

DIAGNOSTIC ACCURACY OF PLEURAL FLUID ADENOSINE DEAMINASE IN PATIENTS WITH TUBERCULOUS PLEURAL EFFUSION KEEPING CLOSED PLEURAL BIOPSY AS A GOLD STANDARD

Ziaullah*, Sajjad Ali*, Muhammad Rafiq*, Saeed Khan*, Anila Basit*,
Zafar Iqbal*, Muhammad Yousaf Khan*, Arshad Javaid*

* Department of Pulmonology,
Post Graduate Medical
Institute, Lady Reading
Hospital Peshawar, Pakistan

Address for correspondence:

Dr. Ziaullah,

Department of Pulmonology,
Post Graduate Medical
Institute, Lady Reading
Hospital Peshawar, Pakistan
E-mail: drzia02@gmail.com

BACKGROUND AND OBJECTIVE: Tuberculosis (TB) and malignancy are the most common causes of exudative pleural effusion, which usually has lymphocytic and exudative characteristics. Adenosine Deaminase (ADA) is a useful biochemical marker for the diagnosis of tuberculous pleural effusion (TPE). The aim of this study was to determine the diagnostic accuracy of pleural fluid ADA in patients with tuberculous pleural effusion while keeping pleural biopsy as a gold standard.

STUDY DESIGN, PLACE AND DURATION: It was a Cross-sectional (validation) study conducted in Pulmonology Department, Post Graduate Medical Institute, Lady Reading Hospital (PGMI/LRH), Peshawar, from March 28, 2011 to September, 27 2011.

MATERIALS AND METHODS: All the patients with pleural effusion fulfilling inclusion criteria were subjected to thoracentesis and Abrams needle biopsy. Pleural fluid was sent to laboratory for measurement of ADA using commercially available ADA kit DIAZYME (Diazyme laboratories Poway, CA 92064, USA) while pleural tissue was sent for histopathological examination. All the investigations were performed by the laboratory to avoid any observer bias.

Results: Out of 144 patients 84 (58.3%) were males and 60 (41.7%) were females. Mean age was 47.21 ± 17.85 SD years. In 84 (58.3%) patients, pleural biopsy was suggestive of tuberculosis. In biopsy proven tuberculous pleural effusion (TPE) pleural fluid ADA ranged from 20-130 U/L with mean pleural fluid ADA level of 53.93 ± 16.12 U/L. In non TB pleural effusion (NTPE), pleural fluid ADA ranged from 10-75 U/L with mean pleural fluid ADA level of 33.25 ± 14.65 U/L. Taking pleural biopsy as gold standard and taking ADA level > 40 U/L as cut off value, the sensitivity, specificity, PPV and NPV of pleural fluid ADA level in the diagnosis of TPE were 90.47% , 76.66%, 84.44% and 85.18% respectively.

CONCLUSION: In appropriate clinical setting pleural fluid ADA level is a useful biochemical marker which aids in the diagnosis of Tuberculous pleural effusion.

KEY WORDS: Tuberculous Pleural Effusion; Pleural Biopsy; Pleural Fluid ADA.

This Article may be cited as: Ullah Z, Ali S, Rafiq M, Khan S, Basit A, Iqbal Z, Khan MY, Javaid A. Diagnostic accuracy of pleural fluid adenosine deaminase in patients with tuberculous pleural effusion keeping closed pleural biopsy as a gold standard. Pak J Chest Med 2015; 21(2): 47-53

INTRODUCTION

Pleural effusion is a common problem and presents a significant contribution to the respiratory physician workload. It is an extrapulmonary manifestation of tuberculosis. It has been reported that in around 25% of patients the TB will

manifest itself with involvement of either pleura or lymph node.¹ Pleural involvement in TB patient is higher in developing countries constituting 30% cases as compared to European countries which accounts for 3-5% cases.^{2,3} The prevalence of TB pleural effusion in Pakistan is about 56.6%.⁴⁻⁶

Diagnostic workup of pleural effusion includes detailed clinical examination, chest x-ray, pleural fluid analysis and closed pleural biopsy. The pleural fluid in tuberculous pleural effusion is lymphocytic and exudate in nature. Apart from TB, the lymphocytic and exudative pleural effusion has diverse etiology that includes malignancy as one of the most common cause. Diagnostic yield of pleural biopsy is about 60-80% in all cases of pleural effusion, and 60-95% in TB pleural effusion.⁷⁻¹¹ In regions with a high burden of tuberculosis, pleural biopsy demonstrating a granulomatous inflammation is used for diagnosis of TB since other granulomatous diseases such as sarcoidosis, mycosis and rheumatoid arthritis account for less than 10% of granulomatous findings in the pleura.¹²

In developed countries, many investigations are available to differentiate tuberculous from malignant and other non TB effusions. They are Adenosine deaminase, interferon, lysozymes, the polymerase chain reaction and other specific antibodies.¹³⁻¹⁷ The closed pleural biopsy is almost obsolete there because of low sensitivity and specificity. Where indicated, pleural biopsy is taken under direct vision using video assisted thoracoscopy.¹⁸ However, the tests mentioned above need specific and / or expensive equipment that are not available in most laboratories particularly in developing countries. Of them, the determination of the ADA level in the pleural fluid appears to be a more suitable marker for our setting because of the ease of performance, rapidity, and cost effectiveness of the ADA assay.¹⁹

In our country, where tuberculosis is a common problem, the common practice is giving anti tuberculous treatment by looking at the pleural fluid analysis at the most. The pleural biopsy is not taken either because of lack of facility or it is considered to be more expensive and invasive. Hence there is always a chance of missing the diagnosis and under or over treatment of pleural TB. The purpose of this study was to find another suitable marker that could be confidently used to diagnose tuberculous effusion in the absence of pleural biopsy in our setting. Pleural fluid ADA is one such marker that has proven its worth in different studies.²⁰⁻²⁴ The aim of this study is to achieve a sensitivity of 85% and specificity of 90% for pleural fluid ADA activity in this study so as to recommend Pleural fluid ADA level as a diagnostic tool for diagnosis of pleural tuberculosis.

OBJECTIVE

The aim of this study was to determine the diagnostic accuracy of pleural fluid adenosine deaminase in patients with tuberculous pleural effusion while keeping pleural biopsy as a gold

standard.

MATERIALS AND METHODS

This cross sectional (Validation) study was conducted in Pulmonology Department of Lady Reading Hospital Peshawar over a period of six months between March and September 2011.

Sample size was 144 using 90% sensitivity, 80% specificity, 56.6 % prevalence of tuberculous pleural effusion,⁴ 7 % margin of error and 95 % confidence interval, under WHO software for sample size determination.

All patients above 18 years of age who were highly suspected of having tubercular pleural effusion were included in the study irrespective of their gender. Patients having transudative or malignant pleural effusions or those already taking anti tuberculous treatment were excluded.

DATA COLLECTION PROCEDURE

Ethical approval for the study was obtained from the Institutional Research Ethical committee. Informed written consent was taken from all patients included in the study. All patients with suspected tuberculous pleural effusion presenting to pulmonology department, fulfilling the inclusion criteria, were included in the study. After taking a detailed medical history and complete examination, the patients were subjected to relevant investigations including pleural fluid examination, cytology, closed pleural biopsy using Abram's needle and measurement of pleural fluid ADA level using commercially available ADA kit DIAZYME (Diazyme laboratories Poway, CA 92064, USA) and expressed in unit/liter (U/L). All the tests were to be done by the same Pathologist with 5 years of experience in the same laboratory to control bias.

All the above information, histopathology report of pleural biopsy and ADA results were recorded in the Performa given at the end of this protocol.

STATISTICAL ANALYSIS

Data were entered and analyzed using Statistical Program for Social Sciences (SPSS) version 15.0. Means \pm standards deviation were calculated for age and pleural fluid ADA activity. Variables such as gender and histopathology result of pleural biopsy were calculated in frequencies and percentages. The diagnostic accuracy of pleural ADA in TB pleural effusion was evaluated in terms of sensitivity, specificity, positive predictive value and negative predictive value against pleural biopsy.

2x2 contingency table was used to determine

Sensitivity, Specificity, Positive Predictive value and Negative Predictive value. (Formulae given in operational definitions above)

RESULTS

A total of 144 patients with exudative pleural effusion were included in this study, of whom 84 (58.3%) were males and 60 (41.7%) were females with male to female ratio of 1.4:1.

The age of the patients ranged from 18 to 76 years with mean age of 47.21 ±17.85 SD years. Majority of the patients (43.1%) were between 40 and 60 years.

In 84 (58.3%) patients, pleural biopsy was suggestive of tuberculosis while in 60 (41.7%) cases pleural biopsy showed non tuberculous pathologies.

Out of 60 patients with non-tuberculous effusion 16 (11.10%) were having primary malignant pleural effusion, 29 (20.1%) were diagnosed with metastatic pleural effusion while the pleural biopsy result of 15 (10.4%) patients was not conclusive.

Tuberculous pleural effusion (TPE) was common in younger age group while non tuberculous pleural effusion (NTPE) was common in older age group.

Pleural fluid ADA level ranged from 09-130 U/L. The mean pleural fluid ADA of the patients was 45.31± 18.55 U/L. In biopsy proven tuberculous pleural effusion (TPE), pleural fluid ADA ranged from 29-130 U/L with mean pleural fluid ADA level of 53.93 ±16.12 U/L. In NTPE Pleural fluid ADA ranged from 09-75 U/L, with mean pleural fluid ADA level of 33.25± 14.65 U/L. (Table 1).

Out of 84 patients with biopsy proven TBE, 76 (90.5%) patients had pleural fluid ADA activity more than 40 U/L while in 8 (9.5%) cases of TPE, pleural fluid ADA was less than 40 U/L. Out of 60 patients with non TPE on pleural biopsy 14 (23.3%) had pleural fluid ADA activity more than 40 U/L while in 46 (76.7%) cases, pleural fluid ADA was less than 40 U/L. (Table 2)

The sensitivity and specificity of pleural fluid ADA was analyzed taking pleural biopsy as gold standard.

TABLE 1: ADENOSINE DEAMINASE LEVEL IN DIFFERENT DIAGNOSES (N=144)

Pleural fluid ADA level (U/L)					
Diagnosis Based on Pleural Biopsy	Number	Minimum	Maximum	Mean	Std. Deviation
TB PE	84	29.00	130.00	53.9345	16.12512
Primary M P E	16	10.90	55.00	32.1063	11.88570
Metastatic Pleural Effusion	29	10.00	72.00	32.9255	14.23035
Non Conclusive	15	09.00	75.00	35.1333	18.51974
Total	144	9.00	130.00	45.3197	18.55089

TBPE: tuberculous pleural effusion, Non TB PE: Non tuberculous pleural effusion.
MPE: Malignant effusion, ADA: Adenosine deaminase

TABLE 2: CROSS TABULATION OF ADENOSINE DEAMINASE LEVEL AND PLEURAL BIOPSY (N=144)

Diagnosis Based on Pleural Biopsy		Diagnosis based on Pleural Biopsy Result			Total
			TB PE	Non TB PE	
Diagnosis based on ADA Level	TB PE	Count	76	14	90
		% within Biopsy result	90.5%	23.3%	62.5%
	Non TB PE	Count	8	46	54
		% within Biopsy result	9.5%	76.7%	37.5%
Total		Count	84	60	144
		% within Biopsy result	100.0%	100.0%	100.0%

TBPE: tuberculous pleural effusion, Non TB PE: Non tuberculous pleural effusion.
ADA: Adenosine deaminase

The sensitivity of pleural fluid ADA in the diagnosis of TB pleural effusion was 90.47% and specificity was 76.66%. Similarly the positive predictive value (PPV) and negative predictive value (NPV) of pleural fluid ADA in the diagnosis of TB pleural effusion was 84.44% and 85.18% respectively.

DISCUSSION

Tuberculosis and malignancy are the most common and important causes of exudative pleural effusion, other causes being para-pneumonic effusions and empyema, rheumatoid arthritis and other connective tissue disorders, sarcoidosis and other fungal and parasitic diseases²⁵. However the ratio of different diseases varies greatly in different countries and regions of the world. In South East Asia including Pakistan, where tuberculosis is prevalent, the most common cause of pleural effusion is tuberculosis and other infections which contribute more than half of the cases^{7,8}. But in developed countries, where tuberculosis is not prevalent, malignant pleural effusion is more common than tuberculous effusion.²⁶

The common diagnostic workup of patients with pleural effusion includes clinical examination, Chest radiograph, examination of the pleural fluid and pleural biopsy. However, routine laboratory findings may not help to differentiate tuberculous etiology of pleural effusion from other causes. The various noninvasive tests of diagnosing tuberculosis in patients with pleural effusions like demonstration of acid fast bacilli or culture are usually difficult and in most cases negative.²⁷

Modern techniques such as those involving the amplification of bacterial DNA by polymerase chain reaction and other comparable systems, which can differentiate tuberculous from a non-tuberculous effusion, are not available for common use in the developing countries like Pakistan. Similarly in developed countries various other parameters like pleural viscosity, C-reactive protein, carcinoembryonic antigen, interleukin, interferon, vascular endothelial growth factor, tumor necrosis factor and pleural fluid T-cells are used for this purpose but these tests need specific and / or expensive equipment that is not available in most laboratories particularly in developing countries.

Keeping in view these limitations, pleural fluid ADA level was utilized in the present study. The determination of the ADA level in the suspected tuberculous pleural effusion appears to be the most promising marker because of the ease, rapidity, and cost effectiveness of the ADA assay.^{28,29}

ADA is enzyme of catabolism of purine bases. It

catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine and is released by T-lymphocytes and macrophages during cellular immune response. ADA activity can fairly differentiate tuberculous etiology from the rest of the causes of pleural effusion.

The different studies have revealed high sensitivity and specificity of ADA for early diagnosis of tuberculous pleural and pericardial effusion, tuberculous ascites and tuberculous meningitis.¹⁹ Piras et al. were the first to report high ADA in tubercular pleural effusion.³⁰ Subsequently several workers explored its efficacy in the diagnosis of tuberculosis¹⁹ and determined that pleural fluid ADA level less than 40 U/L virtually excludes the diagnosis of tuberculosis.³¹ In other terms, an ADA level equal to or more than 40 U/L means the etiology of pleural effusion is nothing but tuberculosis.

This study revealed high level of ADA in pleural fluid of biopsy proven cases of tuberculous pleural effusion as compared to non-tuberculous group. The results were statistically significant between tuberculous and non-tuberculous group (p value <0.001). The cut off level was kept ≥ 40 U/L in our study. However different authors have used different cut off values ranging from 27 to 77 U/L.^{32,33}

In this study we reported sensitivity of 90.47% and specificity of 76.66% for ADA in the diagnosis of TPE.

Literature has reported extremely variable sensitivity and specificity results for ADA. For example a study reported sensitivity and specificity of ADA 78% and 86% respectively in the diagnosis of tuberculous pleural effusion.³⁴ In contrast a study from India reported high sensitivity and specificity for ADA (sensitivity 94.29% and specificity 92.16%).³⁵ Ocana et al in 1983³⁶ and Valdes et al in 1993³⁷ and 1996³⁸ reported 100% sensitivity and specificity, positive predictive value and negative predictive value in larger sample size studies. Perez²⁰ reported the sensitivity and specificity for ADA to be 77 - 100% (average, 93.3%) and 81 - 97% (Average, 91.3%) respectively on summarizing eleven studies, and Chen et al²¹ reported the sensitivity and specificity for ADA as 79 - 100% (average, 88.6%) and 80.5 - 96% (average, 85.4%) respectively on summarizing the results of eight studies.

A Meta-analysis of 40 studies published from 1966 to 1999 showed that the sensitivity range 47.1 to 100%, and specificity range 0% to 100% for ADA in diagnosing TB pleural effusions. However it concluded that the performance of ADA is reasonably good in diagnosing PTE and is adequate to avoid

pleural biopsy in young patients from areas with high prevalence of TB.²²

Another meta-analysis of Sixty-three studies of English language showed sensitivity 0.92 (95% confidence interval 0.90-0.93), specificity 0.90 (95% confidence interval 0.89-0.91), positive likelihood ratio 9.03 (95% confidence interval 7.19-11.35), negative likelihood ratio 0.10 (95% confidence interval 0.07-0.14), and diagnostic odds ratio 110.08 (95% confidence interval 69.96-173.20). It concluded that ADA determination is a relative sensitive and specific test for the diagnosis of tuberculous pleurisy. It recommended that results of ADA assays should be interpreted in parallel with clinical findings and the results of conventional tests.²³ Similarly a Brazilian meta-analysis of nine studies dating from 1987 to 2005 totaling 1674 patients a sensitivity of 91.8% (95% CI: 89.8-93.6%) and a specificity of 88.4% (95% CI: 86.0-90.5%) and concluded that ADA level has high accuracy for diagnosis of tuberculous pleural effusion.²⁴

Age has also been an important complementary variable while deciding about tuberculous or malignant pleural effusion. In our study TPE was commoner in younger age group than NTPE. The mean age of patients with TPE was 41.52±18.40 years while it was 55.17±13.61 years in patients with NTPE. Our findings were comparable with the international studies although the mean age of patients with non TB pleural effusion in our study is lower as compared to international studies. This could be due to the inclusion criteria of our study in which we included patients only up to the age of 80 years. In one study conducted by Porcel JM et al, the mean age of patients with TPE was 30 years while the mean age of patients with NTPE was 68 years.³⁹ Antonangelo et al reported in their study that patients with tuberculous PE were significantly younger than those with NTPE. The mean age of patients with TPE was 36 years while the mean age in patients with NTPE was 58 years.⁴⁰

With respect to gender, it is known that men are more predisposed to both tuberculosis and lung cancer, though the incidence of cancer has been increasing among women over the last few decades.²⁶ As in our study most of the patients with tuberculous pleural effusion were males 54 (64.28%) as compared to females 30 (35.71%).

In our country the prevalence of tuberculosis is quite high and in the light of the results of previous and this study pleural fluid concentration of ADA is a useful biomarker for the diagnosis of tuberculous pleural effusion. In appropriate clinical setting ADA level can provide a reliable basis for deciding to start anti tuberculous therapy even before the results of biopsy

and culture become available and thus the morbidity and mortality associated with late diagnosis and treatment can be avoided. Although we achieved a sensitivity of 90.47% but in our study the specificity of ADA in separating tuberculous from non-tuberculous effusion was quite low (specificity: 76.66%). However, further studies, involving larger number of patients, to evaluate the usefulness of pleural ADA in the diagnosis of TPE are needed in order to draw any conclusion or to achieve higher sensitivity and specificity and to recommend ADA as a routine diagnostic tool for TB. Local data is not available on pleural ADA level so further work is needed.

CONCLUSION

Due to lack of modern and costly investigations, closed pleural biopsy is the main stay of diagnosis in our country but due to the lack of expertise its yield is not high and is not freely available. Due to these limitations pleural fluid ADA level in addition to adequate clinical picture, can be used in decision making to differentiate between tuberculous and malignant pleural effusion. However further studies, involving larger number of patients, to evaluate the usefulness of pleural ADA in the diagnosis of TPE are needed in order to draw any conclusion or to achieve higher sensitivity and specificity and to recommend ADA as a routine diagnostic tool for TB.

REFERENCES

- 1 Gopi A, Madhavan SM, Sharma SK, Sahn SA. Diagnosis and Treatment of Tuberculous Pleural Effusion in 2006. *Chest* 2007; 131; 880-89.
- 2 Wolfgang Frank. Tuberculous Pleural Effusion, Tuberculosis - Current Issues in Diagnosis and Management, Dr. Bassam Mahboub (Ed.), 2013. ISBN: 978-953-51-1049-1, InTech, DOI: 10.5772/54955.
- 3 Light RW. Pleural Diseases, 5th edn. Lippincott, Williams and Wilkins, Baltimore, MD, 2007.
- 4 Rehan M, Alam MT, Aurangzeb M, Imran K, Farrukh SZ, Masroor M, Kumar P. Frequency of various diseases in patients presenting with pleural effusion. *Gomal J Med Sci* 2013; 11: 78-83.
- 5 Ibrahim MT, Saeed MK, Umar M. Frequency of causative factors for pleural effusion: A hospital based study. *Pak Armed Forces Med J* 2010; 6.
- 6 Khan Y, Bilal, Zia S. Etiological spectrum of exudative pleural effusion in a tertiary care hospital based on closed pleural biopsy. *Ann Pak Inst Med Sci* 2011;7:133-136.
- 7 Javaid A, Shah N, Samad A, Amjad M, Ullah Z.

- Aetiology of Pleural effusion. a diagnostic outcome. *JPMI*. 1996; 10:147-153.
- 8 Javaid A, M Amjad, Nasir Shah, A Samad, Zahoorullah. Causes of Exudative Pleural Effusion at LRH. *JCPSP*. 1997; 7:237-239.
 - 9 Ihsanullah, Khan N, Jadoon H, Zaman M, Ahmed A. Yield of Abrams needle pleural biopsy in exudative pleural effusion. *J Ayub Med Coll* 2009; 21(1):116-8.
 - 10 Anwar R, Farooqi JI. Causes of lymphocytic exudative pleural effusion as revealed by percutaneous pleural biopsy: Experience from Peshawar. *Pak J Med Sci* 2005; 21: 39-43.
 - 11 Magsi JA, Khan SU, Awan SR. Pleural biopsy in the diagnosis of lymphocytic exudative pleural effusion. *Ann King Edward Med Coll* 2005; 11:572-4.
 - 12 Chakrabarti B, Ryland I, Sheard J, Warburton CJ, Earis JE. The role of Abrams percutaneous pleural biopsy in the investigation of exudative pleural effusion. *Chest* 2006; 129:1549-55.
 - 13 Ribera E, Ocana I, Martinez-Vazquez JM, Rosell M, Español T, Ruibal A: High level of interferon gamma in tuberculous pleural effusion. *Chest* 1988;93:308-11.
 - 14 Vereza Hernando HR, Masa Jimenez JF, Dominguez Juncal L, Perea Garcia-Buela J, Martin Egana MT, Fotan Bueso J: Meaning and diagnostic value of determining the lysozyme level of pleural fluid. *Chest* 1987;91:342-5.
 - 15 Villena V, Rebollo MJ, Aguado JM, Galan A, Lopez Encuentra A, Palenque E: Polymerase chain reaction for the diagnosis of pleural tuberculosis in immunocompromised and immunocompetent patients. *Clin Infect Dis* 1998;26:212-4.
 - 16 Caminero JA, Rodriguez de Castro F, Carrillo T, Lafarga B, Diaz F, Cabrera P. Diagnosis of pleural tuberculosis by detection of specific IgG anti-antigen 60 in serum and pleural fluid. *Respiration* 1993;60:58-62.
 - 17 Valdes L, Alvarez D, San Jose E, et al. Tuberculous pleurisy: a study of 254 patients. *Arch Intern Med* 1998; 158:2017-21.
 - 18 V.K. Mootha, R. Agarwal, N. Singh, A.N. Aggarwal, D. Gupta and S.K. Jindal Medical Thoracoscopy for Undiagnosed Pleural Effusions: Experience from a Tertiary Care Hospital in North India. *Indian J Chest Dis Allied Sci* 2011;53:21-24.
 - 19 Ocana I, Martinez-Vazquez JM, Segura RM, Fernandez-De-Sevilla T, Capdevila JA. Adenosine deaminase in pleural fluids. Test for diagnosis of tuberculosis pleural effusion. *Chest* 1983; 84:51-3.
 - 20 Perez-Rodriguez E, Jimenez Castro D. The use of adenosine deaminase and adenosine deaminase isoenzymes in the diagnosis of tuberculous pleuritis. *Curr Opin Pulm Med* 2000; 6:259-66.
 - 21 Chen ML, Yu WC, Lam CW, Au KM, Kong FY, Chan AY. Diagnostic value of pleural fluid adenosine deaminase activity in tuberculous pleurisy. *Clin Chim Acta* 2004; 341:101-7.
 - 22 Goto M, Noguchi Y, Koyama H, et al. Diagnostic value of adenosine deaminase in tuberculous pleural effusion: a meta-analysis. *Ann Clin Biochem* 2003; 40:374-81
 - 23 Liang QL, Shi HZ, Wang K, Qin SM, Qin XJ. Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. *Respir Med* 2008; 102(5): 744-54.
 - 24 Morisson P, Neves DD. Evaluation of Adenosine deaminase in the diagnosis of pleural tuberculosis: a Brazilian meta-analysis. *J Bras Pneumol* 2008; 34(4): 217-24.
 - 25 Innes JA, Reid PT. Respiratory disease. In: Boon NA, Colledge NR, Walker BR. Davidson principal and practice of medicine 22nd ed 2014 New York;19:662-3.
 - 26 Parkin DM. Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *Cancer J Clin* 2005; 55:4-108.
 - 27 Molavi A, LeFrock JL. Tuberculous meningitis. *Med Clin North Am* 1985; 69(2):315-331.
 - 28 Gopi A, Madhavan SM, Sharma SK. Diagnosis and Treatment of Tuberculous Pleural Effusion in 2006. *Chest* 2007; 131:880-9.
 - 29 Burgess LJ, Swanepoel CG, Taljaard JJ. The use of adenosine deaminase as a diagnostic tool for peritoneal tuberculosis. *Tuberculosis*. 81:243-8, 2001.
 - 30 Piras MA, Gakis C, Budroni M, Andreoni G. Adenosine deaminase activity in pleural effusions: an aid to differential diagnosis. *Br Med J* 1978; 2(6154):1751-1752.
 - 31 Aggarwal AN, Gupta D, Jindal SK. Diagnosis of tuberculous pleural effusion. *Indian J Chest Dis Allied Sci* 1999; 41(2):89-100.
 - 32 Strankinga WF, Nauta JJ, Straub JP, Stam J.

- Adenosine deaminase activity in tuberculous pleural effusion, a diagnostic test. *Tubercle* 1987;67:137-40.
- 33 Gupta DK, Suri JC, Goel A. Efficacy of adenosine deaminase in diagnosis of pleural effusion. *Indian J Chest Allied Sci* 1990; 32:205-8.
 - 34 Ciledag A, Kaya A, Erol S, Sen E, Celik G. The comparison of pleural fluid TNF-alpha and IL-10 levels with ADA in tuberculous pleural effusion. *Curr Med Chem*. 2010; 17: 2096-100.
 - 35 Gupta BK, Bharat V, Bandyopadhyay D. Sensitivity, Specificity, Negative and Positive Predictive Values of Adenosine Deaminase in Patients of Tubercular and Non-Tubercular Serosal Effusion in India. *Journal of Clinical Medicine Research* 2010; 2:121-6.
 - 36 Ocana I, Martinez-Vazquez JM, Segura RM, Fernandez-De-Sevilla T, Capdevila JA. Adenosine deaminase in pleural fluids. Test for diagnosis of tuberculous pleural effusion. *Chest* 1983; 84:51-3.
 - 37 Valdes L, San Jose E, Alvarez D, Sarandeses A, Pose A, Chomon B, Alvarez-Dobano JM, et al. Diagnosis of tuberculous pleurisy using the biologic parameters adenosine deaminase, lysozyme, and interferon gamma. *Chest* 1993;103:458-6.
 - 38 Valdes L, San Jose E, Alvarez D, Valle JM. Adenosine deaminase (ADA) isoenzyme analysis in pleural effusions: Diagnostic role and relevance to the origin of increased ADA in tuberculous pleurisy. *Eur Respir J* 1996; 9:747-51.
 - 39 Porcel JM, Vives M. Differentiating tuberculous from malignant pleural effusion: A scoring model. *Med Sci Monit* 2003;9:175-80
 40. Antonangelo L, Vargas FS, Seiscento M, Bombarda S, Teixeira L, Sales RK. Clinical and laboratory parameters in the differential diagnosis of pleural effusion secondary to tuberculosis or cancer. *Clinics* 2007;62:585-90