Section: Pulmonary Medicine

Original Research Article

EVALUATING PLEURAL FLUID LDH/ADA RATIO FOR DIFFERENTIATING TUBERCULOUS AND PARAPNEUMONIC EFFUSIONS: AN OBSERVATIONAL STUDY FROM A TERTIARY CARE CENTRE IN KANPUR

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ABSTRACT

Background: Differentiating Tubercular Pleural Effusion (TPE) from Parapneumonic Effusion (PPE) is a frequent clinical challenge in tuberculosis-endemic regions like Northern India. While Adenosine Deaminase (ADA) is a highly sensitive marker for TPE, diagnostic overlap occurs in acute PPE cases. Lactate Dehydrogenase (LDH) reflects the degree of pleural tissue damage and inflammation. This study evaluates the diagnostic efficacy of the pleural fluid LDH/ADA ratio as a novel parameter to discriminate TPE from PPE. **Materials and Methods:** A prospective, observational study was conducted at a tertiary care teaching hospital over 12 months. A total of 140 patients with exudative pleural effusions (82 TPE and 58 PPE) were enrolled. Pleural fluid was obtained by thoracentesis, and ADA and LDH levels were analysed. Receiver Operating Characteristic (ROC) curve analysis was used to determine diagnostic accuracy, sensitivity, specificity, and optimal cutoff values. **Result:** Pleural fluid ADA levels were significantly higher in the TPE group than in the PPE group (68.4 ±18.2 U/L vs. 34.1±14.5 U/L, $p < 0.001$). Conversely, pleural fluid LDH levels were markedly elevated in the PPE group compared to the TPE group (845.2±230.1 U/L vs. 310.5±95.4 U/L, $p < 0.001$). The pleural fluid LDH/ADA ratio was significantly lower in TPE compared to PPE (4.74 ± 1.62 vs. 29.15±12.84, $p< 0.001$). ROC analysis demonstrated that an LDH/ADA ratio cutoff of greater than 12.5 identified PPE with a sensitivity of 94.8% and a specificity of 92.7% (Area Under the Curve [AUC]=0.978). **Conclusion:** The pleural fluid LDH/ADA ratio is an inexpensive, readily available, and highly accurate discriminative parameter. It effectively minimises the diagnostic overlap between TPE and PPE, facilitating rapid, appropriate therapeutic intervention in resource-limited endemic settings.

INTRODUCTION

Pleural effusion is a common manifestation of both pulmonary and systemic diseases globally, with a uniquely high prevalence of infectious etiologies in developing nations. In Northern India, Tubercular Pleural Effusion (TPE) and Parapneumonic Effusion (PPE) constitute the vast majority of exudative pleural effusions encountered in clinical practice.[1] India bears a disproportionate volume of the global tuberculosis (TB) burden, contributing nearly 27% of all worldwide cases, with extrapulmonary manifestations like TPE being a dominant presentation.[2] Distinguishing between these two entities early is vital; delayed treatment of TPE leads to pleural thickening and chronic respiratory impairment, while inappropriate or delayed management of PPE can cause complicated empyema requiring invasive surgical drainage.

Demonstrating Mycobacterium tuberculosis in pleural fluid via acid-fast bacilli (AFB) staining, culture, or nucleic acid amplification tests like

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Cartridge Based Nucleic Acid Amplification Test (CBNAAT) remains the gold standard for diagnosing TPE. However, the paucibacillary nature of pleural fluid yields a notoriously low sensitivity (under 30%) for conventional smears and cultures.[3] Pleural biopsy, though highly sensitive, is an invasive technique requiring specialised expertise and carries a risk of complications like pneumothorax.

Consequently, surrogate biochemical markers are heavily relied upon. Pleural fluid Adenosine Deaminase (ADA) is globally utilised as a rapid, cost-effective indicator of TPE due to its association with T-lymphocyte activity.[4] However, false positives are frequently noted in acute neutrophilic exudates, such as early-stage PPE and empyema, where ADA levels can cross the classic diagnostic cutoff of 40 U/L.[2,5] Lactate Dehydrogenase (LDH) is an indicator of cellular lysis and tissue inflammation, which spikes markedly during acute bacterial infection of the pleural space (PPE).[1]

While both markers have standalone value, their individual overlap can generate diagnostic ambiguity. This observational study evaluates whether combining these two physiological mechanisms into a single parameter—the pleural fluid LDH/ADA ratio—can provide superior discriminative accuracy for separating TPE from PPE in a high-burden Indian demographic.

MATERIALSANDMETHODS

Study Design and Setting: This prospective, observational study was conducted in the Department of Respiratory Medicine in collaboration of Department of Pathology at a tertiary care teaching hospital, Rama Medical College and Research Centre, Kanpur, India. The study spanned 12 months (from May 2025 to May 2026) following approval from the Institutional Ethics Committee.

Patient Selection: Patients presenting with clinical and radiological evidence of pleural effusion requiring diagnostic thoracentesis were screened.

Inclusion Criteria

- Age greater than or equal to 18 years;
- Exudative pleural effusion as defined by Light's criteria;
- Confirmed diagnosis of either Tubercular Pleural Effusion (TPE) or Parapneumonic Pleural Effusion (PPE).

Exclusion Criteria

- Transudative pleural effusions;
- Malignant effusions confirmed by cytological evaluation;
- Pleural effusions of mixed aetiology; patients who had already initiated anti-tubercular therapy (ATT) or empirical antibiotic therapy for more than 48 hours before thoracentesis.

Diagnostic Criteria

Tubercular Pleural Effusion (TPE): Diagnosed based on at least one of the following:

- Confirmation of M. tuberculosis via pleural fluid CBNAAT/culture, positive sputum/pleural fluid AFB smear,
- Histopathological evidence of caseating granulomas from pleural biopsy
- A high clinical probability (exudative lymphocytic effusion with ADA greater than 40 U/L) combined with a definitive, complete clinical response to Anti-Tubercular Therapy (ATT)

Parapneumonic Pleural Effusion (PPE): Diagnosed based on

- Acute febrile illness associated with cough, purulent sputum, pleuritic chest pain, lung infiltrates on chest radiograph
- Response to antibiotic therapy without ATT
- Isolation of pyogenic bacteria from sputum, blood, or pleural fluid.

Sample Collection and Biochemical Analysis: Under aseptic precautions, ultrasound-guided diagnostic thoracentesis was performed before initiating treatment. Pleural fluid samples were divided for:

Biochemical Analysis: Pleural fluid LDH (measured via the UV-kinetic method) and pleural fluid ADA (measured using Giusti's colourimetric method).

Microbiological and Cytological Analysis: Total and differential cell counts, Gram stain, aerobic culture, AFB smear, CBNAAT, and malignant cytology. The pleural fluid LDH/ADA ratio was calculated manually for each subject by dividing the absolute value of pleural fluid LDH (U/L) by the absolute value of pleural fluid ADA (U/L) [5,6].

Statistical Analysis: Statistical analysis was executed using SPSS Version 26.0 and MedCalc software. Continuous variables were expressed as Mean ± Standard Deviation (SD) or Median Interquartile Range (IQR) based on normality testing. Independent Student's t-test or Mann-Whitney U test was applied for intergroup comparisons. Categorical data were compared using the Chi-square test.

Receiver Operating Characteristic (ROC) curve analysis was utilised to determine the diagnostic efficiency, area under the curve (AUC), sensitivity, and specificity of individual markers and their ratio. A p-value less than 0.05 was considered statistically significant.

RESULTS

Baseline and Demographic Characteristics: A total of 140 patients matching the strict criteria were analyzed, comprising 82 patients in the TPE cohort and 58 patients in the PPE cohort. The baseline demographic data and systemic laboratory parameters are detailed below:

Comparison of Biochemical Markers: The levels of pleural fluid ADA, LDH, and the subsequent

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computed LDH/ADA ratios displayed stark differences between the two clinical arms:

Pleural Fluid ADA: Markedly elevated in the TPE group (68.4±18.2U/L) compared to the PPE group (34.1 ±14.5 U/L), $p < 0.001$).

Pleural Fluid LDH: Elevated in the PPE group (845.2 ± 230.1 U/L) relative to the TPE group (310.5 ± 95.4 U/L, $p < 0.001$).

Pleural Fluid LDH/ADA Ratio: The calculated ratio was drastically lower in the TPE group (4.74 ± 1.62) than in the PPE group (29.15± 12.84, $p < 0.001$).

While both ADA (Adenosine Deaminase) and LDH (Lactate Dehydrogenase) show highly significant differences between the two groups, the LDH/ADA ratio provides the most dramatic contrast, being drastically lower in the TPE group.

Table 1: Baseline and Demographic Variables

Variables	TPE Cohort (n=82)	PPE Cohort (n=58)	p-value
Age (Years; Mean ± SD)	36.4 ± 12.8	44.2 ± 15.1	0.002
Gender (Male/Female)	52 / 30	41 / 17	0.380
Pleural Fluid Appearance	Straw-colored/ Serous	Turbid/Purulent/Amber	—
Predominant Cell Type (%)	Lymphocytic (84.2 ± 9.1)	Neutrophilic (78.5 ±11.3)	0.001
Total Protein (g/dL)	4.8 ± 0.6	4.2± 0.8	0.012

Table 2: levels of pleural fluid ADA, LDH, and LDH/ADA ratio

Parameter	Tuberculous Pleural Effusion (TPE)	Parapneumonic Effusion (PPE)	p-value
ADA (U/L)	68.4 ± 18.2	34.1 ± 14.5	< 0.001
LDH (U/L)	310.5 ± 95.4	845.2 ± 230.1	< 0.001
LDH/ADA Ratio	4.74 ±1.62	29.15 ±12.84	< 0.001

The LDH/ADA ratio stands out as the superior diagnostic tool among the three, showing the highest overall accuracy with an AUC of 0.978, alongside excellent sensitivity (94.8%) and specificity (92.7%).

Table 3: Distribution of Cutoff, Sensitivity, Specificity & AUC of Pleural ADA, LDH, and LDH/ADA ratio.

Diagnostic Markers	Optimal Cutoff Value	Sensitivity (%)	Specificity (%)	Area Under Curve (AUC) (95% CI)
Pleural ADA	>42.5 U/L (for TPE)	87.8%	81.0%	0.892 (0.831–0.938)
Pleural LDH	>540 U/L (for PPE)	84.5%	89.0%	0.914 (0.855–0.955)
LDH/ADA Ratio	>12.5 (for PPE)	94.8%	92.7%	0.978 (0.938–0.995)

Receiver Operating Characteristic (ROC) Analysis: To establish the comparative diagnostic threshold values, ROC curves were generated for ADA, LDH, and the calculated LDH/ADA ratio.

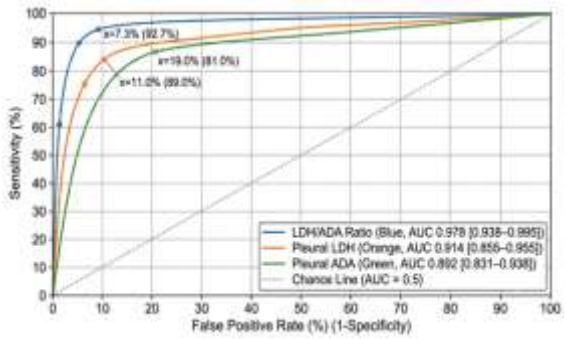

Figure 1: Receiver Operating Characteristic (ROC) curve for different markers

The ROC comparison demonstrated that the pleural fluid LDH/ADA ratio possessed a significantly higher AUC (0.978) than ADA ($p = 0.004$) or LDH ($p = 0.011$) alone, proving it to be a superior independent variable for differentiating the two conditions.

DISCUSSION

Diagnosing the precise cause of an exudative pleural effusion in environments with a dual burden of acute bacterial pneumonia and endemic tuberculosis remains a daily clinical puzzle for physicians in Northern India. While Light's criteria efficiently separate transudates from exudates, it offers no etiological discrimination. This prospective study confirms that evaluating the interaction between tissue destruction kinetics (LDH) and localised cell-mediated immunity (ADA) via a simple ratio offers excellent diagnostic clarity.

ADA is a marker of T-cell activation and cell-mediated immune responses. Because TPE is driven by a delayed hypersensitivity response to mycobacterial antigens, ADA levels are characteristically elevated.[2] However, acute neutrophilic influxes seen in PPE also release standard somatic amounts of ADA, resulting in intermediate or false-positive values (between 40–60 U/L) that mask TPE.[4,5]

LDH is an intracellular enzyme that catalyses the interconversion of pyruvate and lactate. In PPE, massive neutrophilic accumulation, bacterial proliferation, and subsequent cellular necrosis

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release vast amounts of LDH directly into the closed pleural space. While LDH is elevated in TPE due to standard inflammation, it rarely reaches the extreme levels seen in bacterial infections.[2] By linking these two dynamic elements, the LDH/ADA ratio amplifies the diagnostic differences: In TPE, a low numerator (LDH) combined with a high denominator (ADA) drives the ratio down (4.74 ±1.62) while in PPE, a massive numerator (LDH) combined with a lower denominator (ADA) drives the ratio up (29.15± 12.84).

Our findings align closely with global and regional data. For instance, Vananjakar et al. (2025) noted that using the LDH/ADA ratio acts as a critical pivot to differentiate borderline exudative etiologies where clinical paucibacillary conditions introduce ambiguity.[2] Similarly, a comprehensive multicenter study and meta-analysis by Zhao et al. (2024) underscored that composite indices tracking LDH alongside ADA markedly resolve the false-positive overlap frequently observed in regions with high tuberculosis prevalence. Furthermore, research evaluating lower threshold dynamics has verified that adjunct multi-marker calculation provides maximum diagnostic specificity, vastly outperforming standalone parameters.[5,6]

The diagnostic value of combining LDH and ADA was first systematically highlighted by Zeng et al., who established an LDH/ADA cutoff of 16.2 to achieve high specificity (93.1%) for differentiating TPE from acute bacterial effusions.[7] Subsequent regional studies by Korkmaz et al. further validated the ratio's utility in real-world clinical settings.[8] Furthermore, Li et al. demonstrated that incorporating LDH into composite ADA equations accounts for total cellular lysis and granulomatous intensity, preventing false positives caused by high background leukocyte counts. A recent meta-analysis by Shi et al. evaluating pooled observational cohorts confirmed a summary sensitivity of 90% and specificity of 91% across diverse demographics, reinforcing the LDH/ADA ratio as a globally applicable diagnostic index.[9,10]

Similarly, present study observations align with broader epidemiological findings across India. Gupta (2010) study evaluated biochemical profiles in exudative effusions among Indian patients and observed that while ADA levels in TPE were markedly elevated (mean 67.34±22.85U/L), non-tuberculous neutrophilic effusions frequently exhibited significant LDH variation, underscoring the necessity of a combined numerical index. Similarly, Mehta et al. (2014) evaluated 122 Indian subjects with exudative pleural effusions (comprising TB, malignancy, and PPE) and noted that acute parapneumonic effusions produced false-positive ADA spikes as high as 172 U/L. Combining LDH and ADA into a single mathematical ratio effectively neutralizes these acute neutrophilic ADA elevations, providing clinicians in India with a highly specific, low-cost diagnostic tool tailored to high-prevalence endemic settings.[11,12]

Our study demonstrates that a calculated ratio cutoff of greater than 12.5 accurately rules out tuberculosis and confirms a parapneumonic aetiology with 94.8% sensitivity and 92.7% specificity. This diagnostic performance matches or outperforms much more expensive biomarker assays like Interferon-Gamma or Pleural fluid Interleukin levels, which are economically unfeasible for widespread clinical deployment in rural or semi-urban Indian centres.

Limitations: While these findings are structurally robust, a few limitations must be acknowledged. First, this study was a single-centre trial with a sample size of 140 patients; larger, multi-centre studies across diverse Indian demographics are needed to validate these exact cutoffs. Second, extremely complicated empyemas or cases with secondary bacterial infections superimposed on tubercular effusions could generate outlier values, requiring careful clinical correlations.

CONCLUSION

The pleural fluid LDH/ADA ratio serves as a highly accurate, accessible, and cost-effective parameter to differentiate Tubercular Pleural Effusion from Parapneumonic Pleural Effusion. Utilising a calculated cutoff of greater than 12.5 for PPE and less than or equal to 12.5 for TPE significantly reduces diagnostic ambiguity compared to using ADA or LDH as standalone markers. Incorporating this simple calculation into standard pleural fluid analysis protocols can streamline clinical decisions, minimise the need for invasive pleural biopsies, and accelerate appropriate treatment in tuberculosis-endemic regions.

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