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TO STUDY SERUM LDH AND ADENOSINE DEAMINASE LEVELS IN PLEURAL FLUID IN PATIENTS WITH PLEURAL EFFUSION IN A TERTIARY CARE CENTER

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ABSTRACT

Background: Pleural effusion, characterized by excessive fluid accumulation in the pleural cavity, presents diagnostic challenges in differentiating its causes, primarily tuberculous pleuritis (TPE), parapneumonic effusion (PPE), and malignant pleural effusion (MPE). This study evaluates the diagnostic utility of pleural fluid adenosine deaminase (ADA) and lactate dehydrogenase (LDH) levels, as well as their ratio, in categorizing pleural effusions.

Methods: In this cross-sectional study conducted over 18 months at a tertiary care center, 100 adult patients diagnosed with pleural effusion via chest X-ray and ultrasound were included. ADA and LDH levels were measured in pleural fluid, and the LDH/ADA ratio was calculated. Diagnostic performance was assessed using receiver operating characteristic (ROC) analysis.

Results: Among the participants, 37 had TPE, 30 had PPE, and 33 had MPE. The mean ADA levels were significantly higher in TPE (75.2 U/L) compared to PPE (59.2 U/L) and MPE (35.50 U/L). ROC analysis revealed that an ADA cutoff of >36 U/L had a sensitivity of 88.5% and specificity of 53.5% for TPE. LDH levels were also elevated, with a cutoff of ≤1291 U/L for TPE showing limited diagnostic value. Notably, the LDH/ADA ratio of ≤20.81 effectively differentiated TPE, achieving a sensitivity of 84.0% and specificity of 63.4%.

Conclusion: The combination of pleural fluid ADA and LDH levels, particularly the LDH/ADA ratio, serves as a valuable tool for differentiating between TPE, PPE, and MPE. These findings can enhance clinical decision-making and improve patient management strategies, ultimately leading to better prognoses.

Keywords: Pleural effusion, tuberculous pleuritis, adenosine deaminase, lactate dehydrogenase, diagnostic utility, LDH/ADA ratio.

INTRODUCTION

Pleural effusion is the buildup of an abnormal or excessive volume of fluid in the pleural cavity. This condition occurs when fluid formation outpaces absorption, and it can result from pleural, lung, or systemic diseases or as a side effect of specific medications. [1] In a healthy nonsmoking person, normal pleural fluid volume is about 0.26 ± 0.1 ml/kg.[2] In developed countries, the estimated prevalence of pleural effusion is approximately 320 cases per 100,000 people.[3]

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The initial approach to diagnosing pleural fluid is to determine if the effusion is transudative or exudative, typically done using Light's criteria. According to these criteria, pleural fluid is classified as exudative if it meets at least one of the following conditions: the pleural fluid protein-to-serum protein ratio is greater than 0.5, the pleural fluid lactate dehydrogenase (LDH)-to-serum LDH ratio is more than 0.6, or the pleural fluid LDH exceeds two-thirds of the upper limit of the normal serum LDH value.[2]

The primary causes of exudative pleural effusions frequently encountered in clinical practice include tubercular pleural effusion (TPE), parapneumonic effusion (PPE), and malignant pleural effusion (MPE). Differentiating between TPE and PPE, which are treatable conditions, and MPE is crucial, as misdiagnosis or delayed intervention may lead to increased mortality and morbidity. [4]

Adenosine deaminase (ADA) is an enzyme that facilitates the conversion of adenosine to inosine, a key step in purine metabolism. Predominantly found in T-lymphocytes, ADA activity is notably elevated in diseases where cellular immunity is activated.[2] In tuberculous pleural effusion, ADA levels are significantly raised, showing a sensitivity of 99% and specificity of 93%. Various studies have set the pleural fluid ADA diagnostic cutoff for tuberculous pleural effusion between 30 and 70 U/L, with higher ADA levels increasing the likelihood of tuberculosis. Elevated ADA levels may also appear in pleural effusions from conditions like pneumonia, empyema, lymphoma, malignancy, and rheumatoid pleuritis.[5]

Adenosine deaminase (ADA) exists in two molecular forms: ADA1 and ADA2. ADA1 is present in all cells, with the highest activity in lymphocytes and monocytes, while ADA2 is exclusive to monocytes. In tuberculous pleural effusion, ADA2 is the predominant form, whereas ADA1 is more common in other causes of pleural effusion. Using the ratio of ADA1 to total ADA at a threshold below 0.42 can modestly enhance the sensitivity and specificity for diagnosing tuberculous pleural effusion.[6] In cases of lymphocyte-predominant pleural effusion, an ADA level exceeding 40 U/L is highly indicative of tuberculous pleurisy. For lymphocytic pleural effusions unrelated to tuberculosis, the ADA level in pleural fluid generally remains below 40 U/L. [7] Additionally, a pleural fluid lymphocyte-to-neutrophil ratio above 0.75 enhances the diagnostic specificity for tuberculous pleural effusion.[8]

While pleural fluid LDH levels are not particularly effective in distinguishing between different types of exudative pleural effusions, they serve as a valuable marker of the extent of pleural inflammation. A pleural fluid LDH level exceeding three times the upper normal limit of serum LDH is considered a poor prognostic factor in cases of parapneumonic effusion and empyema.[9] A recent study indicated that only 31% of patients with tuberculous pleural effusion (TPE) have a positive microbiological test result.[10]

Guidelines recommend using pleural fluid LDH and glucose to classify patients with complicated parapneumonic effusions (CPPE). However, elevated pleural fluid LDH levels may appear in TPE, parapneumonic effusion (PPE), and malignant pleural effusion (MPE), with values ranging from normal to elevated, which limits LDH's role in determining the cause of pleural effusion. Consequently, distinguishing between TPE and PPE based on elevated pleural fluid ADA and LDH levels remains challenging for clinicians. In light of the aforementioned challenges, the present study aimed to investigate serum LDH and adenosine deaminase (ADA) levels in pleural fluid among patients with pleural effusion at a tertiary care center. The objectives of the study included diagnosing patients with pleural effusion using chest X-ray and ultrasound (USG) of the chest; categorizing pleural effusions based on etiology

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using Light's criteria and the serum LDH/ADA ratio; measuring serum LDH and pleural fluid LDH levels among the study subjects; obtaining adenosine deaminase levels in pleural effusions; and correlating the categories of pleural effusion with the cancer ratio.

MATERIAL & METHODS

After approval from institutional ethical committee, this cross-sectional study was carried out for 18 months duration from Sep 2022 to Feb 2024 in the Department of General Medicine, SAMC & PG Institute, Indore and 100 adult patients aged >18 years of either gender diagnosed with pleural effusion on Chest X ray and USG Chest and admitted in Medicine, pulmonary and medical oncology ward and ICU of our institute were included. Informed written consent was obtained from all patients satisfying the inclusion criteria after explaining the study protocol in detail.

Inclusion Criteria

- Patients between the age of 18 to 70 years; and
- Patients diagnosed with pleural effusion on Chest X ray and USG Chest and admitted in Medicine, pulmonary and medical oncology ward and ICU SAIMS & PG Institute, Indore. This included:
    - Patients who have a diagnosis of malignant pleural effusion (MPE) by cytology or pleural biopsy;
    - Patients who have a diagnosis of TBPE based on a finding of chronic granulomatous inflammation in pleural tissues; and
    - Patients who have a diagnosis of PPE based on exudative effusions related to bacterial pneumonia, lung abscesses or bronchiectasis, and have been in remission and recovery for at least 3 months at the follow-up after antibiotic use.

Exclusion Criteria

- Non-consenting patients; and
- Patients under the age of 18 years were excluded.

METHODOLOGY

Patients admitted to the medicine, pulmonary, medical oncology wards, and ICU who met the inclusion and exclusion criteria were enrolled in the study after obtaining informed consent. A comprehensive clinical evaluation, including relevant personal and family history, physical examination, and necessary hematological, biochemical, radiological, and microbiological investigations, was conducted. Upon confirmation of pleural effusion via chest X-ray and ultrasound (USG), pleural tapping was performed for either therapeutic or diagnostic purposes as required. Serum protein and LDH levels, along with demographic and clinical data—such as age, gender, smoking history, pleural LDH, and ADA levels—were collected for analysis.
Data was recorded using a structured proforma, and pleural effusion was classified as exudative or transudative based on modified Light's criteria. An effusion was classified as exudative if it met one or more of the following conditions:

- Pleural protein to serum protein ratio ≥ 0.5
- Pleural LDH to serum LDH ratio ≥ 0.6
- Pleural LDH greater than two-thirds of the upper limit of normal serum LDH

Statistical Analysis

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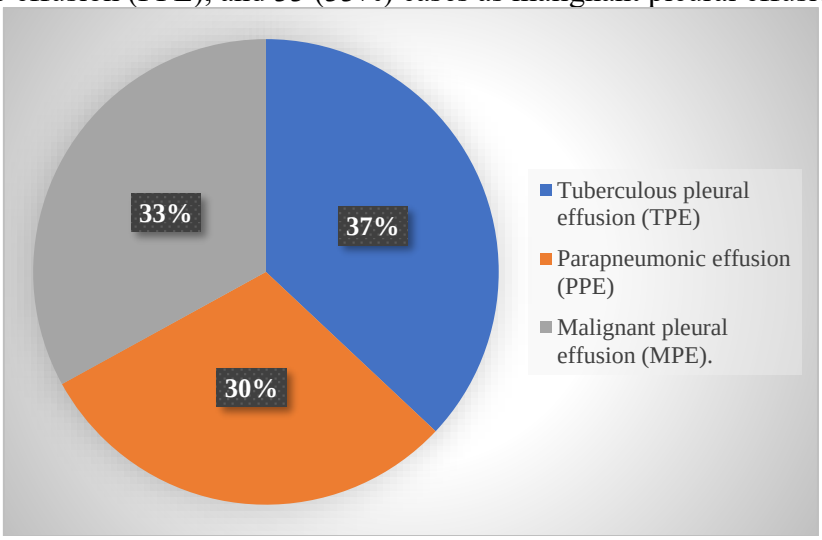
The collected data were entered into a Microsoft Excel Sheet. Tables were generated using Microsoft Word and Microsoft Excel version 2010. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) IBM version 18.0. The categorical variables were expressed as percentages, frequency, and proportions and compared using Pearson's Chi-square test or Fisher's exact test, as appropriate. A $p \leq 0.05$ was considered statistically significant.

RESULTS

Clinicodemographic Profile: The study included 100 patients of pleural effusion out of which 37 (37%) cases were identified as tuberculous pleural effusion (TPE), 30 (31%) cases as parapneumonic effusion (PPE), and 33 (33%) cases as malignant pleural effusion (MPE).



Graph 1. Distribution of study population as per type of pleural effusion

Among 37 TPE patients, there were 4 cases with pleural fluid Cartridge-Based Nucleic Acid Amplification Test positive for AFB, 14 cases with sputum AFB positive, 4 cases with pleural biopsy showing caseating granuloma, and 15 cases with clinical improvement following the initiation of anti-tubercular therapy (ATT). Among the 30 PPE patients, 7 had empyema, 5 had complicated parapneumonic effusion (CPPE), and 18 had uncomplicated parapneumonic effusion (UPPE). For the 33 MPE patients, 8 cases were identified as extrapulmonary malignancies, including malignancies of the stomach, breast, cervix, and larynx, while 25 cases were pulmonary malignancies. The pulmonary malignancies comprised 2 cases of small cell carcinoma, 4 cases of mediastinal lymphoma, 14 cases of adenocarcinoma, and 5 cases of metastatic lung deposits from unknown primary sites.

Table 1: Demographic, comorbidities and pleural fluid analysis of TPE, PPE and MPE

Parameter	TPE (n=37)	PPE (n=30)	MPE (n=33)
Age (years)			
Mean (range)	52.2 (20-68)	44.8 (21-72)	58.6 (27-74)
Gender, n (%)			
Male	31 (83.7%)	19 (63.3)	16 (48.5)
Female	6 (16.3%)	11 (36.7)	14 (51.5)
Comorbidities			
Smoker			14 (42.4%)
DM	2 (5.5%)	3 (10%)	2 (6.1%)
Alcoholic	18 (48.6%)	8 (26.7%)	12 (36.4%)
Pleural fluid analysis			

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Total count (cell/mm3)	1904 (100-6198)	8889.8 (100-64,100)	670 (50-3700)
Lymphocytes (%)	88.5 (60-98)	52.5 (10-95)	85.0 (50-98)
Neutrophils (%)	11.22 (2-40)	46.5 (5-90)	13.5 (2-50)
Protein (g/dL)	4.9 (3.4-6.0)	4.9 (3-7.7)	3.6 (2.6-5.7)
Glucose (mg/dL)	94.8 (30-148)	74.65 (10-166)	79.96 (40-130)
ADA (U/L)	75.2 (25-194)	59.2 (14-181)	35.50 (10-74)
LDH (U/L)	886.4 (138-2214)	1128.8 (334-3120)	1468 (234-4284)
LDH/ADA ratio	14.15 (2.94-42.74)	26.16 (3.46-62.0)	68.20 (3.6-355.06)

Diagnostic Accuracy of ADA, LDH and LDH/ADA Ratio: The diagnostic assessment for tuberculous pleural effusion (TPE), parapneumonic effusion (PPE), and malignant pleural effusion (MPE) using ADA, LDH, and the LDH/ADA ratio in pleural fluid revealed useful cutoff values for differentiation.

- **Adenosine deaminase (ADA)**: The mean ADA value for TPE was 75.2 U/L (25–194 U/L), PPE was 59.2 U/L (14–181 U/L), and for MPE was 35.50 U/L (10–74 U/L). Overall, the mean ADA value of TPE is higher than that of PPE and MPE. On ROC analysis, for TPE, an ADA cutoff value of >36 U/L provided a sensitivity of 88.5% and specificity of 53.5%, with an area under the curve (AUC) of 0.921 (95% CI: 0.610–0.854, P = 0.0001), indicating moderate diagnostic accuracy. (The cutoff value for ADA in the diagnosis of MPE was found to be ≤65 U/L with AUC of 0.742 (sensitivity –93.8%, specificity – 42.6%) with significant (P = 0.001), whereas cutoff ADA value for PPE (≤35 U/L) did not reach a statistical significance (P = 0.843).
- **Lactate dehydrogenase (LDH):** The mean LDH value for TPE was 886.4 U/L (138–2214 U/L), PPE was 1128.8 U/L (334–3120 U/L), and for MPE was 1468 U/L (234–4284 U/L). On ROC analysis, the cutoff value for LDH in the diagnosis of TPE was found to be ≤1291 U/L with AUC of 0.633 (sensitivity –88.5%, specificity – 38.2%) with (P = 0.310), reflecting limited diagnostic value (Graph 3). The cutoff value for LDH in the diagnosis of PPE was found to be >710 U/L with AUC of 0.523 (sensitivity – 74.5%, specificity – 38.5%) (P = 0.714), whereas cutoff LDH value for MPE was >1291 U/L (sensitivity – 46.9%, specificity – 81.0%) with P = 0.465.
- **LDH/ADA Ratio:** The mean LDH/ADA value for TPE was 14.15 (2.94–42.74), PPE was 26.16 (3.46–62.0), and for MPE was 68.20 (3.6–355.06). On ROC analysis, the LDH/ADA ratio for TPE diagnosis, with a cutoff of ≤20.81, yielded a sensitivity of 84.0% and specificity of 63.4%, and an AUC of 0.724 (95% CI: 0.614–0.844, P = 0.0001), suggesting its utility in differentiating TPE from other causes. For PPE, the LDH/ADA ratio cutoff >23.39 had a sensitivity of 52% and specificity of 65.5%, with an AUC of 0.515 (95% CI: 0.380–0.654, P = 0.619), indicating limited diagnostic capability. Finally, for MPE, cutoff value for the LDH/ADA ratio of >20.86 resulted in a sensitivity of 71.1% and specificity of 68.4%, with an AUC of 0.712 (95% CI: 0.571–0.810, P = 0.006), supporting its potential role in identifying MPE. (Graph 4)
- Overall, the ADA level and LDH/ADA ratio, particularly for TPE, demonstrated valuable diagnostic accuracy, with higher AUC values underscoring their clinical utility.

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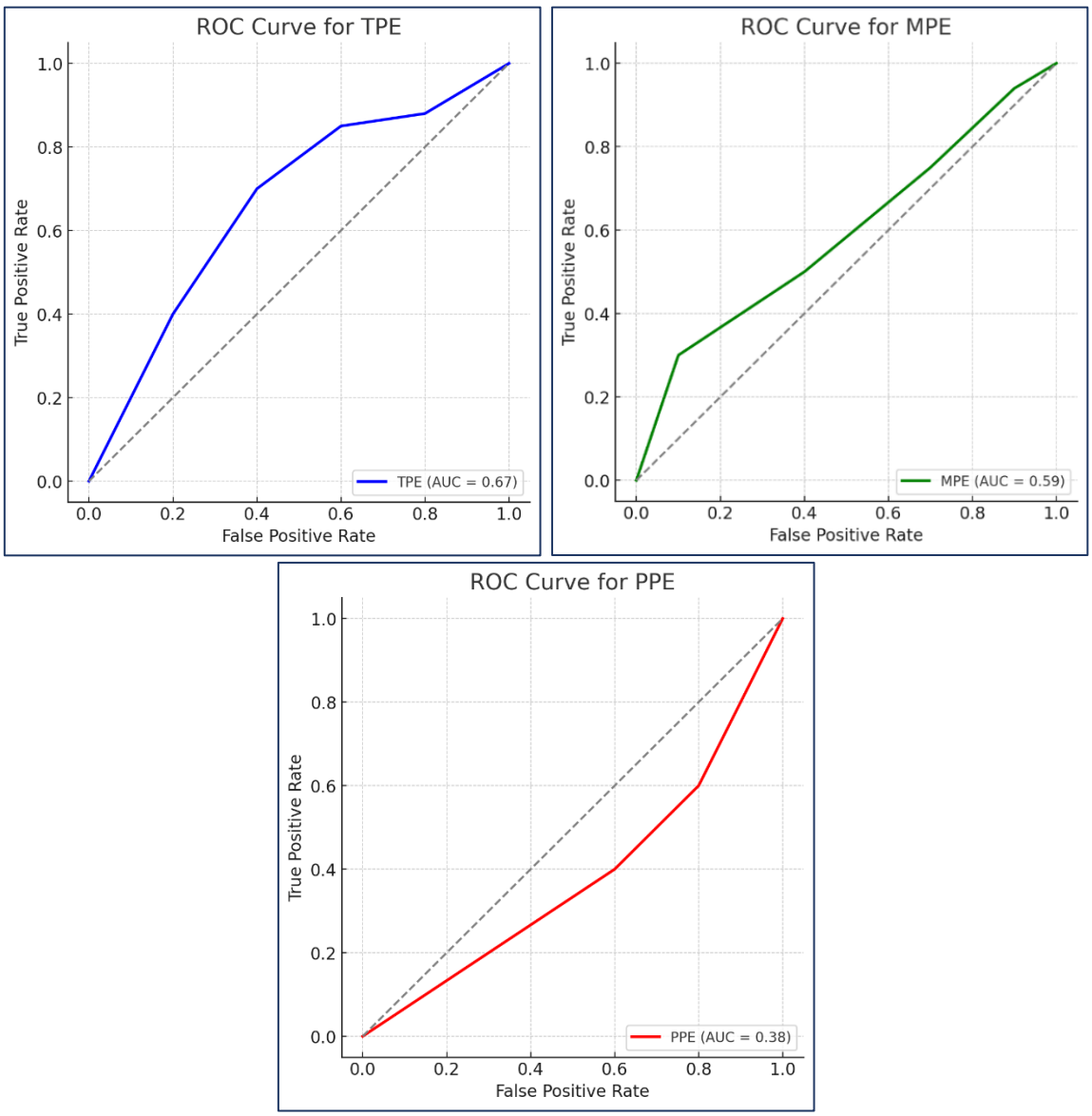

Graph 2. The receiver operating curve for adenosine deaminase in predicting TPE, MPE and PPE

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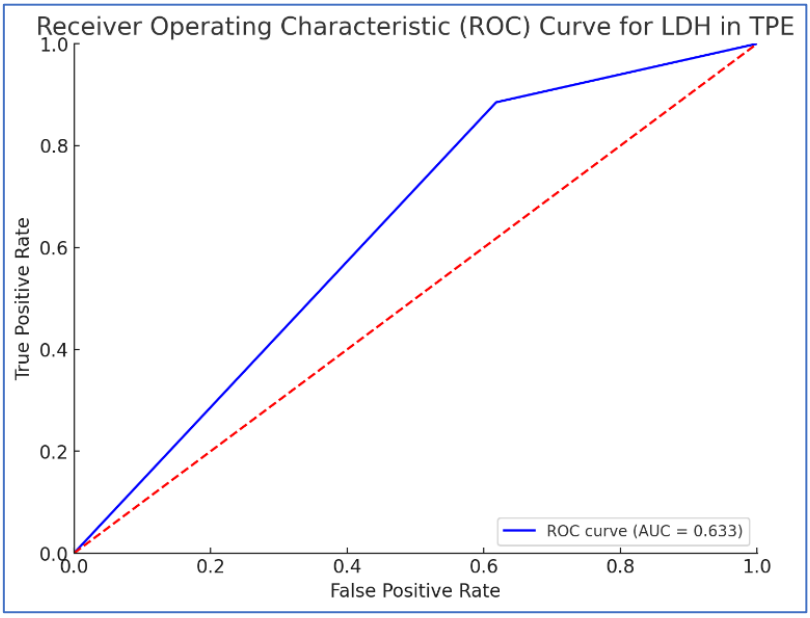
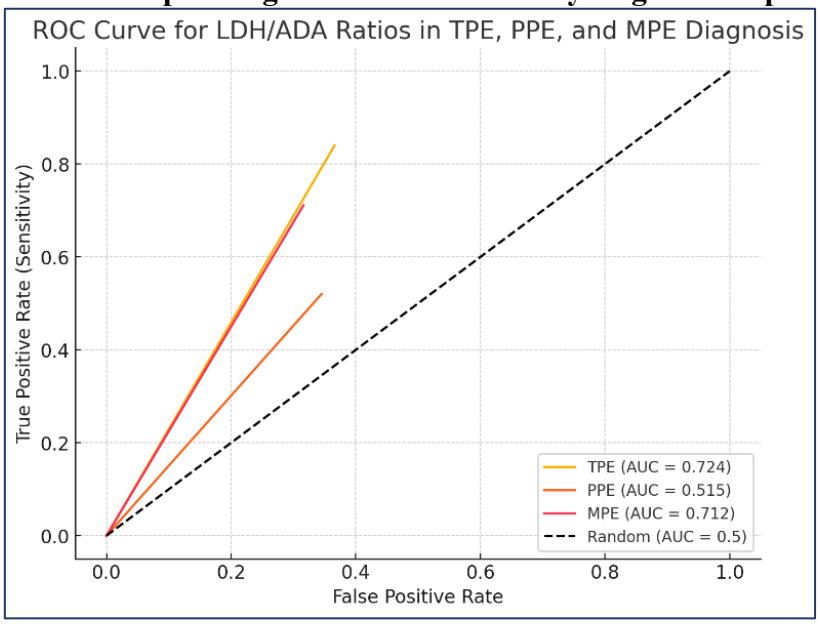


Graph 3. The receiver operating curve for lactate dehydrogenase in predicting TPE.



Graph 4. The receiver operating curve for LDH/ADA in predicting TPE, PPE and MPE

DISCUSSION

The diagnosis of tuberculous pleuritis (TPE) relies on several criteria: a positive acid-fast bacilli (AFB) smear or culture for Mycobacterium tuberculosis in pleural fluid, the presence of chronic granulomatous inflammation in pleural tissue, and clinical improvement following antituberculous therapy (ATT). [11] Conversely, many studies recognize a lymphocytic exudate with an adenosine deaminase (ADA) level greater than 40 U/L as a strong diagnostic indicator for TPE. [12]

The measurement of adenosine deaminase (ADA) levels in pleural fluid has shown high sensitivity and specificity for differentiating tuberculous pleuritis (TPE). However, Zarić et al. reported conflicting results, indicating a specificity of only 70.4% and a sensitivity of 89.2% for ADA levels in the diagnosis of TPE.[13] Additionally, elevated ADA levels can occur in

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pleural effusions resulting from other conditions, including pneumonia, empyema, lymphoma, malignancy, and rheumatoid pleuritis.[5]

In the present study, we reviewed a total of 100 patients with pleural effusion, including 37 with tuberculous pleuritis (TPE), 30 with parapneumonic effusion (PPE), and 33 with malignant pleural effusion (MPE). The mean ADA levels were 75.2 U/L (range 25–194 U/L) for TPE, 59.2 U/L (range 14–181 U/L) for PPE, and 35.50 U/L (range 10–74 U/L) for MPE. Overall, the mean ADA value for TPE was significantly higher than that for PPE and MPE. ROC analysis identified a cutoff ADA value of >36 U/L for diagnosing TPE, with an area under the curve (AUC) of 0.921, yielding a sensitivity of 88.5% and specificity of 53.5% (P = 0.0001). For MPE, the cutoff ADA value was ≤65 U/L, with an AUC of 0.742, a sensitivity of 93.8%, and a specificity of 42.6% (P = 0.001). In contrast, the cutoff ADA value for PPE was ≤35 U/L, which did not achieve statistical significance (P = 0.843). This finding aligns with the study conducted by Indhu et al. [4], which reported that elevated ADA levels in pleural fluid demonstrated high sensitivity and specificity for differentiating tuberculous pleuritis (TPE), with sensitivity at 89.5% and specificity at 54.5%.

Pleural fluid LDH levels reflect the degree of tissue damage and are commonly used as a biomarker to differentiate between complicated and uncomplicated parapneumonic effusions (PPE). [4] In this study, the mean LDH values were 886.4 U/L (range 138–2213 U/L) for tuberculous pleural effusion (TPE), 1128.8 U/L (range 334–3120 U/L) for PPE, and 1468 U/L (range 234–4284 U/L) for malignant pleural effusion (MPE). ROC analysis determined that the cutoff value for LDH in diagnosing TPE was ≤1291 U/L, with an area under the curve (AUC) of 0.633, sensitivity of 88.5%, and specificity of 38.2% (P = 0.310), indicating limited diagnostic value. For PPE, the cutoff LDH value was >710 U/L, with an AUC of 0.523, sensitivity of 74.5%, and specificity of 38.5% (P = 0.714). The cutoff for MPE was >1291 U/L, with sensitivity of 46.9% and specificity of 81.0% (P = 0.465). None of these LDH cutoff values reached statistical significance, likely due to the small sample size. Overall, the results indicated that LDH activity is relatively higher in parapneumonic effusions and MPE compared to TPE, consistent with findings from the study by Indhu et al. that reported similar outcomes. Given the limitations of using pleural fluid ADA and LDH levels alone as biomarkers for differentiating between tuberculous pleuritis (TPE), parapneumonic effusion (PPE), and malignant pleural effusion (MPE), we combined these two parameters to create a predictor for TPE with improved specificity and sensitivity. Our findings demonstrated a significantly lower pleural fluid LDH/ADA ratio in the TPE group compared to both the PPE and MPE groups (P < 0.0001).

The mean LDH/ADA ratio was 14.15 (range 2.94–42.74) for tuberculous pleuritis (TPE), 26.16 (range 3.46–62.0) for parapneumonic effusion (PPE), and 68.20 (range 3.6–355.06) for malignant pleural effusion (MPE). ROC analysis indicated that the LDH/ADA ratio for diagnosing TPE, with a cutoff of ≤20.81, achieved a sensitivity of 84.0% and specificity of 63.4%, with an AUC of 0.724 (95% CI: 0.614–0.844, P = 0.0001), suggesting its utility in distinguishing TPE from other causes. For PPE, the cutoff LDH/ADA ratio of >23.39 yielded a sensitivity of 52% and specificity of 65.5%, with an AUC of 0.515 (95% CI: 0.380–0.654, P = 0.619), indicating limited diagnostic capability. In the case of MPE, a cutoff LDH/ADA ratio of >20.86 resulted in a sensitivity of 71.1% and specificity of 68.4%, with an AUC of 0.712 (95% CI: 0.571–0.810, P = 0.006), supporting its potential role in identifying MPE. The cutoff values of the LDH/ADA ratio for tuberculous pleuritis (TPE) and malignant pleural effusion (MPE) achieved statistically significant results, while the ratio for parapneumonic effusion (PPE) did not reach statistical significance.

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These findings align with the results from Indhu et al.[4], who reported a sensitivity of 84.2% and specificity of 63.6% for the LDH/ADA ratio in diagnosing tuberculous pleuritis (TPE) (P = 0.0001). For parapneumonic effusion (PPE), they reported a sensitivity of 50% and specificity of 66.7% (P = 0.689), while for malignant pleural effusion (MPE), the sensitivity and specificity were 70.6% and 68.6%, respectively (P = 0.007). In contrast, Wang et al. found that a cutoff LDH/ADA ratio of <16.20 yielded a sensitivity of 93.62% and specificity of 93.06% for TPE, with an AUC of 0.9663.[14] The discrepancies in results may be attributed to the relatively small sample size in the current study.

In conclusion, a pleural fluid LDH/ADA ratio of ≤20.81 U/L is indicative of tuberculous pleuritis (TPE), while a ratio of >20.86 U/L suggests malignant pleural effusion (MPE). Thus, the cutoff value of 20.81 U/L can be effectively utilized for the etiological differentiation of pleural effusions.

The limitations of the study include its relatively small sample size, which suggest that further research is needed to validate the results. Additionally, since the study was conducted in a tertiary care centre, the generalizability of the findings may be restricted.

CONCLUSION

In conclusion, this study highlights the diagnostic utility of combining pleural fluid adenosine deaminase (ADA) and lactate dehydrogenase (LDH) levels for differentiating between tuberculous pleuritis (TPE), parapneumonic effusion (PPE), and malignant pleural effusion (MPE). This study demonstrates that the pleural fluid LDH/ADA ratio is a valuable indicator for the etiological differentiation of pleural effusions. This finding could enhance early clinical decision-making in patient management, potentially leading to improved prognoses. By enabling timely and accurate identification of the underlying causes of pleural effusions, clinicians can optimize treatment strategies and improve patient outcomes.

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