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Original Article

The Diagnostic Accuracy of Pleural Fluid Lactate Dehydrogenase to Adenosine Deaminase ratio in Pleural Tuberculosis

Anam Ikram, Muhammad Younus, Rabbia Abbas, Hafiz M. Faisal Nadeem, Amna Cheema, Aisha Saeed

King Edward Medical University/Mayo Hospital Lahore

Abstract

Objective: To determine diagnostic accuracy of the pleural fluid lactate dehydrogenase to adenosine deaminase ratio in diagnosis of pleural tuberculosis.

Methodology: The study was conducted at "Department of the Pulmonology, Mayo Hospital, Lahore from 01-03-2025 to 31-08-2025.Ethical approval was obtained before enrolling 63 Pulmonology outpatients who met the selection criteria. All participants gave Informed consent before participation. Patient data, including name, age, gender, BMI, symptom duration, and medical history (e.g., diabetes, hypertension, smoking, tuberculosis), were recorded. Pleural fluid was collected via thoracentesis by a research team. The sample was divided into two sterile containers: one for LDH and ADA testing, and the other for culture. Pleural tuberculosis was diagnosed with an LDH/ADA ratio <10. Culture results were documented after 4-6 weeks. Data analysis was conducted using SPSS 28.

Results: We found mean age of 42.22±16.56 years. The majority of participants were male (60.3%, n=38), while females constituted 39.7% (n=25) of the study population. Based on LDH/ADA ratio, 76.2% tested positive and 23.8% negative. Culture report confirmed 77.8% positive and 22.2% negative. Using culture as the reference, the LDH/ADA ratio showed sensitivity of 95.92%, specificity of 92.86%, PPV 97.92%, NPV 86.67%, and overall accuracy of 95.24%.

Conclusion: Pleural fluid LDH/ADA ratio was found to be comparable to pleural fluid mycobacterial culture in diagnosing pleural tuberculosis.

Keywords: Diagnostic accuracy, lactate dehydrogenase, pleural fluid, pleural tuberculosis

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Corresponding Author: Dr. Anam Ikram **Email:** anamikram969@gmail.com

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Introduction

Tuberculosis remains one of the most significant global public health challenges, with pleural tuberculosis accounting for a substantial proportion of disease presentations.[1] The worldwide incidence of tuberculosis remains persistently elevated. Population surveys estimate that 14 million have a prevalent condition, corresponding to around 10 million incident cases annually, of which about six million are diagnosed and treated.[2] Around 1.7 billion people are currently infected with M. tuberculosis, with a higher risk of tuberculosis observed in specific population groups such as those with severe mental illness.[3]

Understanding of tuberculosis and expertise in its diagnosis and treatment are essential. Conventional diagnostic modalities are often time- intensive and do not always provide accurate results. Lazarus et al., reported that tuberculosis contributes to 30%-60% of all pleural effusions globally.[1]

Pleural effusions manifest in around 5% of all M. tuberculosis instances. In endemic regions, TB is the predominant cause of the lymphocytic pleural effusion. The definitive diagnostic method is culture of acid-fast bacilli from pleural fluid or a pleural biopsy. Pleural biopsy has been conventional method for diagnosing pleural effusion due to M. tuberculosis, however it entails significant morbidity. Biochemical and molecular indicators for pleural fluid have been established to circumvent intrusive testing.[4]

The majority of tuberculosis pleural effusions are

exudative, characterized by elevated adenosine deaminase ADA levels, a lymphocyte predominance, straw-colored appearance, and a free-flowing nature, while exhibiting a low yield in mycobacterial cultures. Tuberculosis pleurisy may also manifest as a loculated effusions predominantly composed of neutrophils, resembling para-pneumonic effusions.[5]

Many physicians often manage pleural effusion cases without definitive evidence from pathological, cytological, or microbiological assessments. Consequently, pleural LDH/ADA ratio presents a promising diagnostic tool that may complement Light's criteria in differentiating between tuberculous effusion and other cause of pleural effusion.[6,7]

Anar et al. found that the sensitivity, specificity, PPV, and NPV of the pleural fluid LDH/ADA ratio for diagnosing the pleural tuberculosis were 90%, 59.85%, 70.4%, and 84.9%, respectively.[8] In contrast, Wang et al. reported that LDH/ADA ratio achieved a sensitivity of 93.62% and specificity of 93.06% for identifying the pleural tuberculosis.[9] In patients with pleural tuberculosis, the mean LDH/ADA ratio was lower than in other diagnoses 6.2 vs 34.3, $p<0.001$, according to Beukes et al., a score of ≤10 for LDH/ADA indicated 90% specificity and 90% PPVs.[10]

Rationale of the study is to determine diagnostic utility of pleural fluid LDH/ADA ratio in diagnosis of pleural tuberculosis. Literature showed that LDH/ADA ratio can be helpful in diagnosing and replacing culture testing, which is time and cost consuming process. By using LDH/ADA ratio treatment can be initiated early. Nevertheless, varied data has been reported in previous studies and moreover, no local data is available. Therefore, we want to conduct this study to determine the beneficial role of LDH/ADA ratio in locals setting, which is time and cost effective and does not need much expertise. This can help in quick diagnosis and improve the outcome by early treatment.

Methodology

The study was conducted over six months in Department of the Pulmonology at Mayo Hospital, Lahore. A sample size of 63 participants was calculated with the help of WHO sample size calculator based on an estimated pleural tuberculosis prevalence of 60%,[5] with an anticipated sensitivity and specificity of 93.62% and 93.06%,[9] respectively, for the LDH/ADA ratio, using a 95% confidence level and 10% absolute precision. Consecutive patients aged 16–75 years presenting with symptoms suggestive of pleural tuberculosis (cough >14 days, sputum, fever, weight loss >5kg) and lymphocytic exudative effusions with elevated adenosine deaminase (ADA) were enrolled. Exclusion criteria included pregnancy, malignancy, collagen tissue disease, renal failure, and active neurological conditions. After ethical approval and informed consent, demographic and clinical data were recorded. Pleural fluid was obtained via thoracentesis and analyzed for LDH and ADA levels, with an LDH/ADA ratio <10 defined as test-positive. Pleural fluid culture, reported after 4–6 weeks, served as the reference standard for confirming tuberculosis. The analysis of data was performed utilizing SPSS version 28. The sensitivity, PPV, specificity, NPV, and accuracy of LDH/ADA ratio were calculated employing a 2×2 contingency table, with subsequent stratified analysis based on gender, age, BMI, duration of the symptoms, and medical history to evaluate potential effect modification.

Results

We enrolled 63 patients with mean age of 42.22±16.56 years. Patients were stratified into four age groups: 16-30 years (17 patients, mean age 22.94±4.23 years), 31-45 years (21 patients, mean age 37.10±4.92), 46-60 years (15 patients, mean age 53.53±4.44), and ≥61 years (10 patients, mean age 68.80±3.29). The majority of participants were male (60.3%, n=38), while females constituted 39.7% (n=25) of study population.

The majority of patients 51(81%) patients had a BMI ≤25 kg/m², with a mean BMI of 23.51±1.08. The remaining 12(19%) patients had a BMI >25 kg/m², with a mean of 26.17±0.39. The overall mean BMI was 24.02±1.44.

Symptom duration was ≤2 months for 29 patients (mean 1.59±0.50 months) and >2 months for 34 patients (mean 3.47±0.50 months). The overall mean duration was 2.60±1.07 months.

A history of smoking was reported by 63.5% of patients, while 36.5% were non-smokers. Diabetes was present in 30.2%, hypertension in 44.4%, family history of tuberculosis in 25.4%, and weight loss in 69.8%.

Among 48 LDH/ADA-positive patients, mean LDH was 399.92±103.82 U/L, mean ADA was 89.04±13.89 U/L, and mean LDH/ADA ratio was 4.63±1.56. The 15 LDH/ADA-negative patients had higher mean LDH (640.80±121.06 U/L), lower mean ADA (44.07±11.18 U/L), and a higher mean ratio (14.89±2.68).

Culture-positive patients (49) showed mean LDH

404.00±114.18 U/L, mean ADA 88.12±15.48 U/L, and mean ratio 4.80±1.93. Culture-negative patients (14) had mean LDH 643.71±97.43 U/L, mean ADA 44.07±10.00 U/L, and mean ratio 15.02±2.79.

Based on LDH/ADA ratio, 48(76.2%) tested positive and 15(23.8%) negative. Culture report confirmed 49(77.8%) positive and 14(22.2%) negative.

Table 1: *Patient clinical and demographics characteristics (N=63)*

Variable	Category	N(%)
Age (years)	16–30	17 (27.0)
	31–45	21 (33.3)
	46–60	15 (23.8)
	≥60	10 (15.9)
	Mean±SD	42.22±16.56
Gender	Male	38 (60.3)
	Female	25 (39.7)
BMI (kg/m²)	≤25	51 (81.0)
	>25	12 (19.0)
	Mean±SD	24.02±1.44
Duration of Symptoms (months)	≤2	29 (46.0)
	>2	34 (54.0)
Smoking	Yes	40 (63.5)
	No	23 (36.5)
Diabetes	Yes	19 (30.2)
	No	44 (69.8)
Hypertension	Yes	28 (44.4)
	No	35 (55.6)
Family History of TB	Yes	16 (25.4)
	No	47 (74.6)
Weight Loss	Yes	44 (69.8)
	No	19 (30.2)

Using culture as the reference, the LDH/ADA ratio showed sensitivity of 95.92%, specificity of 92.86%, PPV 97.92%, NPV 86.67%, and overall accuracy of 95.24%.

The LDH/ADA ratio maintained high diagnostic performance across subgroups showed in Table-3. The LDH/ADA ratio demonstrated excellent diagnostic accuracy for pleural tuberculosis, with an overall sensitivity of 95.92%, specificity of 92.86%, and accuracy of 95.24% compared to culture. This performance remained consistently high across various demographic and clinical subgroups, supporting its utility as a reliable diagnostic tool in diverse patient populations.

Table 2: *LDH and ADA Levels by Tuberculosis Status (N=63)*

Tuberculosis Status		LDH (U/L) Mean ± SD	ADA (U/L) Mean ± SD	LDH/ADA Ratio Mean ± SD
By LDH/ADA Ratio	Positive (n=48)	399.92±103.82	89.04±13.89	4.63±1.56
	Negative (n=15)	640.80 ± 121.06	44.07 ± 11.18	14.89 ± 2.68
By Culture Report	Positive (n=49)	404.00 ± 114.18	88.12 ± 15.48	4.80 ± 1.93
	Negative (n=14)	643.71 ± 97.43	44.07 ± 10.00	15.02 ± 2.79

Discussion

Pleural fluid lactate dehydrogenase (LDH) and adenosine deaminase (ADA) concentrations are frequently employed as biomarkers to differentiate between tuberculous pleural effusion (TPE) and parapneumonic pleural effusion (PPE). Nonetheless, this distinction can prove to be complex, as LDH concentrations may fluctuate from normative levels to significantly elevated values in PPE, whereas markedly elevated ADA concentrations can be observed in both pathological states. This investigation assessed the pleural fluid LDH/ADA ratio as an innovative parameter for the diagnosis of pleural tuberculosis.[9]

In regions characterized by a high prevalence of tuberculosis (TB), the diagnosis of pleural TB is frequently established in individuals who present with lymphocyte-dominant exudative effusions alongside elevated ADA levels. Two recent minor retrospective studies have suggested that the LDH to ADA ratio is significantly lower in TB-related pleural effusions in comparison to non-TB pleural effusions, implying that this ratio may serve as a valuable diagnostic tool for differentiating pleural TB from other types of pleural exudates.[9,11]

Pleural fluid LDH/ADA ratio was found to be valuable supplementary tool in diagnosing individuals with high pretest chance of the pleural tuberculosis. While confirmation by microbiological tests remains the gold standard, LDH/ADA ratio can help clinicians in regions with high tuberculosis prevalence to initiate treatment promptly.[10]

Amanda et al. [10] reported that ratio of ≤10 showed a specificity of the 90% and PPV of the 95%, with sensitivity of the 78%. This made it a highly effective and therapeutically useful "rule-in" criterion for the pleural tuberculosis, particularly in the high-incidence areas. In our current study, we observed

Table 3: *Diagnostic Performance of LDH/ADA Ratio for Pleural Tuberculosis (Culture as Gold Standard)*

Stratification Variable	Category	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Overall	–	95.92	92.86	97.92	86.67	95.24
Age Group	16–30	90.91	100	100	85.71	94.12
	31–45	94.44	66.67	94.44	66.67	90.48
	46–60	100	100	100	100	100
	≥60	100	100	100	100	100
Gender	Male	93.33	100	100	80	94.74
	Female	100	83.33	95	100	96
BMI (kg/m²)	≤25	100	83.33	95	100	96
	>25	94.74	92.31	97.3	85.71	94.12
Symptom Duration	≤2 months	96	100	100	80	96.55
	>2 months	95.83	90	95.83	90	94.12
Smoking	Yes	96.97	100	100	87.5	97.5
	No	93.75	85.71	93.75	85.71	91.3
Diabetes	Yes	100	100	100	100	100
	No	93.94	90.91	96.88	83.33	93.18
Hypertension	Yes	100	87.5	95.24	100	96.43
	No	93.1	100	100	75	94.29
Family History of TB	Yes	100	100	100	100	100
	No	94.44	90.91	97.14	83.33	93.62
Weight Loss	Yes	96.67	92.86	96.67	92.86	95.45
	No	94.74	–	100	0	–

that LDH/ADA ratio demonstrated excellent diagnostic accuracy for pleural tuberculosis, with an overall sensitivity of 95.92%, specificity of 92.86%, and accuracy of 95.24% when compared to culture. Similarly, Tingting et al. [12] found a sensitivity of 93.9% and specificity of 87.0% for the LDH/ADA ratio.

Jinlin et al.,[9] found pleural fluid LDH and ADA levels, together with LDH/ADA ratios in the TPE patients, was as follows: 364.5 U/L, 33.5 U/L and 10.88 respectively. The use of LDH/ADA ratio as parameter for pleural tuberculosis diagnosis, with sensitivity, specificity, PLR, and NLR recorded at 93.62%, 93.06%, 13.48, and 0.068, respectively, at cut-off threshold of 16.20.

Pleural fluid LDH/ADA ratio, ascertainable through standard biochemical tests, is a strong predictor of pleural tuberculosis at a threshold of 16.20. While we found sensitivity of 95.92%, specificity of 92.86%, PPV 97.92%, NPV 86.67%, and overall accuracy of 95.24% at threshold level ≤10. These results also support the findings of current study. The assessment of this characteristic may assist clinicians in diagnosing pleural tuberculosis.

While in study by Zhi et al.,[13] found mean age of patients was 68 46-76 and male patients were dominant in their study i.e. 56% while female patients were 44%. These results look similar with findings of current study as we found mean age of 42.22±16.56 years. And majority of participants were male 60.3%, n=38, while females constituted 39.7% n=25 of the study population. Zhi et al. [13] found diagnostic accuracy of the PF LDH/ADA ratio for the TPE is modest. LDH/ADA ratio is not supported by available data for TPE diagnosis. The reason behind this different results may be the age group of patients which selected for study as our mean age value and Zhi et al.[13] study different.

Adenosine deaminase ADA, neutrophils, RBCs and lymphocytes are divided into ADA-1 & ADA-2 isoforms. However, in clinical practice, the total ADA level is most commonly measured. ADA-2, which is primarily produced and secreted by mononuclear cells and macrophages, is linked to intracellular infections like TPE, whereas elevated ADA-1 levels are frequently seen in empyema. The LDH, a widespread cytoplasmic enzyme present in nearly all main organ systems, tends to rise nonspecifically in response to cellular injury or necrosis.[14,15]

An increased pleural fluid LDH level in the exudative pleural effusions, like PPE and TPE, indicates damage to pleural or lung tissues and the endothelial injury. Many patients with the TPE experience severe granulomatous inflammation in the pleural tissue, along with infiltration by mononuclear cells and the macrophages. In contrast, pleural tissues in individuals with PPE typically show signs of acute inflammation and neutrophil infiltration, along with a notable presence of pus cells. [16]

In another study by Tingting et al. [12] found ratio of LDH/ADA provides a greater diagnostic value for TPE than single biomarkers and can quickly, conveniently, and affordably identify individuals with TPE while mean age of patients in their patients was 38.74±19.22 years which closest to findings of current study. In their study male patients were dominant like our study findings i.e. 72.6%.

We found mean LDH was 399.92±103.82 U/L, mean ADA was 89.04±13.89 U/L, and mean LDH/ADA ratio was 4.63±1.56 while Tingting et al. [12] found mean LDH was 449293-664 U/L, mean ADA was 41(32-52) U/L, and mean LDH/ADA ratio was 4.623.54-5.67. Also Jinlin et al. [9] found levels of LDH was 364.555-1154 U/L, mean ADA was 33.54.5-75.9 U/L, and mean LDH/ADA ratio was 10.883.65-21.81.

Larry Ellee et al. [17] reported that the LDH/ADA ratio is considerably lower in the TPE compared to the PPE and can be particularly useful in clinical scenarios where the medical thoracoscopy is either unavailable or contraindicated, or when urgent decisions regarding the initiation of the anti-tuberculous treatment must be made due to outbreaks or clinical emergency. Current evidence recommends that LDH/ADA ratio cutoff value of less than 15 effectively differentiates between TPE and PPE. However, interpreting the LDH/ADA ratio needs clinicians to consider pretest probability of the tuberculosis

Diagnostic performance analysis used a pleural fluid LDH/ADA ratio cut-off of 18.63 in study by Xin-Yu et al. [18] Sensitivity, specificity, PLR, NLR, PPV, and NPV were 94.44%, 84.85%, 6.23, 0.065, 77.3%, and 96.6%, respectively. The subsequent meta-analysis confirmed diagnostic accuracy of the pleural fluid LDH/ADA ratio.

These findings support the results of our study. As TPE is primarily diagnosed by bacteriologic and histopathologic examination; however, low positive rate of M. tuberculosis culture, lengthy culture period, invasive nature of the tissue biopsy and other factors make diagnosis challenging. [19] So LDH/ADA ratio may be positively used for the diagnosis of pleural tuberculosis. This finding may assist in early clinical decision-making for patient management, perhaps resulting in improved prognosis and the prevention of unfavorable outcomes.

These findings could be helpful to implement the better diagnostic tool for early diagnosis pleural tuberculosis in local population, in order to improve the diagnostic protocol and early initiation of treatment. It could also help to improve our practice. These findings suggest that LDH/ADA ratio could serve as a valuable indicator of the pleural inflammatory responses.

Conclusion

We concluded that the pleural fluid LDH/ADA ratio is comparably effective as the mycobacterial culture of pleural fluid in the diagnosis of pleural tuberculosis. The present study has illustrated that the pleural fluid LDH/ADA ratio functions as a significant biomarker for the diagnosis of pleural tuberculosis. The LDH/ADA ratio may reflect the attributes of the pleural inflammation and the associated inflammatory response. Therefore, it may facilitate the initial clinical management of patients presenting with pleural effusion.

Ethical Approval: The IRB/EC approved this study via letter no. 354/RC/KEMU dated September 18, 2023.

Conflict of Interest: None

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Authors' Contribution

AI: Conception.

MY, HMFN: Design of the work.

RA,AC,AS: Data acquisition, analysis, or interpretation.

RA, AC, AS: Draft the work.

AI,MY,HMFN: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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