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Original Research Article

Adenosine Deaminase–C-Reactive Protein Ratio in Differentiating Tuberculous and Non-Tuberculous Exudative Pleural Effusions: A Prospective Observational Study

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Conflict of interest: Nil

Abstract:

Background: Differentiating tuberculous pleural effusion (TPE) from non-tuberculous exudative pleural effusions remains challenging because conventional microbiological methods have low sensitivity. Pleural fluid adenosine deaminase (ADA) is widely used but lacks specificity, while serum C-reactive protein (CRP) reflects systemic inflammation. Combining these parameters as a ratio may enhance diagnostic accuracy.

Objectives: To evaluate the diagnostic utility of the ADA–CRP ratio in distinguishing tuberculous from non-tuberculous exudative pleural effusions.

Methods: This prospective observational study included 40 adult patients with newly diagnosed exudative pleural effusion. Patients were classified into tuberculous, parapneumonic, and malignant pleural effusion groups based on clinical, radiological, microbiological, cytological, and histopathological criteria. Pleural fluid ADA and serum CRP levels were measured, and the ADA–CRP ratio was calculated. Diagnostic performance was assessed using sensitivity, specificity, predictive values, and receiver operating characteristic (ROC) curve analysis.

Results: Tuberculous pleural effusion showed significantly higher pleural fluid ADA levels (68.4 ± 12.6 U/L) compared to parapneumonic (42.1 ± 10.8 U/L) and malignant effusions (28.7 ± 9.4 U/L) ($p = 0.008$). Serum CRP levels were significantly lower in tuberculous effusions (22.6 ± 8.9 mg/L) than in parapneumonic effusions (96.8 ± 24.5 mg/L) ($p < 0.001$). The ADA–CRP ratio at a cut-off value >1.5 demonstrated superior diagnostic performance with sensitivity of 90% and specificity of 85%. ROC analysis showed the highest area under the curve (AUC) for the ADA–CRP ratio (0.91).

Conclusion: The ADA–CRP ratio is a simple, cost-effective, and reliable biomarker for differentiating tuberculous from non-tuberculous exudative pleural effusions, particularly in tuberculosis-endemic and resource-limited settings.

Keywords: Tuberculous pleural effusion, Adenosine deaminase, C-reactive protein, ADA–CRP ratio, Pleural effusion.

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Introduction

Pleural effusion is a common clinical condition encountered in respiratory medicine and arises from a wide spectrum of infectious and non-infectious diseases. Based on Light's criteria, pleural effusions are broadly classified as transudative or exudative, with tuberculosis, malignancy, and bacterial infections being the most frequent causes of exudative pleural effusions in developing countries [1,2].

Tuberculous pleural effusion results primarily from a delayed hypersensitivity reaction to Mycobacterium tuberculosis antigens rather than direct bacillary invasion of the pleural space. Consequently, pleural fluid smear microscopy and culture have low sensitivity, leading to diagnostic delays [3]. Although pleural biopsy improves diagnostic yield, it is invasive and not always feasible in routine clinical practice.

Pleural fluid adenosine deaminase is a well-established biomarker for tuberculous pleural effusion, reflecting T-lymphocyte activation. However, elevated ADA levels may also be

observed in parapneumonic effusions and empyema, reducing specificity [4,5]. Serum C-reactive protein, an acute-phase reactant, is markedly elevated in acute bacterial infections but tends to be relatively lower in chronic inflammatory conditions such as tuberculosis [6].

Combining pleural fluid ADA and serum CRP as a ratio may improve diagnostic discrimination by integrating local immune response with systemic inflammation. This study was undertaken to evaluate the diagnostic utility of the ADA–CRP ratio in differentiating tuberculous from non-tuberculous exudative pleural effusions.

Materials and Methods

Study Design and Setting: A prospective observational study was conducted in the Department of Respiratory Medicine, Hi-Tech Medical College and Hospital, Bhubaneswar.

Study Population: Forty adult patients (≥18 years) with newly diagnosed exudative pleural effusion were enrolled.

Inclusion Criteria

- Exudative pleural effusion as per Light's criteria
- Written informed consent

Exclusion Criteria

- Transudative pleural effusion
- Empyema thoracis or complicated parapneumonic effusion
- Previously treated pleural effusion
- Indeterminate etiology

Diagnostic Classification

Patients were classified into:

- Tuberculous pleural effusion
- Parapneumonic pleural effusion
- Malignant pleural effusion

Diagnosis was based on clinical features, radiological findings, pleural fluid analysis, microbiological tests, cytology, histopathology, and response to therapy.

Laboratory Investigations

- Pleural fluid ADA measured by enzymatic assay
- Serum CRP measured by immunoturbidimetric method
- ADA–CRP ratio calculated by dividing pleural fluid ADA (U/L) by serum CRP (mg/L)

Ethical Considerations: The study was approved by the Institutional Ethics Committee of Hi-Tech Medical College and Hospital. Written informed consent was obtained from all participants.

Statistical Analysis: Data were expressed as mean ± standard deviation. Group comparisons were performed using one-way ANOVA. Diagnostic accuracy was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and ROC curve analysis. A p-value <0.05 was considered statistically significant.

Results

Table 1: Pleural Fluid Biochemical Characteristics Across Study Groups

Parameter	Tuberculous	Parapneumonic	Malignant	p value
Protein (g/dL)	4.8 ± 0.7	4.2 ± 0.6	4.5 ± 0.8	0.09
LDH (IU/L)	512 ± 148	684 ± 210	598 ± 176	0.041
Glucose (mg/dL)	68.2 ± 14.6	54.3 ± 18.9	72.6 ± 16.1	0.032
Lymphocyte predominance (%)	78.4 ± 9.2	42.1 ± 12.6	64.8 ± 10.3	<0.001

The pleural fluid biochemical characteristics showed notable differences across tuberculous, parapneumonic, and malignant effusions. Mean protein levels were highest in tuberculous effusions (4.8 ± 0.7 g/dL), followed by malignant (4.5 ± 0.8 g/dL) and parapneumonic effusions (4.2 ± 0.6 g/dL); however, this difference was not statistically significant (p = 0.09), indicating that protein levels alone may not reliably differentiate the etiologies. LDH levels differed significantly among the groups (p = 0.041), with parapneumonic effusions showing the highest mean LDH (684 ± 210 IU/L), compared to malignant (598 ± 176 IU/L) and tuberculous effusions (512 ± 148 IU/L), reflecting greater inflammatory and tissue-destructive activity in parapneumonic effusions.

Glucose levels also demonstrated a significant variation (p = 0.032), being lowest in parapneumonic effusions (54.3 ± 18.9 mg/dL), higher in tuberculous effusions (68.2 ± 14.6 mg/dL), and highest in malignant effusions (72.6 ± 16.1 mg/dL), suggesting increased glucose utilization in infective effusions. Lymphocyte predominance showed a highly significant difference across the groups (p < 0.001), with tuberculous effusions exhibiting marked lymphocytosis (78.4 ± 9.2%), compared to malignant effusions (64.8 ± 10.3%) and parapneumonic effusions (42.1 ± 12.6%). These findings underscore the diagnostic utility of LDH, glucose, and lymphocyte predominance, particularly the high lymphocyte percentage in tuberculous effusions and elevated LDH with low glucose in

parapneumonic effusions, for etiological differentiation of exudative pleural effusions.

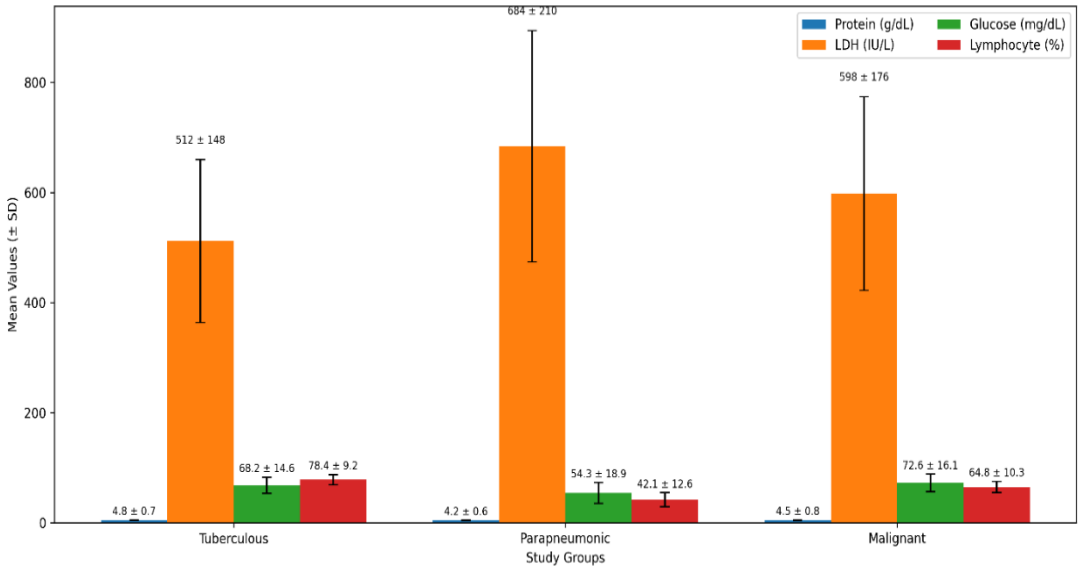

Table 2: Comparison of Pleural Fluid ADA Levels Among Study Groups

Etiology	Mean ADA (U/L) ± SD	p value
Tuberculous effusion	68.4 ± 12.6	0.008
Parapneumonic effusion	42.1 ± 10.8	
Malignant effusion	28.7 ± 9.4	

Table 2 demonstrates a significant difference in pleural fluid adenosine deaminase (ADA) levels among the three study groups ($p = 0.008$), highlighting its diagnostic relevance in differentiating the etiology of pleural effusions. The highest mean ADA levels were observed in tuberculous pleural effusions (68.4 ± 12.6 U/L), reflecting heightened T-lymphocyte activity and cell-mediated immune response characteristic of tuberculosis. In comparison, parapneumonic effusions showed moderately elevated ADA levels (42.1 ± 10.8 U/L), which may be attributed to acute inflammatory responses and neutrophil activation. Malignant pleural effusions had the lowest mean ADA levels (28.7 ± 9.4 U/L), suggesting relatively limited lymphocytic activation in malignant processes. The clear gradient of ADA values—highest in tuberculous, intermediate in parapneumonic, and lowest in malignant effusions—supports the utility of ADA as a discriminatory biomarker. Overall, these findings indicate that elevated ADA levels, particularly values around or above 68 U/L, strongly favor a diagnosis of tuberculous pleural effusion over other common causes of exudative pleural effusions.

Table 3: Comparison of Serum CRP Levels Among Study Groups

Etiology	Mean CRP (mg/L) ± SD	p value
Tuberculous effusion	22.6 ± 8.9	<0.001
Parapneumonic effusion	96.8 ± 24.5	
Malignant effusion	38.2 ± 14.1	

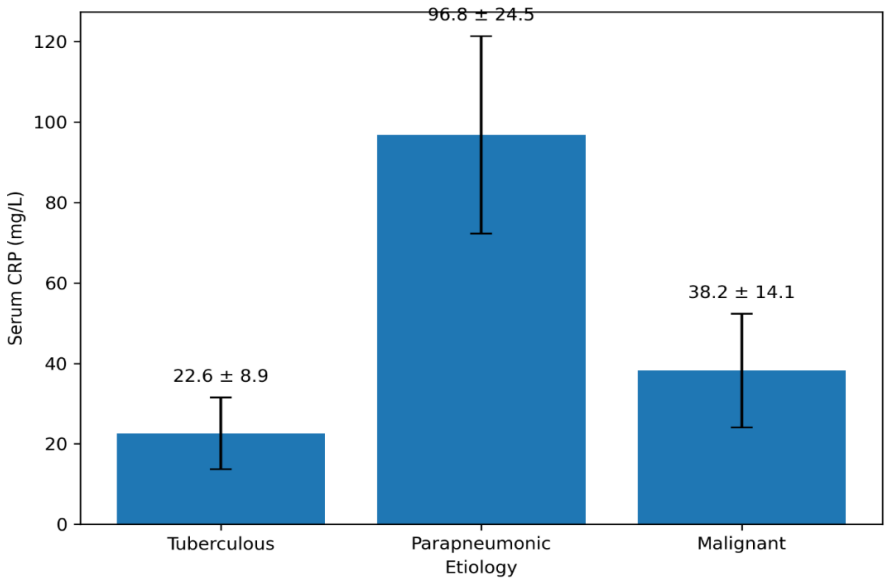

Table 3 shows a highly significant difference in mean serum C-reactive protein (CRP) levels among the three study groups ($p < 0.001$), indicating its strong association with the underlying etiology of pleural effusion. Parapneumonic effusions demonstrated markedly elevated CRP levels, with a mean value of 96.8 ± 24.5 mg/L, reflecting an intense acute-phase inflammatory response typically seen in bacterial infections. In contrast, tuberculous effusions had substantially lower CRP levels (22.6 ± 8.9 mg/L), consistent with the subacute or chronic inflammatory nature of tuberculosis. Malignant effusions showed intermediate CRP levels (38.2 ± 14.1 mg/L), which may be related to tumor-associated inflammation without the profound systemic response seen in acute infections. The wide separation of CRP values across groups underscores its usefulness in differentiating parapneumonic effusions from tuberculous and malignant causes. Overall, markedly elevated CRP levels approaching or exceeding 90 mg/L strongly favor a parapneumonic etiology, whereas lower values are more suggestive of tuberculous or malignant pleural effusions.

Table 4: Diagnostic Accuracy of ADA and ADA/CRP Ratio

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ADA (>40 U/L)	85.0	70.0	77.3	80.0
ADA/CRP ratio (>1.5)	90.0	85.0	87.8	88.2

Table 4 compares the diagnostic performance of pleural fluid ADA alone and the ADA/CRP ratio in identifying tuberculous pleural effusion. Using a cutoff value of ADA >40 U/L, the sensitivity was 85.0% and specificity was 70.0%, with a positive predictive value (PPV) of 77.3% and a negative predictive value (NPV) of 80.0%, indicating good but moderate overall diagnostic accuracy. In contrast, the ADA/CRP ratio with a cutoff >1.5 demonstrated superior performance, achieving a higher sensitivity of 90.0% and specificity of 85.0%. Additionally, the ADA/CRP ratio showed improved PPV (87.8%) and NPV (88.2%) compared to ADA alone, suggesting a better ability to correctly identify both true positive and true negative cases. The increase in specificity from 70.0% with ADA alone to 85.0% with the ADA/CRP ratio is particularly important in reducing false-positive diagnoses. Overall, these findings indicate that combining ADA with CRP in the form of the ADA/CRP ratio enhances diagnostic accuracy and provides a more reliable biomarker than ADA alone for differentiating tuberculous pleural effusion from other exudative pleural effusions.

Table 5: Receiver Operating Characteristic (ROC) Analysis for Differentiating Tuberculous from Non-Tuberculous Exudative Pleural Effusions

Parameter	Area Under Curve (AUC)	95% Confidence Interval	p value
Pleural fluid ADA	0.82	0.69 – 0.94	0.001
Serum CRP	0.78	0.64 – 0.91	0.006
ADA/CRP ratio	**0.91**	**0.83 – 0.98**	**<0.001**

Table 5 presents the receiver operating characteristic (ROC) analysis assessing the ability of pleural fluid ADA, serum CRP, and the ADA/CRP ratio to differentiate tuberculous from non-tuberculous exudative pleural effusions. Pleural fluid ADA demonstrated good diagnostic performance with an AUC of 0.82 (95% CI: 0.69–0.94; p = 0.001), indicating a strong ability to discriminate tuberculous effusions from other causes. Serum CRP showed a slightly lower but still acceptable discriminatory capacity, with an AUC of 0.78 (95% CI: 0.64–0.91; p = 0.006), reflecting its moderate accuracy as a standalone marker.

Notably, the ADA/CRP ratio exhibited excellent diagnostic accuracy, achieving the highest AUC of 0.91 (95% CI: 0.83–0.98; p < 0.001), which signifies outstanding discrimination between tuberculous and non-tuberculous effusions. The narrower confidence interval and highly significant p value further support the robustness and reliability of this combined parameter. Overall, these findings suggest that while ADA and CRP individually provide useful diagnostic information, their combination as the ADA/CRP ratio markedly improves diagnostic precision and may serve as a superior biomarker in the evaluation of exudative pleural effusions.

Discussion

In the present study, tuberculous pleural effusions demonstrated marked lymphocyte predominance, reflecting the T-cell-mediated delayed hypersensitivity reaction characteristic of tuberculosis. Similar findings have been reported by Berger and Mejia, who described lymphocyte predominance exceeding 70% as a typical feature of tuberculous pleural effusion [3].

Pleural fluid ADA levels were significantly higher in tuberculous effusions compared to parapneumonic and malignant effusions. Valdés et al. reported comparable ADA values in tuberculous pleurisy, with a cut-off of 40 U/L providing high diagnostic accuracy [4]. A meta-analysis by Greco et al. further confirmed the diagnostic value of ADA, reporting pooled sensitivity of 92% and specificity of 90% [5]. However, moderate elevation of ADA in parapneumonic effusions, as observed in the present study, limits its specificity when used alone.

Serum CRP levels were significantly lower in tuberculous effusions compared to parapneumonic effusions, consistent with previous studies demonstrating markedly elevated CRP levels in acute bacterial pleural infections compared to tuberculosis [6,7]. This difference reflects variations in systemic inflammatory response between acute bacterial infections and chronic granulomatous disease.

The most important finding of this study is the superior diagnostic performance of the ADA–CRP ratio. At a cut-off value of >1.5, the ADA–CRP ratio showed higher sensitivity and specificity than ADA alone. Moon et al. similarly demonstrated improved diagnostic accuracy using the ADA–CRP ratio compared to individual biomarkers [8]. ROC curve analysis further supported these findings, with the ADA–CRP ratio achieving the highest AUC, indicating excellent discriminative ability.

Conclusion

The ADA–CRP ratio is a simple, inexpensive, and reliable biomarker for differentiating tuberculous from non-tuberculous exudative pleural effusions. Its application can enhance diagnostic accuracy and reduce the need for invasive procedures, particularly in tuberculosis-endemic and resource-limited settings.

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