusion among the patients in control group was: metastasis (23.28%), mesothelioma (5.47%), inflammation (32.87%), fibrosis (36.98%), and fungal infection (1. 36%) as shown in Table-2.

The mean ADA level in case group was 39.90 ± 22.13 IU/L. Meanwhile, the measured amounts of ADA in the control group were 30.74 ± 38.27 IU/L. The difference of ADA level between these two groups of patients showed a p-value of 0.167 hence, considered as statistically insignificant.

Table-3 demonstrates the frequency of individuals in each studied group with ADA level of greater than 40 (as a diagnostic cut-off for TB). Bar chart for these amounts also shown in figure-1.

Also, sensitivity, specificity, positive predictive value and negative predictive value of ADA test were measured 35%, 86.30%, 58.33%, and 70.79% respectively (Table-4). The ROC curve of ADA test measures

shown in Figure-2.

Discussion

Tuberculous pleurisy is the result of a delayed hypersensitivity reaction to Mycobacterium tuberculosis bacilli (8).

Nowadays, obtaining thoracoscopic biopsies of pleura is the modality of choice for diagnosing tuberculous pleurisy between the majority of physicians. But, this procedure is invasive and has its own risks and dangers. So that, finding an alternative diagnostic method which is minimally invasive and safer with the same accuracy seems to be necessary (16, 17).

Adenosine deaminase (ADA) is known as a useful biomarker, especially for detecting tuberculosis in endemic areas (18-20). Initially, in the 1970s, it was introduced as a serologic biomarker for detecting lung cancer. After that, Perez et al. demonstrated the usefulness of ADA in diagnosing of tuberculous pleurisy (3, 21). An ADA level of greater than 40 IU/L in a lymphocyte dominant pleural fluid is generally acceptable for diagnosing pleural TB (9, 11). Also, several studies have been conducted in patients with non-tuberculous lymphocytic pleural effusion, among them, ADA levels exceeding 40 U/L detected in less than 3% of cases (11, 22, 23).

Technically, the predictive value of an indicator such as ADA does not only depend on its sensitivity and specificity, but also the incidence of the disease in the study region is also effective and in areas with high prevalence of disease, the positive predictive value increases. The high prevalence of pleural tuberculosis in patients with pleural effusion in our region suggests that the ADA level of the pleural fluid may have a higher predictive value based on the previous studies (8, 9, 11, 15, 24, 25).

In this study, 113 patients (73 males and 40 females) with unexplained pleural effusion were evaluated for probable pleural tuberculosis by using thoracoscopic examination and biopsy. Meanwhile, the ADA level was measured for all individuals regardless of pathologic findings. The diagnosis of pleural TB established only in 40 individuals according to the histopathologic reports. The ADA level among these tuberculous pleurisy patients was 39.90 ± 22.13 IU/L compared to a level of 30.74 ± 38.27 IU/L in non-tuberculous individuals, which was not statistically significant. Based on our results, the ADA test yield a sensitivity, specificity, positive predictive value and negative predictive value of 35%, 86.30%, 58.33%, and 70.79% respectively.

In a study performed by Van et al., the causes of pleural effusion were evaluated among 95 patients in Netherland. According to their results, they have found tuberculous pleurisy just in five patients, among them the high ADA activity was only detected in four individuals. On the other hand, the underlying pathologies other than TB could raise the ADA activity based on their study. The authors conclude that the high ADA activity level in a country with low tuberculosis incidence is not accurate enough to establish the diagnosis of tuberculous pleurisy (26).

Tian et al. found a sensitivity and specificity of 84.4% and 91.8% for ADA in diagnosing tuberculous pleurisy by evaluating 190 patients with pleural effusion. The cause of pleural effusion was TB in 141 patients of their study population (27).

The difference between the results of our study compared to the recently mentioned research is explainable by the high overall incidence of TB in the country in which Tian et al., performed their study.

Valdes et al., in their study revealed that measuring pleural ADA level is a useful parameter for the diagnosis of tuberculous pleurisy by evaluating 405 patients with pleural effusion. All 91 cases of pleural TB in their study showed an ADA level of greater than 47 IU/L, compared to the elevation just in 5% of non-tuberculous patients (14).

Zemlin et al. demonstrated that measuring the ADA_2 isoenzyme is more accurate and it is superior to ADA in diagnosing tuberculous pleurisy by performing a study on 951 pleural fluid samples, including 387 patients with TB. They suggested that measuring ADA_2 level is better to use as a routine test among patients with pleural effusion in endemic areas for TB (11).

The inconsistency between the results is due to the variable prevalence of TB and different sample sizes in which mentioned studies were performed.

List Of Abbreviations

ADA: Adenosine deaminase

CT: Computerized Tomography

TB: Tuberculosis

SPSS: Statistical Package for the Social Science (Software)

ROC-Curve: Receiver Operating Characteristic Curve

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Tabriz University of Medical Science under the registration number of 5/d/8716-94/5-6/3.

Consent for Publication

A written informed consent was obtained from each participant. patients were excluded from the study in cases which they were not willing to participate in the study.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

Authors' contributions

F.R., M.S., S.B.R. and S.P. conceived of the presented idea. F.R. and M.S. diagnosed the disease and selected the patients. F.R., M.S. and S.B.R. provided the management methods, F.R. and S.P. collected the data sets, S.P. acquired additional data from the database. F.R. and S.P. wrote the manuscript. S.P. analyzed the data, M.S. and S.B.R. made a revision on the manuscript. M.S. supervised the whole project.

Acknowledgments

References

1. Celik G, Kaya A, Poyraz B, Ciledag A, Elhan A, Oektem A, et al. Diagnostic value of leptin in tuberculous pleural effusions. 2006;60(11):1437-42.

2. Valdes L, Alvarez D, San Jose E, Juanatey J, Pose A, Valle JM, et al. Value of adenosine deaminase in the diagnosis of tuberculous pleural effusions in young patients in a region of high prevalence of tuberculosis. 1995;50(6):600-3.

3. Blanco Vaca F Fau - Mayos Perez M, Mayos Perez M Fau - Perez Dominguez C, Perez Dominguez C Fau - Gomez Gerique JA, Gomez Gerique Ja Fau - Rubio Gil J, Rubio Gil J Fau - Cornudella Mir R,

Cornudella Mir R Fau - Gonzalez Sastre F, et al. [Analysis of adenosine deaminase and its subfractions as a diagnostic parameter in tuberculous pleural effusion]. (0014-2565 (Print)).

4. Mardanian S, Sarkisova E, Andreasian N, Badalian L, Khanoian A, Sagoian I, et al. Activity of pleural fluid adenosine deaminase in tuberculous pleurisy. 2002(2):37-9.

5. Moosazadeh M, Nasehi M, Bahrampour A, Khanjani N, Sharafi S, Ahmadi SJIRCMJ. Forecasting tuberculosis incidence in iran using box-jenkins models. 2014;16(5).

6. Krenke R, Safianowska A, Paplinska M, Nasilowski J, Dmowska-Sobstyl B, Bogacka-Zatorska E, et al. Pleural fluid adenosine deaminase and interferon gamma as diagnostic tools in tuberculosis pleurisy. 2008;59(Suppl 6):349-60.

7. Castro DJ, Nuevo GD, Perez-Rodriguez E, Light RJERJ. Diagnostic value of adenosine deaminase in nontuberculous lymphocytic pleural effusions. 2003;21(2):220-4.

8. Smach M, Garouch A, Charfeddine B, Ben AA, Dridi H, Krayem B, et al., editors. Diagnostic value of serum and pleural fluid adenosine deaminase activity in tuberculous pleurisy. Annales de biologie clinique; 2006.

9. Khow-ean N, Booraphun S, Aekphachaisawat N, Sawanyawisuth KJSAJoTM, Health P. Adenosine deaminase activity level as a tool for diagnosing tuberculous pleural effusion. 2013;44(4):655.

10. Shibagaki T, Hasegawa Y, Saito H, Yamori S, Shimokata KJTR. Adenosine deaminase isozymes in tuberculous pleural effusion. 1996;127(4):348-52.

11. Zemlin A, Burgess L, Carstens MJTIJoT, Disease L. The diagnostic utility of adenosine deaminase isoenzymes in tuberculous pleural effusions. 2009;13(2):214-20.

12. Safianowska A, Krenke R, Dmowska-Sobstyl B, Bogacka-Zatorska E, Domagała-Kulawik J, Chazan RJAiRM. Adenosine deaminase activity in tuberculous and malignant pleural effusions. 2006;74(1):5-9.

13. Sakuraba M, Masuda K, Hebisawa AJATcs. Article Pleural Effusion Adenosine Deaminase (ADA) Level and Occult Tuberculous Pleurisy. 2009;15(5):295.

14. Valdés L, San José E, Alvarez D, Sarandeses A, Pose A, Chomón B, et al. Diagnosis of tuberculous pleurisy using the biologic parameters adenosine deaminase, lysozyme, and interferon gamma. 1993;103(2):458-65.

15. Andreasyan NA, Hairapetian HL, Sargisova YG, Mardanyan SS, Badalyan LT, Khanoyan ASJMSM. Activity of adenosine deaminase and its isoforms in pleural fluid in tuberculous pleuritis. 2002;8(10):CR708-CR12.

16. Koegelenberg CF, Diacon AHJR. Pleural controversy: Closed needle pleural biopsy or thoracoscopy—Which first? 2011;16(5):738-46.

17. Haridas N, Suraj K, Rajagopal T, James P, Chetambath RJJoc, JCDR dr. Medical thoracoscopy vs closed pleural biopsy in pleural effusions: a randomized controlled study. 2014;8(5):MC01.

18. Carstens M, Burgess L, Maritz F, Taljaard JJTIJoT, Disease L. Isoenzymes of adenosine deaminase in pleural effusions: a diagnostic tool? 1998;2(10):831-5.

19. Atalay F, Ernam D, Hasanoglu HC, Karalezli A, Kaplan ÖJCb. Pleural adenosine deaminase in the separation of transudative and exudative pleural effusions. 2005;38(12):1066-70.

20. Titarenko O, D'iakova M, Perova T, D'iakova A, Popov MJKld. Informative value of adenosine deaminase and 2-deoxyadenosine deaminase in the diagnosis of tuberculous pleurisy. 2002(5):11-4.

21. de Oteyza Pérez C, Chantres M, Rebollar J, Muñoz MY, García FM, Pérez MB, et al., editors. Adenosine deaminase in pleural effusions. Its usefulness in the diagnosis of tuberculous pleurisy. Anales de medicina interna (Madrid, Spain: 1984); 1989.

22. Wang H, Yue J, Yang J, Gao R, Liu JJH, Acute LTJo, et al. Clinical diagnostic utility of adenosine deaminase, interferon-γ, interferon-γ—induced protein of 10 kDa, and dipeptidyl peptidase 4 levels in tuberculous pleural effusions. 2012;41(1):70-5.

23. Krenke R, Korczynski PJCoipm. Use of pleural fluid levels of adenosine deaminase and interferon gamma in the diagnosis of tuberculous pleuritis. 2010;16(4):367-75.

24. Xu H, Jiang R, Li L, Sha W, Xiao HJTIJoT, Disease L. Diagnostic value of adenosine deaminase in cerebrospinal fluid for tuberculous meningitis: a meta-analysis. 2010;14(11):1382-7.

25. Chen M-L, Yu W-C, Lam C-W, Au K-M, Kong F-Y, Chan AY-WJCca. Diagnostic value of pleural fluid adenosine deaminase activity in tuberculous pleurisy. 2004;341(1-2):101-7.

26. Slaats E, Wagenaar JJEjord. Adenosine deaminase activity, not diagnostic for tuberculous pleurisy. 1987;71(1):15-8.

27. Tian R, Gao ZJZjhhhxzzZjhhzCjot, diseases r. Clinical investigation of the diagnostic value of interferon-gamma, interleukin-12 and adenosine deaminase isoenzyme in tuberculous pleurisy. 2004;27(7):435-8.

Tables

Table-1. Demographic data of studied individuals

P-value	Total	In Group B	In Group A		
-	113	73	40	Number of Patients	
0.006	49.77 ± 18.71	53.31 ± 18.61	43.32 ± 17.31	Age (years)	
0.453	73	49	24	Male	Gender
	40	24	16	Female	
0.957	42	28	14	Yes	Smoking
	71	45	26	No	
0.045	55 (48.6%)	25 (34.2%)	30 (75%)	Cough	Signs and Symptoms
0.000	46 (40.7%)	10 (13.7%)	36 (90%)	Pleuritic Chest Pain	
0.19	75 (66.3%)	36 (49.3%)	39 (97.5%)	Dyspnea	
0.000	32 (28.3%)	25 (34.2%)	7 (17.5%)	Weight Loss	
0.036	35 (30.9%)	15 (20.5%)	20 (50%)	Fever	

Table-2. Surgical and paraclinical findings of patients

Total	In Group B	In Group A		
113	73	40	Number of Patients	
113 (100%)	73 (100%)	40 (100%)	Pleural Effusion	CT-Scan Findings
39 (34.5%)	22 (30.!%)	17 (42.5%)	Pleural Effusion + Pleural Thickening	
113 (100%)	73 (100%)	40 (100%)	Pleural Effusion	Thoracoscopic Findings
1 (1.3%)	0 (0.0%)	1 (2.5%)	Solitary Nodule	
50 (44.2%)	22 (30.1%)	28 (70%)	Miliary Nodules	
24 (21.2%)	0 (0.0%)	24 (60%)	Caseous Necrosis	
27 (23.9%)	0 (0.0%)	27 (67.5%)	Adhesion Bonds	
46 (40.7%)	34 (46.5%)	12 (30%)	Pleural Thickening	
7 (6.2%)	0 (0.0%)	7 (17.5%)	Edema	
40 (35.4%)	0 (0.0%)	40 (100%)	Tuberculosis	Histologically Confirmed Diagnosis
17 (15%)	17 (23.2%)	0 (0.0%)	Metastasis	
4 (3.5%)	4 (5.4%)	0 (0.0%)	Mesothelioma	
24 (21.2%)	24 (32.8%)	0 (0.0%)	Inflammatory	
27 (23.9%)	27 (36.9%)	0 (0.0%)	Fibrosis	
1 (0.8%)	1 (1.3%)	0 (0.0%)	Fungal Infection	

Table-3. Measured ADA level of the patients

P-value	Total	In Group B	In Group A	ADA Level
0.993	24 (21.2%)	10 (13.7%)	14 (35%)	≥ 40
	89 (78.7%)	63 (86.3%)	26 (65%)	< 40

Table-4. Characteristics of the ADA test and its diagnostic power for diagnosing TB (CI: Confidence Interval, TB: Tuberculosis)

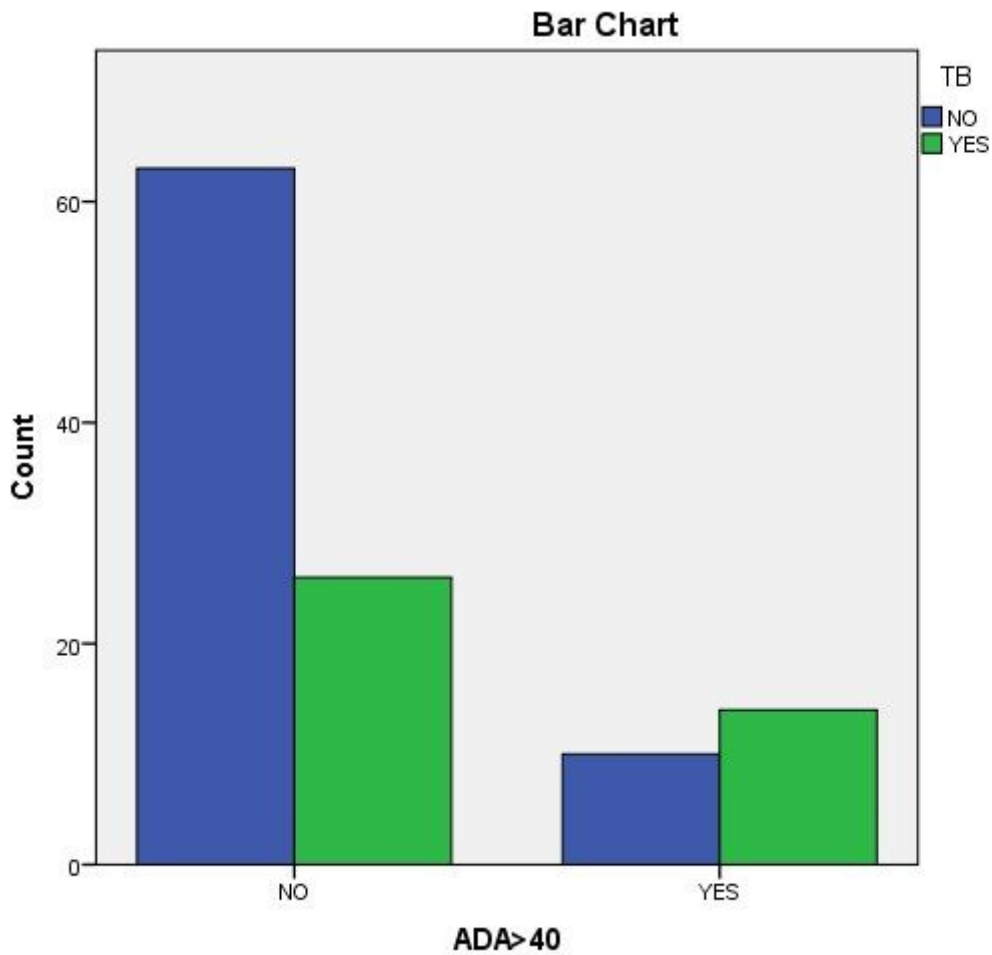|	Value	95% CI
Sensitivity	35.00%	20.63% to 51.68%
Specificity	86.30%	76.25% to 93.23%
Positive Predictive Value	58.33%	40.67% to 74.4.09%
Negative Predictive Value	73.00%	65.47% to 75.59%

Figures

Figure 1

Frequency of patients with ADA activity level of greater than 40 in each TB-positive and TB-Negative groups (ADA: Adenosine deaminase, TB: Tuberculosis)
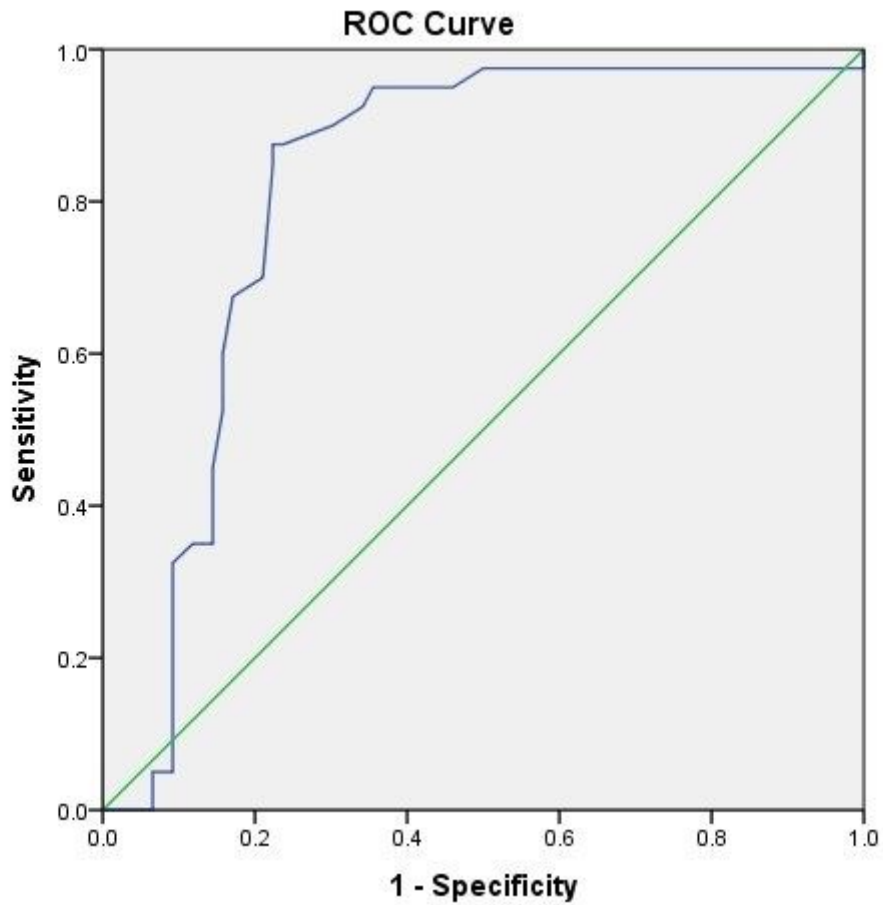
Figure 2

ROC curve for sensitivity and specificity of ADA biomarker (ADA: Adenosine deaminase)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.doc