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Research Article

Diagnostic Accuracy of the Pleural Fluid Lactate Dehydrogenase to Adenosine Deaminase Ratio in Tuberculous Pleural Effusion: A Cross - Sectional Study in a Tertiary Care Hospital

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Abstract

Tuberculous pleural effusion (TPE) poses significant diagnostic difficulties, especially in regions where tuberculosis (TB) is prevalent. In this prospective study, we evaluated the diagnostic performance of the Lactate Dehydrogenase (LDH) to Adenosine Deaminase (ADA) ratio as a tool for identifying TPE among patients presenting with suspected pleural TB. The practicality and affordability of LDH and ADA measurements in pleural fluid make this approach particularly valuable for resource-limited healthcare environments such as India.

A total of 66 patients with exudative, lymphocyte-predominant pleural effusions and a high pretest probability of TB were enrolled, with an equal number exhibiting ADA levels above and below 40 IU/L. Etiological diagnoses incorporated clinical history, radiological findings, and biochemical and cytological assessment of pleural fluid. The mean participant age was 48.3 years, and male patients predominated (72.7%). Frequent presenting symptoms included cough, breathlessness, fever, chest pain, and other constitutional complaints. Common comorbidities among participants were systemic hypertension, type 2 diabetes mellitus, and chronic kidney disease.

Biochemical analysis of pleural fluid revealed mean levels of glucose at 80.86 mg/dl, protein at 6.24 g/dl, ADA at 46.14 IU/l, and LDH at 817.09 U/l. ADA demonstrated robust diagnostic performance with an area under curve (AUC) of 0.940. Setting an optimal cutoff of 16.89 IU/l provided 86.7% sensitivity and 88.9% specificity for detecting TB-related effusions.

In summary, pleural fluid ADA and LDH are highly sensitive and specific in distinguishing exudative from transudative effusions. The LDH/ADA ratio serves a pivotal role in differentiating TPE from other exudative etiologies such as parapneumonic or malignant effusions, especially given TPE's tendency for intermediate ADA values due to its paucibacillary nature. Relying on the LDH/ADA ratio can streamline diagnostics and reduce dependence on simultaneous testing, which is particularly advantageous in resource-limited settings. Optimizing these diagnostics can facilitate earlier treatment, thereby improving patient outcomes and reducing morbidity associated with TPE.

Keywords: *Extra Pulmonary Tuberculosis; Exudative Pleural Effusion; Lactate Dehydrogenase; Adenosine Deaminase; Tuberculous Pleural Effusion; Co Morbidities*

Abbreviations

ADA: Adenosine Deaminase; AUC: Area Under the Curve; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus; EPTB: Extrapulmonary Tuberculosis; LDH: Lactate Dehydrogenase; MTB: *Mycobacterium tuberculosis*; PF: Pleural Fluid; TPE: Tuberculous Pleural Effusion

Introduction

The accumulation of fluid within the pleural space presents different forms: serous fluid accumulation is termed pleural effusion, pus denotes empyema, blood indicates hemothorax, and chyle accumulation is chylothorax. This fluid buildup can result from multiple pathophysiological mechanisms such as increased hydrostatic pressure, decreased oncotic pressure, or inflammation. Pleural effusion poses a significant diagnostic challenge, as approximately 15 to 20% of cases remain undiagnosed despite comprehensive evaluation [1].

Pleural effusion, which is a commonly observed clinical manifestation, is associated with more than 50 recognized diseases and disorders. In most parts the of world, subtypes of exudative effusions often seen in clinical practice include tuberculous pleural effusion (TPE), para pneumonic effusion (PPE), and malignant pleural effusion (MPE). It is crucially important to differentiate TPE and PPE, which are curable conditions, from MPE, as misdiagnosis and delayed treatment can result in significant mortality and morbidity [2].

Based on pathological abnormality and mechanism of formation, effusions may be transudative or exudative. Transudates occur when there are alterations of mechanical factors influencing formation or reabsorption. Exudates result from inflammation or irritation or other disease process involving the pleura, resulting in increased permeability.

Tuberculosis is one of the major public health problems faced by mankind. Until the corona virus pandemic, TB was the leading cause of death from single infectious agent. When the Tb showed declining trend globally, India had 19% increase from previous year with 19 lakh new cases. It mostly affects lungs most common extra pulmonary site is pleura followed by lymph nodes [3]. Microbiological report of pleural TB will be negative most of the times due to its paucibacillary nature of *M. tuberculosis* [4].

Waiting for the culture results can delay the initiation of treatment; therefore, we need a diagnostic aid in such patients to differentiate Tuberculous pleural effusion from other effusions. A pleural biopsy is beneficial in establishing an etiological diagnosis for exudative pleural effusion, especially when malignancy is suspected or detailed pleural fluid studies are inconclusive [5].

However, complications associated with the procedure and limited availability of expertise in tier one and two healthcare setups can be challenging. Inflammatory markers such as Lactate Dehydrogenase (LDH) and Adenosine Deaminase (ADA) can play a crucial role in differentiating tuberculous pleural effusion from other parapneumonic effusions.

There are many studies in Western literature but very few studies in Indian literature, which have assessed the role of pleural fluid lactate dehydrogenase and Adenosine Deaminase in differentiating between tuberculous pleural effusion from other para-pneumonic effusions. Using only Adenosine Deaminase and lactate dehydrogenase level lowers the cost of the diagnostic procedure which is important in developing countries like India. There is hence a role for defining the best cost effective and diagnostic approach for quicker diagnosis of pleural effusion and hence the need for the present study.

Objectives of the Study

1) To determine diagnostic accuracy of LDH/ADA ratio in patients with high pretest probability for pleural TB.
2) To compare its accuracy to that of isolated pleural fluid ADA levels in a lymphocyte predominant effusion. (LPE is one with >75% lymphocytes and /or a lymphocyte/neutrophil ratio > 0.75).

Materials and Methods

Method of collection of data

Source of data: Patients with pleural effusion admitted to Ramaiah hospitals under respiratory medicine department, Bengaluru.

Methods of data collection

Ethics approval and informed consent: Data collection began following approval from the Institutional Ethics Committee. Informed consent was obtained from each participant, detailing study procedures and providing a patient information sheet.

Data collection

Demographic data (age, sex, gender, name, occupation, BMI, comorbidities) were initially recorded on a structured proforma. This information was subsequently transferred to Microsoft Excel spreadsheets for systematic management and analysis.

Clinical information encompassed

Chief Complaints: Reasons for seeking medical attention. - Physical Examination: General physical examination (GPE) and systemic findings. - Investigations: Results from radiological and laboratory tests.

Study subjects

Inclusion criteria:

1. Patients aged > 18 years with lymphocyte-predominant exudative pleural effusion.
2. Patients diagnosed with tuberculous pleural effusion based on history, clinical examination, and appropriate imaging modalities.

Exclusion criteria

1. Pleural effusions with ADA levels of 100 and above were excluded.
2. Transudative pleural effusions.
3. Malignant exudative pleural effusions.
4. Low pre-test probability patients.
5. Chylothorax, haemothorax.
6. Patients who are hemodynamically unstable.
7. Patients who are unwilling to take part in study.

Study design

The present study is a cross-sectional study from august 2022 to July 2024.

Sample size calculation

Sample size = 66.

Based on previous study conducted by Beukes A, Shaw J A, Diacon A H, Irusen E M and Koegelenberg C F N, the sensitivity of LDH/ ADA ratio for detecting pleural TB was 78% at the cut off score of 12.5. Considering a similar sensitivity in our study, sample size can be calculated as follows.

The sample size (n) is calculated using the formula:

$$n = Z\alpha^2 \frac{Sn(100-Sn)}{d^2}$$

Where Zα = Standard table value for 95% confidence interval

Sn = Sensitivity of previous study 78%

100-Sn = 22%

d = precision= 10% absolute precision

$$n = Z\alpha^2 \frac{Sn(100-Sn)}{d^2}$$

$$n = (1.96)^2 \frac{78 \times 28}{10^2} = 65.92$$

n ~ 66.

Statistical analysis

Statistical methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and salts on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance. The following assumptions on data is made, Assumptions: 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent.

Receiver operating characteristic curve (ROC) analysis was performed to find the predictability of study variables for predicting the outcome.

Results and Discussion

66 patients with pleural effusion were included in the present study, the statistical analysis of patients is being presented.

Age in years	No. of patients	%
>18 - <30	13	19.69%
>30 - <40	15	22.72%
>40 - <50	12	18.18%
>50 - <60	13	19.69%
>60 - <70	7	10.6%
>70 - <80	4	6%
>80 - <90	2	3%
Total	66	100%

Table 1: *Age distribution of patients.*

In the present study it was observed age group of above 18 to 60 were involved with approximate equal percentage. With a mean age of 48.30 years and standard deviation of 18.757.

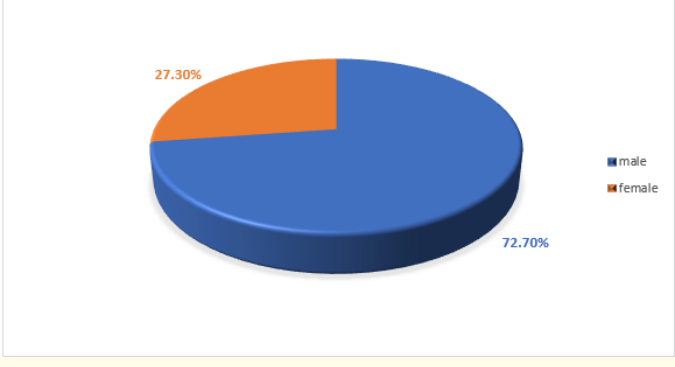


Figure 1: *Gender distribution of patients.*

In the present study out of 66 patients 48 and 18 were male and female gender respectively comprising 72.7% of males and 27.3% of females.

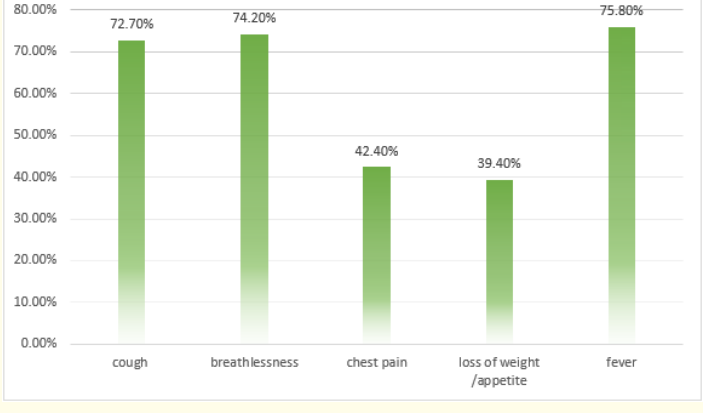


Figure 2: *Distribution of chief presenting complaints.*

Among 66 patients in the present study had cough, breathlessness and fever as the predominant symptoms 72.7%, 74.2%, 75.8% respectively, followed by chest pain and loss of appetite/weight/generalized weakness 42.4% &39.4% each.

Chief complaints	No. of patients (n=66)	%
Fever	50	75.8%
Cough	48	72.7%
Breathlessness	49	74.2%
Chest pain	28	42.4%
Loss of weight/appetite	26	39.4%

Table 2: *Distribution of chief presenting complaints.*

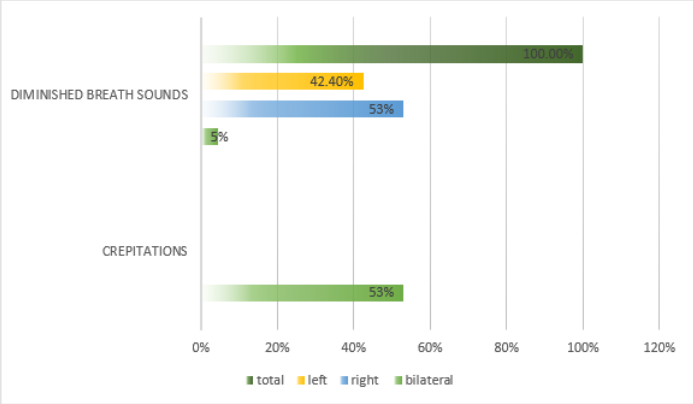


Figure 3: *Clinical signs of patients studied.*

Upon examination, all 66 patients were found to have decreased intensity of breath sounds, predominantly on the right side followed by the left, with 5% showing bilateral decrease. Additionally, crepitations were noted in 53% of patients, along with decreased tactile fremitus and a dull note on percussion of the infra scapular and infra-axillary areas.

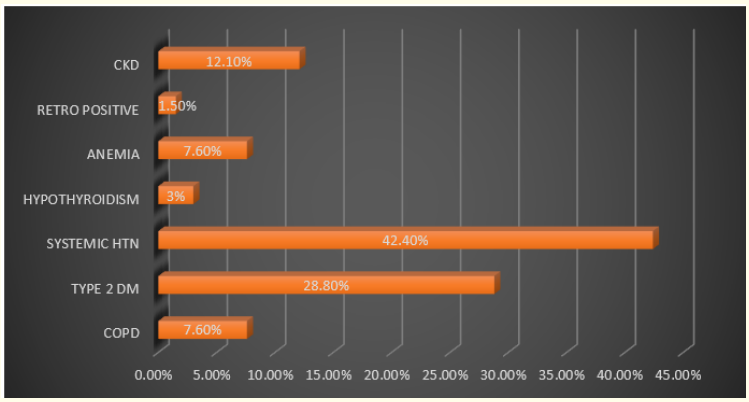


Figure 4: *Incidence of comorbidities.*

In the current study, out of 66 patients, 42.4% had systemic hypertension, 28.8% had type 2 diabetes mellitus, 12.1% had chronic kidney disease (CKD), 7.6% had chronic obstructive pulmonary disease (COPD) and anemia, 3% had hypothyroidism, and one patient was retrovirus positive. Consistent with existing literature, immunocompromised patients are prone to developing tuberculous infections. Notably, anemia and diabetes, along with hypertension and CKD, were the major comorbid conditions observed.

	No. of patients (n = 66)	%
Systemic hypertension (HTN)	28	42.4%
DM	19	28.8%
CKD	8	12.1%
Anemia	5	7.6%
COPD	5	7.6%
Hypothyroidism	2	3%
HIV	1	1.5%

Table 3: *Incidence of comorbidities.*

Pulmonary TB concomitant with effusion

MTB in sputum and pleural fluid

Mycobacterium tuberculosis (MTB) was detected in both sputum and pleural fluid samples of 4 patients, indicating a tuberculosis infection affecting both the lungs and the pleural space in these individuals.

	No. of patients (n = 66)	%
Sputum positive TB	4	6.06

Table 4: *Sputum TB-PCR.*

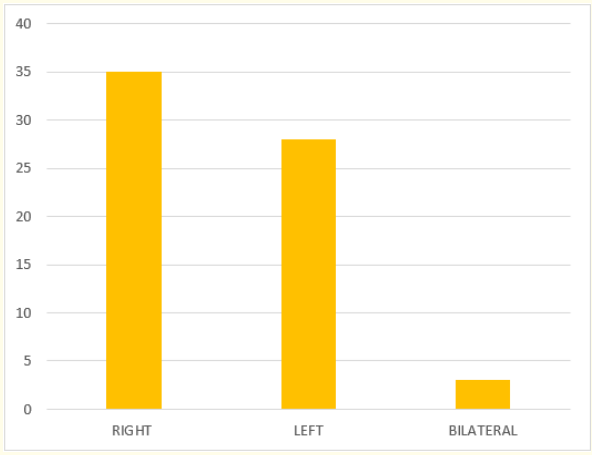


Figure 5: *Distribution of site of pleural effusion.*

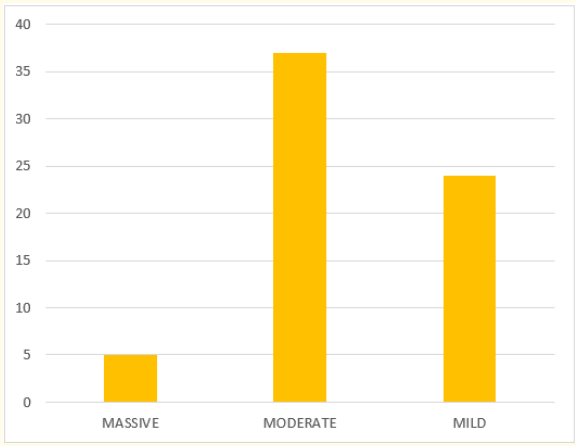


Figure 6: *Severity of effusion based on Ultrasonographic (USG) evaluation.*

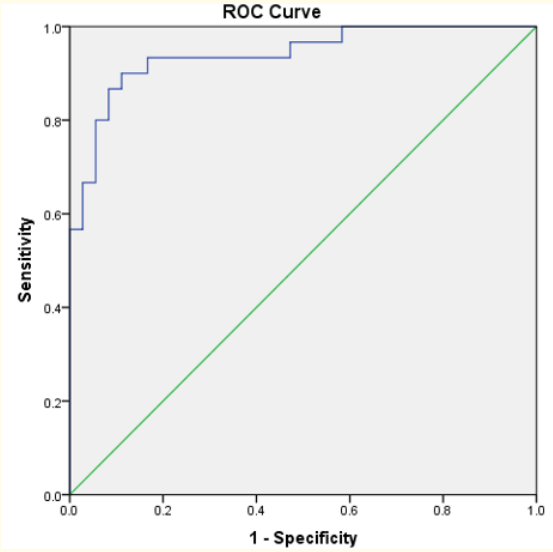
Biochemical and pathological analysis of pleural fluid

Parameters	Mean	Std. deviation
PF Glucose	80.86 mg/dl	24.77
PF Protein	6.24 g/dl	8.737
PF ADA	46.14 IU/l	18.940
PF LDH	817.09 U/l	608.207
PF total counts	1272.15/mm^3	919.51
PF Lymphocytes	935.64/mm^3	658.99
PF Neutrophils	324.20/mm^3	553.03

Table 5: *Analysis of pleural fluid parameters.*

In our study, we measured four parameters in a group of subjects: glucose, protein, adenosine deaminase (ADA), and lactate dehydrogenase (LDH). The mean glucose level was 80.86 mg/dl with a standard deviation of 24.77, indicating that glucose levels were relatively consistent with moderate variability among the subjects. The protein level had a mean of 6.24 g/dl and a higher standard deviation of 8.737, suggesting greater variability and potential differences in protein concentrations within the group. ADA levels showed a mean of 46.14 IU/l with a standard deviation of 18.940, reflecting moderate variability. The LDH levels had the highest mean at 817.09 U/l and a substantial standard deviation of 608.207, indicating significant variability and potential outliers in the LDH concentrations. These variations in standard deviations highlight the differing degrees of dispersion around the mean for each parameter, which could be crucial for interpreting the overall health and metabolic state of our subjects.

ROC curve



Figure

Area under the curve (AUC)

AUC value: The AUC is 0.940, indicating excellent discrimination ability of the classifier. An AUC close to 1 suggests that the classifier is very good at distinguishing between positive and negative classes.

Coordinates of the curve

- Sensitivity and specificity: The report lists various thresholds with corresponding sensitivity (true positive rate) and 1-specificity (false positive rate).
- High sensitivity: The sensitivity is high (close to 1) across a wide range of threshold values, indicating that the classifier correctly identifies a high proportion of positive cases.
- Decreasing 1-specificity: As the threshold increases, 1-specificity decreases, meaning fewer false positives are identified, enhancing the classifier's accuracy.

Confidence interval

Asymptotic 95% confidence interval: The confidence interval for the AUC is (0.883, 0.997), which is narrow, indicating a high level of precision in the estimate of the AUC.

Key threshold values

- Thresholds and performance: The report provides specific threshold values at which the classifier's performance is measured:
- For a threshold of 8.375474, the sensitivity is 1.000, and 1-specificity is 0.694.
- For a threshold of 16.893333, the sensitivity is 0.867, and 1-specificity is 0.111.

- For higher thresholds, such as 122.606061, the sensitivity drops to 0, indicating that at this extreme, the classifier fails to identify any positive cases.

Summary

- Overall performance: The classifier performs exceptionally well, as indicated by the high AUC value and consistently high sensitivity across a broad range of thresholds.
- Precision: The narrow confidence interval around the AUC suggests reliable performance metrics.
- Threshold analysis: Different thresholds allow for tuning the balance between sensitivity and specificity depending on the specific application needs.

This report shows that the LDH/ADA ratio is a highly effective test variable for the classifier, offering excellent discriminatory power and reliable performance metrics.

Based on the recorded data in the report, here are some key threshold values (cut-off points) for the LDH/ADA ratio, along with their corresponding sensitivity and specificity values:

Key Cut-Off Points for LDH/ADA Ratio

1. Threshold: 8.375474

- Sensitivity (True Positive Rate): 1.000
- 1 - Specificity (False Positive Rate): 0.694
- Specificity: 0.306

3. Threshold: 16.893333

- Sensitivity: 0.867
- 1 - Specificity: 0.111
- Specificity: 0.889

4. Threshold: 10.956791

- Sensitivity: 0.967
- 1 - Specificity: 0.472
- Specificity: 0.528

Optimal cut-off point

The optimal cut-off point is often chosen to balance sensitivity and specificity, depending on the clinical or practical requirements. Based on the data:

- Threshold: 16.893333
- Sensitivity: 0.867 (86%) (High true positive rate)
- Specificity: 0.889 (88%) (low false positive rate).

Discussion

The LDH/ADA ratio is an increasingly recognized diagnostic tool for tuberculous pleural effusion (TPE), particularly useful when isolated ADA or LDH values are affected by regional, demographic, or comorbidity-related biochemical variability. In our cohort of 66 patients, an LDH/ADA ratio threshold of approximately 16.9 achieved an excellent balance, with sensitivity of 0.867, specificity of 0.889, and an area under the ROC curve (AUC) of 0.940, underscoring its robust discriminatory power for TPE.

Similar findings have been reported in multiple recent studies. For example, Guo., *et al.* demonstrated that the LDH/ADA ratio is significantly lower in tuberculous pleural effusions (mean 6.2) compared to non-tuberculous exudative effusions (mean 34.3), with an AUC of 0.92, closely aligning with our results [6]. Additionally, Begim., *et al.* evaluated pleural fluid samples and found that the LDH/ADA ratio reliably differentiated tuberculous from other exudative effusions, supporting its diagnostic value across populations with diverse comorbidities [8].

The optimal cutoff values reported in the literature vary between approximately 10 and 21, reflecting demographic, regional, and methodological differences [6,7,9]. This variability highlights the importance of validating local thresholds for clinical application. For instance, Besir., *et al.* noted a strong performance of the LDH/ADA ratio at a cutoff near 14.5 in a Turkish cohort, emphasizing regional biochemical and epidemiological influences [10].

The LDH/ADA ratio also aids in differentiating TPE from other causes of exudative pleural effusion. Typically, TPE exhibits low LDH/ADA ratios due to marked ADA elevation [6,7]. In contrast, malignant pleural effusions tend towards higher ratios because of higher LDH and relatively lower ADA values [8]. Parapneumonic effusions often present with elevated levels of both LDH and ADA but generally have higher ratios than TPE, facilitating clinical distinction [8,9]. Rheumatologic or autoimmune pleural effusions generally show higher ratios due to varying inflammatory profiles [7].

Our cohort characteristics, including a predominance of middle-aged males and high prevalence of coexisting conditions such as hypertension and diabetes, align with global TPE epidemiology [6,8]. These comorbidities may influence pleural biochemical markers and shift ideal diagnostic cutoffs, underscoring the need to interpret the LDH/ADA ratio within clinical context [6,8].

Given observed inter-population differences and assay variability, widespread multicentre studies are necessary to refine and standardize LDH/ADA ratio cutoffs [6,8,9]. Recent advances utilizing decision-tree analyses that integrate LDH/ADA ratio with other pleural fluid parameters have achieved up to 90% diagnostic accuracy, suggesting promising directions for enhanced diagnostic algorithms [9].

In summary, the LDH/ADA ratio is a simple, accessible, and cost-effective adjunct in the diagnostic workup of tuberculous pleural effusion. Despite variation in optimal cutoffs, our findings and contemporary literature suggest thresholds near 16.9 offer valuable clinical utility. Future research should focus on validating norm-referenced cutoffs in diverse populations, accounting for comorbidities, age, and local disease prevalence, thereby optimizing the global deployment of this diagnostic marker.

Conclusion

This study confirms the robust utility of the pleural fluid LDH/ADA ratio as a diagnostic adjunct for tuberculous pleural effusion (TPE), demonstrating strong sensitivity and specificity (AUC = 0.940) at an optimal threshold of approximately 16.9. Our results are consistent with, yet finely attuned to, regional and ethnic differences in biochemical markers, emphasizing the need for locally validated cutoffs. Integrating the LDH/ADA ratio with clinical symptoms and examination findings significantly improves diagnostic accuracy, supporting earlier and more targeted management-especially critical in resource-limited settings where rapid, cost-effective testing is a priority.

Importantly, our findings underscore that comorbidities such as hypertension and diabetes can influence biochemical profiles, reinforcing the necessity to interpret the LDH/ADA ratio within the context of individual patient factors. While the ratio enhances discrimination between TPE and other causes of pleural effusion, future large-scale, multicentric studies are warranted to further refine threshold values and clarify its utility in distinguishing pleural TB from malignancy, parapneumonic effusions, and other exudative processes.

In summary, when used as part of a comprehensive diagnostic approach, the LDH/ADA ratio emerges as a reliable, accessible, and cost-effective tool, offering significant clinical benefit in the diagnosis and management of tuberculous pleural effusion across diverse healthcare settings.

Conflict of Interest

Nil.

Bibliography

1. Light Richard W. "Pleural Effusions". *The New England Journal of Medicine* 342.25 (2000): 1827-1833.
2. Wang J., *et al*. "The pleural fluid lactate dehydrogenase/adenosine deaminase ratio differentiates between tuberculous and parapneumonic pleural effusions". *BMC Pulmonary Medicine* 17.1 (2017): 168.
3. World Health Organization. Global Tuberculosis Report 2021. WHO (2021).
4. Beukes Amanda., *et al*. "The utility of pleural fluid lactate dehydrogenase to adenosine deaminase ratio in pleural tuberculosis". *Respiration* 100.1 (2020): 59-63.
5. Pandit S., *et al*. "Role of pleural biopsy in etiological diagnosis of pleural effusion". *Lung India* 27.4 (2010): 202-204.
6. Guo Y., *et al*. "Pleural fluid lactate dehydrogenase/adenosine deaminase ratio for the differentiation of tuberculous and nontuberculous exudative pleural effusions". *BMC Pulmonary Medicine* 21.1 (2021): 414.
7. Begim AE., *et al*. "Diagnostic value of pleural fluid lactate dehydrogenase/adenosine deaminase ratio in exudative pleural effusions". *Experimental and Clinical Transplantation* 19.4 (2021): 680-684.
8. Besir H., *et al*. "The value of pleural fluid LDH/ADA ratio in the differential diagnosis of exudative pleural effusion". *International Journal of General Medicine* 16 (2023): 773-780.
9. Wu W., *et al*. "Diagnostic performance of machine learning models using pleural fluid parameters in patients with exudative pleural effusions". *European Journal of Internal Medicine* 116 (2023): 68-75.
10. Peker N., *et al*. "Diagnostic performance of the lactate dehydrogenase to adenosine deaminase ratio in pleural effusion differentiation". *Tuberkuloz ve Toraks* 69.4 (2021): 380-388.

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