

The Significance of ADA Level among the Suspected Tuberculosis Cases, Experience at a Tertiary Care Teaching Hospital, Lahore

Significance of ADA level among the Suspected Tuberculosis

Maryam R Tarar¹, Tahir Naeem², Nusrat Alavi³, Urfa Shafi¹, Aneela Khawaja² and Asma Ejaz²

ABSTRACT

Objective: To determine the significance of ADA activity in combination with differential cell count (WBC) and other biochemical variables (Lactate dehydrogenase (LDH), Erythrocyte sedimentation rate (ESR), Proteins).

Study Design: descriptive cross-sectional study

Place and Duration of Study: This study was conducted at the Pathology department of Shalamar Teaching Hospital, Lahore from March, 2017 till February, 2020.

Materials and Methods: A total of 352 samples from patients of all ages and both genders were included in which either pleural, ascetic or other sterile body fluids (3cc each) were examined. ADA level of ≥ 40 units/mL was deemed suggestive of TB and measured by the spectrophotometric method.

Results: Among 352 patients, the mean age was 51.9 ± 18 , with equal male female ratio. ADA level ≥ 40 units/mL was noticed in 35.51% samples. Positive correlation of ADA with LDH (.472), ESR (.195) and WBC (.240). Positive correlation of LDH with lymphocytes (.194) and Negative correlation with polymorph leucocytes (-.190). Lymphocytic Neutrophil ratio was 0.19 with SD of 24.5.

Conclusion: Tuberculosis is the widespread infectious disease especially in low-income and under-developed countries. In tuberculous pleuritis ADA level of ≥ 40 U/mL in lymphocyte-predominant effusions makes the identification of tubercle bacilli more credible. This method shows positive correlation of ADA with other biochemical factors as well. This efficient test is easy to perform with rapid turnaround time for diagnosis of tuberculosis.

Key Words: Adenosine deaminase enzyme (ADA), Lactate dehydrogenase enzyme (LDH), Tuberculosis.

Citation of article: Tarar MR, Naeem T, Alavi N, Shafi U, Khawaja A, Ejaz A. The Significance of ADA Level among the Suspected Tuberculosis Cases, Experience at a Tertiary Care Teaching Hospital, Lahore. Med Forum 2022;33(4):85-88.

INTRODUCTION

Tuberculosis (TB) known as a global health challenge (threat), accounting for the 10 leading causes of mortality in lower and lower-middle income countries¹. One out of four healthy individuals carry Mycobacterium tuberculosis (MTB) in their body; and about 5-10% of carriers have a life time risk of

converting into active disease. In 2019, World Health Organization estimated 10 million people including children acquired the active disease and 1.4 million died of it^{2, 3}. Pakistan is among the 8 countries with the highest burden of TB and among the top 5 who have the largest gap between the actual disease and the reported cases. Improved access to diagnosis and treatment and intensified efforts to reduce under-reporting are required to bring the disease under control and meet 2025 and 2030 targets of "End TB Strategy" and "Sustainable Development Goals"^{4, 5}.

Timely diagnosis and treatment play a pivotal role in monitoring of TB. Although, culturing the MTB or a positive PCR from sputum or other specimens is considered the gold standard for diagnosis but these facilities are not available to majority of patients in Pakistan. Alternative methods include chest radiology, AFB smear examination and raised ESR in a suspected case but the sensitivity and specificity of these investigations for a definitive diagnosis are limited⁶.

Adenosine Deaminase (ADA) enzyme, converts Adenosine to Inosine. Its levels is also increased in TB in which cellular immune response is stimulated⁷. The

¹. Department of Pathology, Shalamar Medical & Dental College, Lahore.

². Department of Pathology, University College of Medicine & Dentistry (UoL), Lahore.

³. Department of Pathology, Rahbar Medical & Dental College, Lahore.

Correspondence: Dr. Nusrat Alavi, Associate Professor of Pathology, Rahbar Medical & Dental College, Lahore.

Contact No: 0323-4065416

Email: nusratpinky@hotmail.com

Received: September, 2021

Accepted: January, 2022

Printed: April, 2022

activity is high not only in the serum but also in the other body fluids which may accumulate in patients suffering from Tuberculous Effusions. Although, qualitative Polymerase Chain Reaction (PCR) and biopsy are used for definitive diagnosis of TB in these situations but they are neither widely available nor pocket friendly in Pakistan nor other developing countries. One of the hindrances in controlling TB in low socioeconomic countries is the absence of well-timed and suitable diagnosis. Knowledge of ADA activity is helpful for the early detection of tuberculosis since the results are accessible within 24 hours and they allow for the timely initiation of anti-tuberculous medication to improve patient outcome^{5,6}. We conducted this study to establish a correlation between raised ADA levels in body fluids along with raised Erythrocytes Sedimentation Rate (ESR) and a relative or absolute peripheral and/or fluid lymphocytosis, and subsequently revise our institutional guidelines for the initiation of anti-TB therapy in such patients.

MATERIALS AND METHODS

It was a single center health care descriptive cross-sectional study done in Shalamar Teaching Hospital, Lahore. Approval for the study was taken from the Institutional Review Board of hospital (SMDC/IRB/02-11/067).

Inclusion Criteria: All age groups and both genders Patients presenting with pleural, pericardial or ascitic effusion in whom TB was suspected and ADA levels were included.

Exclusion Criteria: Repeated hospital visits during study period to avoid duplication Patients already on Anti-TB therapy and fluid positive for malignant cells.

The data was collected retrospectively from the electronic medical records of patients. Three hundred and fifty-two patients’ records between 1st March 2017 and 28th February 2020 were reviewed in which either pleural, ascitic or other sterile body fluids were sent for examination. All ages and both genders were included. ADA level of ≥ 40 units/mL was deemed suggestive of TB. Pleural fluid ADA was assessed by the spectrophotometric technique described by Giusti and Galanti⁸.

Statistical Analysis of data was done by using SPSS version 22. Quantitative variables i.e., percentages and frequencies were used for categorical variables. Mean and SD (standard deviation) were used for describing continuous variables. Pearson correlation (2-tailed) was used for describing correlation between ADA and other variables. Statistically, P-value of <0.05 was regarded to be significant.

RESULTS

Three hundred and fifty two (352) patients with male female ratio of 1:1(176 male and 176 females) was included, with Mean age of 51.9 ± 18 . (Minimum age 13-year and maximum age 94 years). The positive correlation of ADA with other variables is given in Table 1. Lymphocytic Neutrophil ratio was 0.19 with SD of 24.5.

Table No.1: Pearson correlation of ADA (N=352)

Correlation N=352	ADA	LDH	LYMPHOS	POLYMORPHS	ESR	WBC
ADA	1	.472**	.047	-.041	.195**	.240**
LDH	.472**	1	.194**	-.190**	.287**	.284**
LYMPHOS	.047	.194**	1	-.983**	.077	.335**
POLYMORPHS	-.041	-.190**	-.983**	1	-.064	-.326**
ESR	.195**	.287**	.077	-.064	1	.062
WBC	.240**	.284**	.335**	-.326**	.062	1

**correlation is significant at the 0.01 level (2-tailed)

Table No.2: Showing Biochemical parameters, ADA levels and cell count

Pleural fluid parameter	Tuberculous	Non-tuberculous	p-value
ADA IU/L	82.3±74.76	12.04±9.79	.003
LDH U/L	1616.77 ± 4029	268±402.22	.14
Protein g/dL	5.86±7.08	3.51±11.83	0.00
Cell count cells/mL	2024 ± 3035.77	739.3 ± 1793.48	0.91

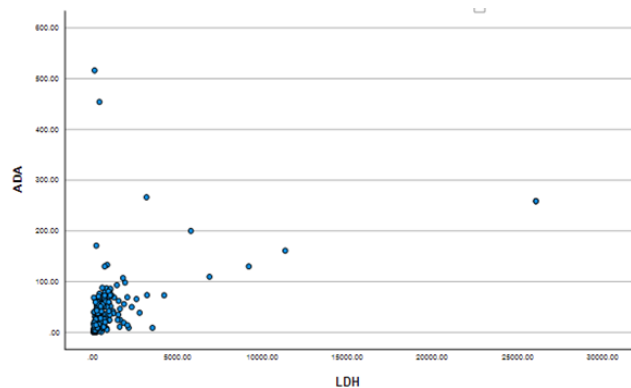


Figure No.1: Coefficient of correlation between ADA and LDH in tuberculous effusions (N=352)

ADA shows positive correlation with LDH, ESR and WBC; while LDH shows negative correlation only with polymorphs but positive correlation with rest of the variables. Lymphocytic Neutrophil ratio is 0.19 with SD of 24.5.

Biochemical parameters (LDH U/L and protein g/dL), ADA levels and cell count in pleural effusion of tuberculous and non-tuberculous studied cases is presented in Table 2.

Graphical correlation of ADA and LDH is given in Figure 1.

DISCUSSION

Pleural fluid ADA level has to be interpreted with other chemical and cytological parameters for early diagnosis and management. The ADA assay is suitably quick, cheap and non-invasive method for estimation of tuberculous effusions. Currently, the disease burden is still challenging due to delayed culture results and non-affordability of molecular testing in most of the settings^{3,7}.

Two national studies by Rasheed et al, has indicated 40% and 68.74% frequency of tuberculous effusion with high level of ADA^{10, 11}; while studies from other regions have given different frequencies^{12, 13}. Our data (35.51%) uniquely represents an urban population residing in thickly populated low-income areas. Beukes has documented ADA and LDH ratio to be of diagnostic value for management of tuberculous effusions¹⁴.

L/N ratio >0.75 is a diagnostic criterion for tuberculous effusion along with high ADA level. Jha et al; and Joseph and Hemamalini have positive correlation of ADA with LN ratio^{9, 12}. In our study, 35% cases had L/N ratio >0.75 evaluation of patient with tuberculous effusion. It was concluded that ADA when combined with differential cell count remains a useful test in diagnosis of TB similar to our study¹³

Similarly, studies have shown fairly positive correlation between ADA, LDH, absolute lymphocyte count, ESR and WBCs; as seen in our study (p-value <0.05). Negative correlation was found between ADA and polymorphs, which is also in concordance with other studies^{14, 15}.

CONCLUSION

Tuberculosis is the widespread infectious disease especially in low-income and under-developed countries. ADA level of ≥ 40 U/mL in lymphocyte-predominant effusions makes the identification of mycobacterium tuberculosis more credible. This test is adopted as a quick low-cost tool with rapid turnaround time for diagnosis of tuberculosis. ADA estimation is recommended in all patients suspected of tuberculous effusions with exudative lymphocyte predominance. ADA estimation done in conjunction with TLC/DLC is

a reliable tool for the diagnosis and start of therapy in suspected TB cases.

Limitations of the Study: ADA level estimation was done along with LN ratio, LDH, and cell count. Positives cases in our study were not confirmed by gold standard, nucleic acid amplification testing (PCR) due to financial constraints. In the absence molecular testing, this proves to be cost effective rapid technique for diagnosis and early treatment of Tuberculosis.

Acknowledgments: All the authors are thankful for the contributions made by Ebrahim Tahir (student Government College, Lahore) to convert all the data from Excel to SPSS; Dr. Tayyaba Rashid and Dr. Masood Afzal (Demonstrators at Shalamar Medical & Dental college, Lahore) for organizing and entering data.

Author's Contribution:

Concept & Design of Study: Maryam R Tarar
Drafting: Tahir Naeem, Nusrat Alavi

Data Analysis: Urfa Shafi, Aneela Khawaja and Asma Ejaz

Revisiting Critically: Maryam R Tarar, Tahir Naeem

Final Approval of version: Maryam R Tarar

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. World Health Organization. Available online: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>
2. Young M, Craig J. Urgent global action is needed on multi drug-resistant tuberculosis (MDR-TB)—can small cone moxa contribute to a global response? *European J Integrative Med* 2020; 37:101072. <https://doi.org/10.1016/j.eujim.2020.101072>
3. Quadir N, Rahman SA, Ahmad J, Das AK, Arora N, Sheikh JA, et al. Development and Validation of Signature Sequence-Based PCR for Improved Molecular Diagnosis of Tuberculosis. *J Molecular Diagnostics* 2021;23(9):1138-44. <https://doi.org/10.1016/j.jmoldx.2021.05.014>
4. Pande T, Vasquez NA, Cazabon D, Creswell J, Brouwer M, Ramis O, et al. Finding the missing millions: lessons from 10 active case finding interventions in high tuberculosis burden countries. *BMJ Global Health* 2020;5(12): e003835. <https://doi.org/10.1136/bmjgh-2020-003835>
5. Tahseen S, Siddiqui MR, Khanzada FM, Bhutto MM, Baloch AQ, Van Gemert W, et al. Implementing universal rifampicin testing for TB in Pakistan: results and implications for the TB

- response. *Int J Tubercu Lung Dis* 2020;24(8):795-801. <https://doi.org/10.5588/ijtld.19.0688>
6. Samad A, Bukhari AA, Sartaj S, Fayyaz N, Akhter N, Naeem N, et al. Tuberculous Mastitis in Females of South Punjab: A Clinicopathological Analysis of Ten Years from Pakistan. *Biomedica* 2020;36(1): 30-37.
 7. Liu R, Li J, Tan Y, Shang Y, Li Y, Su B, et al. Multicenter evaluation of the acid-fast bacillus smear, mycobacterial culture, Xpert MTB/RIF assay, and adenosine deaminase for the diagnosis of tuberculous peritonitis in China. *Int J Infect Dis* 2020; 90:119-24. <https://doi.org/10.1016/j.ijid.2019.10.036>
 8. Zhao T, Chen B, Xu Y, Qu Y. Clinical and pathological differences between polymorphonuclear-rich and lymphocyte-rich tuberculous pleural effusion. *Ann Thorac Med* 2020;15(2): 76-83. https://dx.doi.org/10.4103%2Fatm.ATM_15_20
 9. Jha R, Mehata RK, Koirala P. Lymphocyte-Neutrophil Ratio in the Diagnosis of Tubercular Pleural Effusion in a Tertiary Care Centre: A Descriptive Cross-Sectional Study. *Birat J Health Sci* 2021;6(2):1517-21. <https://doi.org/10.3126/bjhs.v6i2.40351>
 10. Rasheed H, Khan EH, Shafi M, Rafiq A, Ali A, Shuaib SL. Diagnostic Accuracy of Adenosine deaminase enzyme (ADA) in the diagnosis of tuberculous pleural effusion. *J Rawal Med Coll* 2020;24(4):311-15. <https://doi.org/10.37939/jrmc.v24i3.1318>
 11. Rasheed H. Role of adenosine deaminase enzyme (ADA) in differentiating tuberculous pleural effusion from malignant pleural effusion. *Adv Basic Med Sci* 2018;2(2): 63-67.
 12. Varghese J, Hemamalini G. Study of adenosine deaminase and lymphocyte/neutrophil ratio in combination as diagnostic tool for tubercular pleural effusion. *IAIM* 2020;7(8): 26-30.
 13. Rousta F, Sokouti M, Rouy SB, Parsay S. Diagnostic value of pleural fluid adenosine deaminase among the patients with pleural tuberculosis. <https://orcid.org/0000-0003-1013-200X>
 14. Beukes A, Shaw JA, Diacon AH, Irusen EM, Koegelenberg CF. The utility of pleural fluid lactate dehydrogenase to adenosine deaminase ratio in pleural tuberculosis. *Respiration* 2021; 100(1):59-63. <https://doi.org/10.1159/000509555>
 15. Binegdie AB, Ashagire AW, Brandli O, Sherman C, Schluger NW, Schoch O. Value of Adenosine Deaminase in the diagnosis of tuberculous pleurisy at Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia. *J Pan African Thoracic Soc* 2022;1-6. https://dx.doi.org/10.25259/JPATS_32_2021