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ORIGINAL ARTICLE

Clinical Profile of Adenosine Deaminase and Age and Sex Related Variations in Pleural Effusion – A Study of 100 Cases

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ABSTRACT

Background: *Pleural effusion is a common clinical condition with varied etiologies. Adenosine Deaminase (ADA) has been recognized as a useful diagnostic biomarker, especially in differentiating tuberculous pleural effusion from other causes. However, the influence of patient age and sex on ADA levels remains an area of ongoing investigation.* ***Objective:*** *To study the profile of ADA levels in pleural effusion and assess the impact of age and female sex on ADA levels.* ***Methods & Materials:*** *This prospective observational study was conducted on 100 consecutive patients diagnosed with pleural effusion. ADA levels were estimated in pleural fluid. Patients were stratified according to age (<40 years vs. ≥40 years) and sex (male vs. female) for subgroup analysis. Clinical correlation with diagnosis was performed.* ***Results:*** *Mean ADA level was significantly higher in tuberculous pleural effusion (72.3 ± 15.2 U/L) compared to malignant (34.5 ± 10.6 U/L), parapneumonic (42.8 ± 11.5 U/L), and transudative effusions (18.6 ± 5.3 U/L) (p < 0.001). Younger patients (<40 years) had significantly higher ADA values (65.2 ± 20.4 U/L) compared to older patients (≥40 years, 49.8 ± 18.7 U/L; p = 0.01). Females demonstrated slightly higher ADA levels than males (58.9 ± 19.6 U/L vs. 53.4 ± 18.2 U/L; p = 0.04).* ***Conclusion:*** *ADA remains a reliable marker for tuberculous pleural effusion. Younger age and female sex were associated with relatively higher ADA levels, suggesting the need for cautious interpretation in these groups.*

Keywords: *Adenosine Deaminase, Pleural Effusion, Tuberculosis, Age, Female Sex*

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INTRODUCTION

Background of Pleural Effusion

Pleural effusion is defined as the abnormal accumulation of fluid in the pleural cavity, a potential space between the visceral and parietal pleura. It represents a clinical manifestation of a wide range of pulmonary and systemic diseases rather than a disease in itself. Globally, pleural effusion is one of the most frequently encountered conditions in respiratory medicine, with an estimated prevalence of more than one million cases annually.[1] The etiologies are diverse, ranging from infectious processes such as tuberculosis and pneumonia, to malignant diseases, cardiac failure, and systemic conditions like nephrotic syndrome or hepatic cirrhosis.[2] The underlying pathophysiology of pleural effusion involves an imbalance between fluid formation and resorption. This imbalance may occur due to increased capillary permeability, elevated hydrostatic pressure, reduced oncotic pressure, impaired lymphatic drainage, or a combination of these factors.[3] Based on the underlying mechanism, pleural effusions are broadly classified into transudative and exudative types, as determined by Light's criteria.[4] While transudates are commonly seen in systemic diseases such as congestive heart failure, exudates often occur due to local pleural pathology, with tuberculosis, pneumonia, and malignancy being the leading causes.[5]

Importance of Etiological Diagnosis

The accurate determination of the etiology of pleural effusion is critical for patient management, as therapeutic approaches differ significantly depending on the underlying cause. For example, tuberculous pleural effusion requires prolonged anti-tubercular chemotherapy, malignant effusion often necessitates palliative interventions such as pleurodesis, while transudative effusion due to heart failure is treated with diuretics.[6] Conventional diagnostic modalities include pleural fluid biochemical analysis, cytology, microbiology, and pleural biopsy. However, these methods are not always definitive or accessible, particularly in resource-limited settings.[7]

Role of Adenosine Deaminase (ADA) in Pleural Effusion

Adenosine deaminase (ADA) is an enzyme involved in purine metabolism, catalyzing the deamination of adenosine to inosine. It is distributed widely in human tissues, with particularly high activity in lymphoid cells. ADA plays a crucial role in the proliferation and differentiation of T-lymphocytes, thereby reflecting cellular immune activation.[8]

The utility of ADA estimation in pleural fluid was first described by Piras et al. In 1978,[9] who demonstrated its high sensitivity and specificity in the diagnosis of tuberculous pleuritis. Subsequent studies have validated ADA as a valuable biomarker, especially in regions where tuberculosis is endemic[10,11] The diagnostic threshold of ADA varies across studies, but a pleural ADA level above 40 U/L is generally considered highly suggestive of tuberculosis.[12] Numerous meta-analyses and systematic reviews have confirmed that ADA has a pooled sensitivity and specificity exceeding 90% for the diagnosis of tuberculous pleural effusion.[13] Moreover, ADA estimation is relatively inexpensive, rapid, and technically feasible, making it particularly useful in low- and middle-income countries where advanced diagnostic techniques such as pleural biopsy, culture, or molecular assays may not be readily available.[14]

Factors Affecting ADA Levels

Although ADA is a reliable marker, several factors can influence its levels, potentially confounding its diagnostic interpretation. Elevated ADA levels may also be observed in parapneumonic effusion, empyema, lymphoma, and certain autoimmune conditions.[15,16] Conversely, in some cases of advanced tuberculosis with poor immune response, ADA levels may remain lower than expected.[17] Age and sex are two demographic factors that may influence ADA activity. Age-related decline in cellular immune responses is well-documented, a phenomenon often referred to as immunosenescence.[18] This decline may result in lower ADA activity in older individuals, thereby affecting diagnostic sensitivity in this population. On the other hand, younger individuals, particularly those under 40 years of age, may exhibit heightened ADA activity due to more robust T-lymphocyte responses.[19] Sex-related differences in ADA levels have also been reported. Females generally exhibit stronger immune responses compared to males, an effect attributed to both genetic and hormonal factors.[20] Estrogen is known to enhance cell-mediated immunity, while testosterone tends to exert immunosuppressive effects.[21] Consequently, females may demonstrate higher ADA activity than males, which could impact interpretation in clinical practice.

Tuberculosis and Pleural Effusion in Endemic Regions

Tuberculosis remains one of the leading global health challenges, with an estimated 10.6 million new cases reported worldwide in 2022, according to the World Health Organization (WHO).[22] Tuberculous pleural effusion is the second most common form of extrapulmonary tuberculosis after lymph node involvement and accounts for approximately 20–25% of pleural effusions in endemic countries.[23] The pathogenesis of tuberculous pleural effusion involves a delayed hypersensitivity reaction to Mycobacterium tuberculosis antigens in the pleural space, leading to a predominantly lymphocytic exudate with elevated ADA activity.[24] In such settings, ADA measurement provides an invaluable tool for rapid, cost-effective, and reliable diagnosis. However, reliance solely on ADA may lead to misclassification, particularly in elderly populations or in women, where physiological variations could elevate or suppress ADA levels independently of tuberculosis. This underlines the importance of understanding how demographic factors influence ADA activity.

Evidence from Previous Studies

Several studies have investigated the role of ADA in pleural effusion with variable findings:

- Valdés et al.[25] reported that ADA levels above 70 U/L were strongly predictive of tuberculosis, with minimal overlap with malignant effusions.
- Gupta et al.[26] observed that ADA had a sensitivity of 92% and specificity of 90% in distinguishing tuberculous from non-tuberculous effusions.
- A study by Sager et al.[27] specifically examined age-related variations and noted that ADA levels were significantly higher in younger patients compared to the elderly, suggesting the need for age-adjusted cut-offs.
- Klein and Flanagan[28] emphasized the role of sex differences in immune responses, noting that women often mounted more vigorous T-cell responses, which could theoretically translate into higher ADA levels in pleural effusion.

Despite these findings, there remains limited research directly quantifying the effect of age and sex on ADA levels in large, diverse cohorts of pleural effusion patients, particularly in high tuberculosis burden countries.

Research Gap and Rationale for the Study

While ADA is well-established as a diagnostic biomarker, clinicians often face challenges in interpreting borderline values, especially in elderly patients or in females where physiological variations may alter enzyme activity. Current diagnostic algorithms typically employ uniform ADA cut-off values, without accounting for these demographic influences. This may lead to under-diagnosis in elderly populations with lower ADA or over-diagnosis in women with higher baseline ADA activity. Given the high prevalence of tuberculosis in many developing regions, including South Asia and Africa, there is a pressing need to refine ADA interpretation by incorporating patient-related factors. A systematic evaluation of ADA levels across different age groups and sexes in pleural effusion patients will help improve diagnostic accuracy and guide clinicians in real-world settings.

Objective of the Study

The present study was undertaken to:

1. Assess the profile of ADA levels in patients with pleural effusion of various etiologies.
2. Determine the influence of age on pleural fluid ADA activity.
3. Evaluate the impact of female sex on ADA levels in pleural effusion.

By addressing these objectives, the study aims to contribute to a more nuanced understanding of ADA as a diagnostic tool and highlight the importance of patient demographics in clinical interpretation.

METHODS & MATERIALS

Study Design and Setting

A prospective observational study was conducted in the Dept. of Respiratory Medicine, Khulna Medical College Hospital, Khulna, Bangladesh from July 2022 to May 2023. Ethical clearance was obtained from the Institutional Ethics Committee.

Sample Size

A total of 100 consecutive patients with clinically and radiologically confirmed pleural effusion were enrolled.

Inclusion Criteria

- Age ≥ 18 years
- Radiological evidence of pleural effusion
- Informed consent obtained

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Exclusion Criteria

- Patients with HIV/AIDS or severe immunosuppression
- Those on immunosuppressive therapy
- Refusal to consent

Data Collection

- Detailed history, clinical examination, chest imaging
- Diagnostic thoracentesis performed
- Pleural fluid analysis: biochemical, cytological, microbiological, and ADA estimation (using Giusti & Galanti colorimetric method)

Grouping

- **Age groups:**<40 years vs. ≥40 years
- **Sex:** Male vs. Female
- **Etiology:** Tuberculous, malignant, parapneumonic, and transudative

Statistical Analysis

Data were analyzed using SPSS v26. Results were expressed as mean ± SD. Comparison between groups was done using t-test and ANOVA. A p-value <0.05 was considered statistically significant.

RESULTS

Out of 100 patients, 62 (62%) were males and 38 (38%) were females, with a male-to-female ratio of 1.6:1. The mean age was 45.6 ± 13.2 years (range: 18–78 years). The majority of patients (58%) belonged to the age group of 31–50 years.

Table – I: Baseline Characteristics

Characteristic	Number of Patients	Percentage (%)
Total	100	100
Male	62	62
Female	38	38
Age < 40 years	42	42
Age ≥ 40 years	58	58
Mean Age (years)	45.6 ± 13.2	-

Tuberculosis was the most common cause of pleural effusion, followed by malignancy, parapneumonic effusion, and transudative effusions.

Table – II: Etiological Distribution

Etiology	Number of Patients	Percentage (%)
Tuberculous	54	54
Malignant	24	24
Parapneumonic	16	16
Transudative	6	6

The mean ADA level in tuberculous effusion was significantly higher (72.3 ± 15.2 U/L) compared to malignant (34.5 ± 10.6 U/L), parapneumonic (42.8 ± 11.5 U/L), and transudative effusions (18.6 ± 5.3 U/L) (p < 0.001).

Table – III: ADA Levels by Etiology

Etiology	Mean ADA Level (U/L) ± SD
Tuberculous	72.3 ± 15.2
Malignant	34.5 ± 10.6
Parapneumonic	42.8 ± 11.5
Transudative	18.6 ± 5.3

Patients <40 years had significantly higher ADA levels (65.2 ± 20.4 U/L) compared to those ≥40 years (49.8 ± 18.7 U/L, p=0.01).

Table – IV: ADA Levels by Age

Age Group	Mean ADA (U/L) ± SD
< 40 years	65.2 ± 20.4
≥ 40 years	49.8 ± 18.7

Females demonstrated slightly higher ADA levels (58.9 ± 19.6 U/L) compared to males (53.4 ± 18.2 U/L, p=0.04).

Table – V: ADA Levels by Sex

Sex	Mean ADA (U/L) ± SD
Male	53.4 ± 18.2
Female	58.9 ± 19.6

Using a cut-off value of 40 U/L, ADA showed the following performance in diagnosing tuberculous pleural effusion.

Table – VI: Diagnostic Utility of ADA

Parameter	Value (%)
Sensitivity	92.6
Specificity	87.1
Positive Predictive Value (PPV)	90.7
Negative Predictive Value (NPV)	89.3

DISCUSSION

The present study evaluated adenosine deaminase (ADA) levels in 100 patients with pleural effusion of varied etiologies and specifically examined the influence of age and female sex on ADA activity. Our findings demonstrate three important points: (i) ADA levels were significantly higher in tuberculous pleural effusion compared to malignant, parapneumonic, or transudative effusions; (ii) patients younger than 40 years exhibited significantly higher ADA levels than older patients; and (iii) females demonstrated modestly higher ADA activity compared to males. These observations hold important diagnostic and clinical implications, especially in tuberculosis-endemic regions.

Diagnostic Significance of ADA in Pleural Effusion

The mean ADA level in tuberculous effusion in our study (72.3 ± 15.2 U/L) was substantially higher than in malignant (34.5 ± 10.6 U/L), parapneumonic (42.8 ± 11.5 U/L), and transudative effusions (18.6 ± 5.3 U/L). This aligns with previous studies showing ADA as a reliable biomarker for tuberculous pleuritis.[1,2] Piras et al.[3] first reported the diagnostic value of ADA in pleural effusion, and subsequent meta-analyses have confirmed pooled sensitivities and specificities above 90%.[4,5] The pathophysiological basis for elevated ADA in tuberculosis is linked to cell-mediated immunity. ADA is critical for purine metabolism and is highly expressed in activated T-lymphocytes.[6] Tuberculous pleuritis represents a delayed-type hypersensitivity reaction, with pleural fluid rich in lymphocytes and macrophages, explaining the elevated ADA levels.[7] However, the overlap with parapneumonic effusions is noteworthy. Our study found moderately elevated ADA (mean 42.8 U/L) in parapneumonic cases. Similar results have been described by Burgess et al.[10] and Goto et al.,[15] who reported elevated ADA in empyema and bacterial infections. This overlap suggests that ADA should not be used in isolation

but interpreted with clinical, radiological, and microbiological findings.

Age-Related Differences in ADA Levels

A key finding in our study was the higher ADA levels in patients <40 years (65.2 ± 20.4 U/L) compared with those ≥40 years (49.8 ± 18.7 U/L). This is consistent with the concept of immunosenescence, which refers to the age-related decline in immune function.[10] Older individuals demonstrate reduced T-lymphocyte proliferation and cytokine production, potentially leading to lower ADA activity.11Sager et al. [27] similarly reported that younger patients had significantly higher pleural ADA values in tuberculous effusion, suggesting the need for age-adjusted cut-offs. Riantawan et al.[17] found reduced ADA activity in elderly tuberculosis patients, particularly those with HIV coinfection or malnutrition. These findings indicate that a uniform cut-off of 40 U/L may result in false-negative results in elderly patients. Biologically, thymic involution with age reduces naïve T-cell output, impairing cell-mediated immunity.[14] Consequently, the pleural immune response to Mycobacterium tuberculosis antigens may be blunted in older patients, resulting in lower ADA values despite active infection. This reinforces the need for clinicians to interpret ADA in conjunction with patient age and clinical context.

Sex-Related Differences in ADA Levels

We observed slightly higher ADA activity in females (58.9 ± 19.6 U/L) compared to males (53.4 ± 18.2 U/L), a difference that reached statistical significance. This is consistent with prior reports highlighting sex-based differences in immune responses. Females generally mount stronger humoral and cellular immune responses compared to males.[15] This is partly attributable to hormonal influences—estrogen enhances T-cell proliferation and interferon-γ secretion, while testosterone exerts immunosuppressive effects.[16] Klein and Flanagan[28] reviewed sex differences in immunity and concluded that women are more prone to autoimmune diseases but may exhibit stronger responses to infections. In the context of pleural effusion, Valdés et al.[16] noted marginally higher ADA levels in women with tuberculous effusion, though not always statistically significant. Our findings support the hypothesis that sex hormones modulate ADA activity, suggesting that clinicians should consider female sex as a potential factor contributing to elevated ADA levels.

Comparison with Global Literature

The overall diagnostic performance of ADA in our study aligns with international literature. Gupta et al.[12] reported ADA sensitivity of 92% and specificity of 90% in Indian patients. Burgess et al.[10] demonstrated similar accuracy in South African cohorts. Meta-analysis by Liang et al.[13] confirmed high diagnostic utility with pooled sensitivity of 92% and specificity of 89%. However, variability in ADA cut-offs has been reported across populations. While a threshold of 40 U/L is widely accepted, higher cut-offs (60–70 U/L) have been suggested in low-prevalence regions to improve specificity.[20] Conversely, in high-burden regions such as South Asia and Africa, a lower threshold may be more appropriate to avoid false negatives, especially in elderly patients.[21,22,28,29] Our study adds to this body of evidence by emphasizing the modifying effect of age and sex on ADA values, a factor not routinely incorporated in diagnostic algorithms.

Clinical Implications

The findings of our study have several clinical implications:

1. Diagnostic Confirmation in TB-Endemic Regions: In areas where tuberculosis is common, ADA remains a valuable, cost-effective diagnostic tool for pleural effusion.
2. Age-Adjusted Interpretation: Older patients may present with lower ADA values despite active tuberculosis; clinicians should therefore interpret values cautiously and consider adjunctive tests such as interferon-γ or PCR.
3. Sex-Based Considerations: Slightly higher ADA levels in females may predispose to false positives if cut-offs are rigidly applied.
4. Multimodal Approach: ADA should be combined with clinical, radiological, and microbiological findings rather than used in isolation.

Limitations

While our study provides important insights, certain limitations must be acknowledged. First, this was a single-center study with a relatively small sample size, which may limit generalizability. Second, we did not analyze ADA isoenzymes (ADA1 vs. ADA2), which may further improve specificity in distinguishing tuberculosis from other causes. Third, other confounding factors such as HIV status, nutritional deficiencies, and comorbidities were not extensively analyzed. Finally, follow-up data to confirm treatment response were not included.

Future Directions

Future research should aim at:

- Multicenter studies with larger cohorts to validate age- and sex-specific ADA thresholds.
- Evaluation of ADA isoenzymes, particularly ADA2, which is more specific for tuberculosis-related effusions.[23]
- Integration of ADA with novel biomarkers such as interferon-γ, IP-10, and nucleic acid amplification tests for improved diagnostic accuracy.[24]
- Development of diagnostic algorithms incorporating demographic adjustments to optimize clinical decision-making.

CONCLUSION

In summary, our study reaffirms ADA as a valuable biomarker for differentiating tuberculous from non-tuberculous pleural effusion. Importantly, ADA activity is influenced by age and female sex, with younger patients and females exhibiting higher values. These demographic factors must be considered to avoid misinterpretation and improve diagnostic accuracy, particularly in tuberculosis-endemic settings. Our findings highlight the need for age- and sex-adjusted ADA interpretation and support the integration of ADA into multimodal diagnostic strategies.

REFERENCES

1. *Light RW. Pleural diseases. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2018.*
2. *Hooper C, Lee YCG, Maskell N. Investigation of a unilateral pleural effusion in adults: British Thoracic Society pleural disease guideline. Thorax. 2010;65(Suppl 2):ii4–ii17.*
3. *Porcel JM. Pleural effusions: pathophysiology, diagnosis, and management. Curr OpinPulm Med. 2016;22(4):350–357.*
4. *Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972;77(4):507–513.*
5. *Porcel JM, Light RW. Diagnostic approach to pleural effusion in adults. Am Fam Physician. 2006;73(7):1211–1220.*
6. *Koegelenberg CFN, Diacon AH, Bolliger CT. Transthoracic ultrasonography for the respiratory physician. Respiration. 2012;84(4):337–350.*
7. *Diacon AH, et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J. 2003;22:589–591.*

8. *Ungerer JP, Oosthuizen HM, Bissbort SH, Vermaak WJ. Serum adenosine deaminase: isoenzymes and diagnostic applications. Clin Chem. 1992;38(7):1322–1326.*
9. *Piras MA, et al. Adenosine deaminase activity in pleural effusions: diagnostic value in tuberculous pleurisy. Clin Chim Acta. 1978;92:19–25.*
10. *Burgess LJ, et al. The use of adenosine deaminase and interferon gamma in the diagnosis of tuberculous pleuritis. Chest. 1996;109(2):414–419.*
11. *Sharma SK, Banga A. Pleural fluid adenosine deaminase in the diagnosis of tuberculous pleural effusion. Indian J Chest Dis Allied Sci. 1991;33(2):81–85.*
12. *Gupta BK, et al. Role of ADA estimation in differentiation of tuberculous and non-tuberculous pleural effusions. J Clin Med Res. 2010;2(2):79–84.*
13. *Liang QL, Shi HZ, Wang K, Qin SM, Qin XJ. Diagnostic accuracy of ADA in tuberculous pleurisy: a meta-analysis. Respir Med. 2008;102(5):744–754.*
14. *WHO. Global tuberculosis report 2023. Geneva: World Health Organization; 2023.*
15. *Goto M, et al. Clinical evaluation of ADA in pleural effusions. Respir Med. 2003;97:1066–1072.*
16. *Valdés L, et al. ADA isoenzymes in the diagnosis of tuberculous pleural effusion. Chest. 1993;103(3):458–465.*
17. *Riantawan P, Chaowalit P, Wongsangiem M, Rojanaraweewong P. Diagnostic value of ADA in tuberculous pleural effusion with reference to HIV coinfection and age. Respirology. 1999;4(4):321–325.*
18. *Pawelec G. Age and immunity: What is "immunosenescence"? Exp Gerontol. 2018;105:4–9.*
19. *Andrade RS, et al. Age-dependent immune responses and ADA activity. Clin Biochem. 2007;40:1234–1240.*
20. *Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016;16(10):626–638.*
21. *Markle JG, Fish EN. Sex-dependent immune modulation by hormones. Nat Rev Immunol. 2014;14(12):740–750.*
22. *WHO. Global tuberculosis report 2023. Geneva: World Health Organization; 2023.*
23. *Seibert AF, Haynes J Jr, Middleton R, Bass JB Jr. Tuberculous pleural effusion: twenty-year experience. Chest. 1991;99(4):883–886.*
24. *Dheda K, et al. Tuberculous pleural effusion: from pathogenesis to diagnostic biomarkers. Clin Chest Med. 2006;27(2):229–246.*
25. *Valdés L, et al. ADA activity in pleural fluids: diagnostic implications. Eur Respir J. 1993;6:349–355.*
26. *Gupta BK, et al. Role of ADA estimation in differentiation of tuberculous and non-tuberculous pleural effusions. J Clin Med Res. 2010;2(2):79–84.*
27. *Sager R, et al. Influence of age on ADA levels in pleural effusion. Respiration. 2010;79:437–444.*
28. *Perez-Rodriguez E, et al. ADA2 as a specific marker for TB pleural effusion. Eur Respir J. 1999;14:1383–1388.*
29. *Trajman A, et al. Diagnostic accuracy of interferon-gamma for TB effusion. Chest. 2008;133(4):1021–1028.*