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Research Article

ROLE OF PLEURAL FLUID ADENOSINE DEAMINASE TO SERUM C-REACTIVE PROTEIN RATIO IN DETERMINING THE ETIOLOGICAL CAUSE OF EXUDATIVE PLEURAL EFFUSION: AN OBSERVATIONAL CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Exudative pleural effusion is a common clinical condition with diverse etiology, predominantly tuberculosis, malignancy, and parapneumonic infections. Differentiating these causes using routine pleural fluid analysis alone remains challenging. Pleural fluid adenosine deaminase (ADA) and serum C-reactive protein (CRP) are individually recognized biomarkers, but their combined ratio may offer superior diagnostic discrimination.

Objective: To assess the role of pleural fluid ADA to serum CRP (ADA/CRP) ratio in determining the etiological cause of exudative pleural effusion.

Methods: An observational cross-sectional study was conducted on 51 patients with confirmed exudative pleural effusion in the Department of Respiratory Medicine, National Institute of Medical Sciences and Research, Jaipur, over 18 months. Pleural fluid was analyzed for biochemical parameters, cytology, and ADA using a standard enzymatic colorimetric assay. Serum CRP was estimated using immunoturbidimetric method. The ADA/CRP ratio was calculated and compared among tubercular (TPE), malignant (MPE), and empyema/parapneumonic (PPE) groups using one-way ANOVA and post-hoc testing. Statistical analysis was performed with SPSS version 25.

Results: Among 51 patients (mean age 53.39 ± 17.26 years; 62.7% male), tubercular pleural effusion was the most common etiology (47.1%, n = 24), followed by empyema/parapneumonic effusion (31.4%, n = 16) and malignant pleural effusion (21.6%, n = 11). Mean pleural fluid ADA was highest in TPE (110.03 ± 21.15 U/L), intermediate in PPE (53.48 ± 25.20 U/L), and lowest in MPE (19.82 ± 6.29 U/L). Mean serum CRP was highest in PPE (109.17 ± 17.45 mg/L), reflecting acute bacterial inflammation. The ADA/CRP ratio showed the most significant discrimination: 1.97 ± 0.53 (TPE), 0.49 ± 0.23 (PPE), and 0.32 ± 0.08 (MPE) ($p < 0.001$). All malignant effusions had ADA/CRP ratio < 0.8, and most tubercular effusions had ratios > 1.5, forming a clear diagnostic gradient. Pleural fluid biochemical parameters — LDH, polymorphs, lymphocytes, total cell count, and glucose — differed significantly across groups ($p < 0.001$).

Conclusion: The pleural fluid ADA/serum CRP ratio is a simple, cost-effective, and reliable biomarker for differentiating tubercular from malignant and parapneumonic exudative pleural effusions. Its strong discriminatory gradient makes it a

practical adjunct in clinical settings, particularly where invasive procedures or advanced diagnostics are not readily accessible.

KEYWORDS: Pleural Effusion, Adenosine Deaminase, C-reactive Protein, ADA/CRP Ratio, Tuberculosis, Exudative Effusion, Biomarker Diagnosis.

Introduction

Pleural effusion — the pathological accumulation of fluid in the pleural space — is a frequently encountered clinical condition that may arise from a broad spectrum of underlying diseases[1]. Under physiological conditions, approximately 5–15 mL of fluid is maintained in the pleural space, produced by the parietal pleura and reabsorbed through lymphatic channels[2]. This balance is disrupted by alterations in hydrostatic pressure, oncotic pressure, or pleural membrane permeability, resulting in fluid accumulation[1]. Classification into transudative and exudative categories using Light's criteria — based on pleural fluid protein, lactate dehydrogenase (LDH), and their serum ratios — constitutes the first diagnostic step[4]. However, while Light's criteria reliably identify exudative effusions, they do not differentiate the specific etiology within this category, which requires further biochemical, cytological, and microbiological analysis.

Exudative pleural effusions carry significant diagnostic and therapeutic implications. In high-burden developing nations like India, tuberculosis (TB) remains the predominant cause of exudative effusion, while malignancy and parapneumonic infections are leading causes in developed countries[3]. The clinical, radiological, and biochemical profiles of these three major etiologies often overlap, making definitive diagnosis a challenge in routine practice. Invasive procedures such as pleural biopsy, thoracoscopy, and bronchoalveolar lavage, while definitive, carry procedural risks and are resource-intensive — limitations particularly relevant in primary and secondary care facilities across low-income settings.

Adenosine deaminase (ADA), an intracellular enzyme integral to purine metabolism and lymphocyte maturation, is markedly elevated in the pleural fluid of patients with tuberculous pleuritis due to T-lymphocyte activation[4]. Multiple meta-analyses have validated pleural fluid ADA as a sensitive and specific marker for tuberculous pleural effusion (TPE), with reported sensitivities of 88–95% and specificities of 85–93%[7]. However, ADA can also be elevated in empyema, lymphoma, and rheumatoid pleuritis, reducing its specificity when used alone.

C-reactive protein (CRP), synthesized by the liver in response to pro-inflammatory cytokines, is a well-established acute-phase reactant[16]. Serum CRP rises markedly in acute bacterial infections — including parapneumonic effusions and empyema — while remaining comparatively lower in tubercular and malignant effusions. This complementary pattern prompted the exploration of the combined ADA/CRP ratio as a diagnostic index that integrates local pleural inflammation (ADA) with systemic inflammatory response (CRP), potentially improving etiological discrimination.

Dole et al. (2024) demonstrated that an ADA/CRP ratio cut-off of 0.54 distinguished tuberculous from non-tuberculous effusions with sensitivity and specificity exceeding 90% and 88%, respectively[22]. Rabbi et al. (2023) reported a ratio cut-off of 1.25 with an AUC of 0.94 for differentiating TPE from MPE.23 Swetha et al. (2021) found that a cut-off of 1.2 achieved 78.95% sensitivity and 83.33% specificity[29]. Despite this growing evidence, large-scale prospective validation across diverse etiological groups — including empyema — remains limited, and regional data from Indian tertiary care centers are particularly sparse.

The present study was therefore conducted to evaluate the diagnostic utility of the pleural fluid ADA/serum CRP ratio in distinguishing the three major causes of exudative pleural effusion - tuberculosis, malignancy, and parapneumonic/empyema - and to characterize associated clinical, radiological, and biochemical correlates in a tertiary care hospital setting in North India.

Methods

Study Design and Setting

This was a hospital-based observational cross-sectional study conducted in the Department of Respiratory Medicine, National Institute of Medical Sciences and Research (NIMS University), Jaipur, Rajasthan, India, over a period of 18 months.

Participants

Inclusion criteria: Patients of either gender aged >18 years presenting with exudative pleural effusion, who were hemodynamically stable and provided written informed consent, were eligible.

Exclusion Criteria

Patients with transudative pleural effusion were excluded. Immunocompromised patients and those with comorbidities (diabetes mellitus, hypertension, bronchial asthma, epilepsy, cardiac disease) were also excluded to minimize confounding effects on CRP levels and biomarker interpretation.

Sample Size

The sample size was computed using the formula $n = (Z^2\alpha \cdot \sigma^2) / (2d^2)$, where $Z\alpha = 1.96$ at 95% confidence interval, σ represents the standard deviation of the mean pleural fluid ADA/serum CRP ratio, and d is the expected mean deviation. The calculation yielded $n = 51.4$, rounded to 51 patients.

Sampling Technique

Purposive sampling was employed. All eligible patients presenting to the outpatient and inpatient services of the Department of Respiratory Medicine during the study period were enrolled consecutively after meeting inclusion criteria.

Data Collection

A semi-structured case report form was used to record demographic data (age, sex), presenting symptoms (breathlessness, cough, chest pain), smoking history and intensity, physical examination findings, and imaging data. Thoracentesis was performed under aseptic conditions to obtain pleural fluid for analysis.

Diagnostic Classification

The final etiological diagnosis for each patient was established using the following standard methods:

- Empyema/parapneumonic effusion: Pleural fluid culture and sensitivity, Gram stain, turbid or frankly purulent fluid appearance
- Malignant pleural effusion: Pleural biopsy, pleural fluid cytology, thoracoscopy-guided biopsy with confirmed malignancy
- Tubercular pleural effusion: Pleural fluid AFB smear, CBNAAT/GeneXpert, pleural biopsy, thoracoscopy-guided biopsy, and Mycobacterium tuberculosis culture

Exudative effusions were classified using Light's criteria (pleural fluid protein/serum protein >0.5, pleural fluid LDH/serum LDH >0.6, or pleural fluid LDH >2/3 the upper limit of normal serum LDH)[4].

Biomarker Estimation

Pleural fluid ADA was measured using a standard enzymatic colorimetric assay (Giusti method). Serum CRP was quantified by an immunoturbidimetric method. The ADA/CRP ratio was calculated for each patient as:

ADA/CRP ratio = Pleural fluid ADA (U/L) / Serum CRP (mg/L)

Standard pleural fluid biochemical analysis included LDH, total protein, glucose, total cell count, and differential cell count (polymorphs and lymphocytes).

Statistical Analysis

All data were analyzed using SPSS version 25 and Microsoft Excel. Continuous variables are presented as mean ± standard deviation (SD); categorical variables as frequency (n) and percentage (%). Differences in ADA, CRP, and ADA/CRP ratio across etiological groups were tested using one-way ANOVA; a p-value <0.05 was considered statistically significant. Associations between categorical variables were tested using the Chi-square test.

Ethical Considerations

The study was approved by the Institutional Scientific and Ethics Committee of NIMS University, Jaipur. Written informed consent was obtained from all participants or their legally acceptable representatives in both English and Hindi. Participation was voluntary with freedom to withdraw at any time without consequence to medical care.

Results

Demographic and Clinical Characteristics

A total of 51 patients with confirmed exudative pleural effusion were enrolled. The mean age was 53.39 ± 17.26 years, indicating a broad age range within the cohort. Males constituted 62.7% (n = 32) and females 37.3% (n = 19), demonstrating a clear male predominance (Table 1). All 51 patients (100%) presented with chest pain, 47 (92.2%) with breathlessness, and 42 (82.4%) with cough.

Table 1: Demographic profile of study participants (n = 51)

Variable	n	%
Sex: Male	32	62.7
Sex: Female	19	37.3
Smoker	26	51.0
Non-smoker	25	49.0
Heavy smoker (≥20 cigarettes/bidis per day)	19	37.2
Moderate smoker (10–19/day)	6	11.8
Light smoker (1–9/day)	1	2.0

Smoking and Etiological Diagnosis

Smoking intensity showed a statistically significant association with final diagnosis (p = 0.028). Heavy smokers (≥20/day) were predominantly diagnosed with malignant pleural effusion (81.8%), while non-smokers were more commonly associated with tubercular effusion (66.7%) and parapneumonic effusion (50.0%). This dose-response relationship between smoking burden and malignant etiology is clinically consistent with known risk.

Etiological Distribution

Tubercular pleural effusion (TPE) was the most common diagnosis, present in 24 patients (47.1%), followed by empyema/parapneumonic effusion (PPE) in 16 patients (31.4%), and malignant pleural effusion (MPE) in 11 patients (21.6%) (Table 2). Infective causes collectively accounted for 78.4% of all exudative effusions in this cohort.

Table 2: Etiological diagnosis of exudative pleural effusion (n = 51)

Diagnosis	n	%
Tubercular pleural effusion/empyema	24	47.1
Empyema/parapneumonic effusion	16	31.4
Malignant pleural effusion	11	21.6
Total	51	100

Radiological and Ultrasonographic Findings

Chest X-ray showed right and left lower zone opacities

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with equal frequency (35.3% each), bilateral haziness in 21.6%, left hemiopaque lung in 5.9%, and right hemiopaque lung in 2.0%. On USG thorax, moderate effusion was the most common finding (45.1%), followed by mild effusion (25.5%), loculated effusion (21.6%), and massive effusion (7.8%). Left-sided effusion was most frequent (41.2%), followed by right-sided (37.3%) and bilateral (21.6%).

The association between USG-based effusion characteristics and final diagnosis was statistically significant ($p = 0.010$). Massive effusion was observed exclusively in malignant cases (36.4%), while loculated effusion was more common in tubercular (29.2%) and parapneumonic (18.8%) groups, consistent with the chronic inflammatory and fibrinous process in these conditions.

Pleural Fluid Biochemical and Cytological Profile

Pleural fluid biochemical parameters demonstrated significant inter-group differences, except for total protein (Table 3). Empyema/PPE exhibited markedly elevated LDH (1209.69 ± 516.75 IU/L) and polymorph predominance (71.88 ± 20.48%), with the highest total cell count (9180.94 ± 3088.87 cells/µL). In contrast, TPE and MPE showed lymphocyte predominance (79.75 ± 16.67% and 68.18 ± 16.01%, respectively) and comparatively lower LDH. Pleural fluid glucose was lowest in PPE (66.38 ± 16.68 mg/dL), reflecting high metabolic activity by inflammatory cells. All inter-group differences for LDH, glucose, polymorphs, lymphocytes, and total cell count were statistically significant ($p < 0.001$).

Pleural Fluid ADA, Serum CRP, and ADA/CRP Ratio

One-way ANOVA demonstrated highly significant differences in pleural fluid ADA, serum CRP, and ADA/CRP ratio across all three etiological groups ($p < 0.001$ for all) (Table 4).

Pleural fluid ADA was highest in TPE (110.03 ± 21.15 U/L), reflecting intense T-lymphocyte activation in tubercular disease. Serum CRP was highest in PPE (109.17 ± 17.45 mg/L), consistent with the acute systemic inflammatory response of bacterial infection. The ADA/CRP ratio showed the most powerful discrimination: TPE values (mean 1.97 ± 0.53) were markedly separated from both PPE (0.49 ± 0.23) and MPE (0.32 ± 0.08).

ADA/CRP Ratio Distribution by Etiology

Distribution analysis of ADA/CRP ratio ranges further confirmed the diagnostic gradient (Table 5). All 11 malignant effusions had an ADA/CRP ratio below 0.8. The majority of tubercular effusions had ratios above 1.5. Empyema/parapneumonic effusions clustered in the intermediate range (0.3–1.0). This non-overlapping pattern at the extremes establishes a clear clinical decision threshold.

Table 3: Pleural fluid biochemical and cytological parameters by etiological group

Parameter	PPE (Mean ± SD)	MPE (Mean ± SD)	TPE (Mean ± SD)	p-value
LDH (IU/L)	1209.69 ± 516.75	332.36 ± 183.14	368.46 ± 230.47	<0.001
Protein (g/dL)	4.36 ± 0.52	4.26 ± 0.40	4.40 ± 0.40	0.680
Glucose (mg/dL)	66.38 ± 16.68	89.18 ± 21.38	106.13 ± 19.91	<0.001
Polymorphs (%)	71.88 ± 20.48	31.36 ± 16.45	20.04 ± 16.64	<0.001
Lymphocytes (%)	27.19 ± 19.83	68.18 ± 16.01	79.75 ± 16.67	<0.001
Total Cell Count (cells/µL)	9180.94 ± 3088.87	2310.91 ± 976.21	2243.08 ± 1098.77	<0.001

PPE = parapneumonic/empyema; MPE = malignant pleural effusion; TPE = tubercular pleural effusion.

Table 4: Pleural fluid ADA, serum CRP, and ADA/CRP ratio by etiological group

Parameter	PPE (Mean ± SD)	MPE (Mean ± SD)	TPE (Mean ± SD)	p-value
Pleural fluid ADA (U/L)	53.48 ± 25.20	19.82 ± 6.29	110.03 ± 21.15	<0.001
Serum CRP (mg/L)	109.17 ± 17.45	61.34 ± 12.11	60.05 ± 20.38	<0.001
ADA/CRP Ratio	0.49 ± 0.23	0.32 ± 0.08	1.97 ± 0.53	<0.001

Table 5: Distribution of ADA/CRP ratio ranges by etiology

ADA/CRP Ratio Range	PPE (n = 16)	MPE (n = 11)	TPE (n = 24)
< 0.8	Majority	All (100%)	None
0.8 – 1.5	Minority	None	Few
> 1.5	None	None	Majority

Discussion

This observational cross-sectional study demonstrates that the pleural fluid ADA/serum CRP ratio provides strong, statistically significant discrimination among the three most common causes of exudative pleural effusion — tuberculosis, malignancy, and parapneumonic/empyema — and represents a clinically practical, low-cost diagnostic adjunct in resource-limited settings.

The demographic profile of the study cohort, with a mean age of 53.39 years and 62.7% male predominance, aligns with existing Indian epidemiological data. Gupta et al. similarly reported a male-predominant age distribution in tertiary-level pleural effusion cases in India, reflecting greater tobacco exposure, occupational risk, and tuberculosis susceptibility among males[30]. The observation that malignant effusion was significantly more common in heavy smokers (≥20 sticks/day; 81.8% of MPE cases) reinforces the well-established causal association between tobacco exposure and lung malignancy-related pleural involvement.

Tuberculosis was the dominant etiology in this cohort (47.1%), consistent with India's status as a high-TB-burden nation. This pattern contrasts with Western series where malignancy and parapneumonic effusions predominate[3]. The high proportion of infective causes (78.4% collectively) in this dataset underscores the need for accessible non-invasive diagnostic tools in settings where AFB culture turnaround is delayed and thoracoscopy may not be available.

The biochemical and cytological profile followed expected patterns. Empyema/PPE showed marked LDH elevation, neutrophil predominance, and low glucose, consistent with intense acute inflammation and metabolic consumption by bacteria and neutrophils. TPE and MPE both showed lymphocyte predominance, which is the source of diagnostic ambiguity when ADA is used alone — since lymphocyte-rich malignant effusions (particularly lymphomatous) can occasionally raise ADA, reducing specificity. This is precisely the diagnostic gap that the ADA/CRP ratio bridges.

The ADA/CRP ratio emerged as the most discriminatory parameter across all groups ($p < 0.001$), outperforming ADA or CRP used individually. The inverse behavior of these two markers across etiologies creates a biologically rational index: ADA rises with T-lymphocyte activity (tuberculosis), while CRP rises with acute bacterial inflammation (empyema). In malignant effusions, neither stimulus is strongly active, and both values remain comparatively low, yielding the lowest ratio. The mean ADA/CRP ratio of 1.97 in TPE versus 0.49 in PPE and 0.32 in MPE, combined with non-overlapping range distributions, suggests potential clinical cut-off thresholds. These findings are highly concordant with prior studies: Dole et al.reported a cut-off of 0.54 with >90% sensitivity and >88% specificity;22 Rabbi et al. found an AUC of 0.94 at a cut-off of 1.25;23 Lee et al. identified a cut-off of 5.62 (in a slightly different assay calibration) with 89% sensitivity and 88% specificity[31]. The present study's data are consistent with this growing evidence base, validating the ratio in a diverse Indian tertiary-care cohort.

The USG findings further reinforced etiological trends. Massive effusion occurred exclusively in malignant cases, while loculated effusions were more frequent in tubercular and parapneumonic groups, consistent with the fibrinous exudate and organization characteristic of chronic infection. These findings replicate earlier observations by Maskell et al. and Fartoukh et al. on ultrasound morphology in pleural disease.

The integrative strength of this study lies in the clinical practicality of its findings. Both ADA and CRP are inexpensive, routinely available, and technically simple assays accessible in the majority of district and secondary care hospitals. Their combination avoids the need for expensive molecular tests or invasive biopsy in a substantial proportion of patients, particularly when the ratio falls clearly in the extreme ranges (>1.5 for TB, <0.8 for malignancy). This is particularly relevant in settings where thoracoscopy is unavailable, patients are unfit for biopsy, or rapid decision-making is required for empirical anti-TB therapy.

Limitations

This study has important limitations. The sample size of 51 patients is relatively small, limiting the statistical power for subgroup analyses and ROC curve generation with robust confidence intervals. The single-center design at a tertiary care hospital in Jaipur may not reflect the etiological distribution and biomarker profiles across geographically diverse populations. The cross-sectional design precludes assessment of longitudinal treatment response or biomarker change over time. Immunocompromised patients and those with major comorbidities were excluded, meaning the utility of the ratio in HIV-positive patients or those on steroids — who may have atypical ADA and CRP responses — remains uncharacterized. Rare causes of exudative effusion (rheumatoid pleuritis, drug-induced effusions, chylothorax) were not systematically represented. Formal ROC analysis with area under the curve (AUC) estimation and prospective cut-off validation was not performed in this dataset and represents a priority for future study.

Conclusion

The pleural fluid ADA/serum CRP ratio provides clinically meaningful, statistically robust discrimination among tubercular, malignant, and parapneumonic exudative pleural effusions. Tubercular effusions consistently showed the highest ratio values (mean 1.97), empyema/parapneumonic effusions intermediate values (mean 0.49), and malignant effusions the lowest values (mean 0.32), with highly significant inter-group differences ($p < 0.001$). All malignant effusions demonstrated ADA/CRP ratio < 0.8, while most tubercular effusions exceeded 1.5, forming a clear diagnostic

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gradient that enables point-of-care decision-making. Given that both biomarkers are widely available, inexpensive, and technically simple, the ADA/CRP ratio represents a practical and reliable adjunct for etiological diagnosis of exudative pleural effusion, particularly in high-TB-burden, resource-limited settings. Larger multicenter prospective studies are recommended to establish validated cut-off values, formal sensitivity/specificity estimates, and AUC data across diverse populations.

Ethics Approval

Institutional Scientific and Ethics Committee, National Institute of Medical Sciences and Research, Jaipur Running title: ADA/CRP ratio in exudative pleural effusion.

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NIMS University, Rajasthan, Jaipur

Conflict of Interest

None declared

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