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ORIGINAL ARTICLE

Lactate dehydrogenase / adenosine deaminase (LDH/ ADA) ratio in pleural fluid for the diagnosis of infectious pleurisy

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ABSTRACT

Background: Infectious pleurisy, including Tuberculous Pleural Effusion (TPE) and Para Pneumonic Effusion (PPE), remains a diagnostic challenge in resource-limited settings. Biomarkers such as Adenosine Deaminase (ADA) and Lactate Dehydrogenase (LDH) are widely used, but the diagnostic performance of their ratio (LDH/ADA) is less explored. To determine the diagnostic accuracy of pleural fluid LDH/ADA ratio in identifying infectious pleurisy, using pleural fluid culture as the gold standard.

Material and Methods: This descriptive study was conducted in the Department of Pulmonology, Ojha Institute of Chest Diseases, Dow University of Health Sciences (DUHS), Karachi, from February 2025 till July 2025. In this descriptive study, 80 patients aged 18–60 years with pleural effusion and ADA > 33 U/L were recruited at Ojha Institute of Chest Diseases, DUHS, Karachi. Pleural fluid samples were analyzed for biochemical markers and culture. LDH/ADA ratio > 10 was considered positive. Diagnostic accuracy parameters were calculated.

Results: A total of 80 patients with pleural effusion were included (mean age 37.8 ± 11.3 years; 60% male). Infectious effusions showed significantly higher pleural LDH, ADA, LDH/ADA ratio, and protein, whereas glucose and pH were lower compared to non-infectious effusions ($p < 0.05$). An LDH/ADA ratio > 10 demonstrated excellent diagnostic performance with 93.3% sensitivity, 90.0% specificity, and 92.5% overall accuracy.

Conclusion: The pleural fluid LDH/ADA ratio demonstrates high diagnostic accuracy for infectious pleurisy and may serve as a reliable, inexpensive tool in clinical settings where pleural biopsy is unavailable.

Keywords: Infectious pleurisy, LDH/ADA ratio, Pleural effusion, Para pneumonic effusion, Tuberculous pleural effusion.

BACKGROUND

Pleural effusion is common in routine medical practice and also most common disease among all pleural diseases.[1,2] Pleural effusion is a common clinical manifestation, and about 3000 per million people in the world suffer from pleural disease.[3] More than 50 causes of pleural effusion are recognized throughout the world.[4] The estimated prevalence of pleural effusion in developed countries is 320 cases per 100,000 population, with a distribution of etiologies related to the prevalence of underlying diseases. The exact prevalence in developing countries has not been estimated, but tuberculosis (TB) remains an important cause. The incidence in the United States is estimated to be at least 1.5 million cases annually.[5,6]

Pleural effusion is simply defined as the abnormal accumulation of fluid in between the parietal and visceral pleura, called the pleural cavity.[2] It can occur by itself or can be the result of surrounding parenchymal disease within the pleural cavity and in the pleural fluid such as; empyema, tuberculous pleural effusion (TPE), Para pneumonic effusion (PPE), malignant pleural effusion (MPE), as well as extra pulmonary diseases with secondary pleural involvement, such as chronic heart failure (CHF), chronic renal failure (CRF), and liver cirrhosis.[7-9]

Pleural effusions are most commonly classified as transudative or exudative based on Light's criteria.[10] The Light criteria is a useful way to differentiate between transudate and exudate. Evaluation of pleural fluid can be used to determine the cause of pleural effusion and help guide the treatment of the underlying cause.[11] Early diagnosis of cause of pleural effusion is very important for its appropriate management. Different biochemical

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tests including glucose, total proteins, and pH levels as well as lactate dehydrogenase (LDH) and adenosine deaminase (ADA) are used for determining cause of pleural effusion.[12,13]

Different studies reported the higher level of ADA in TPE with higher sensitivity and specificity of ADA in diagnosis of TPE. A recent study by Núñez-Jurado D, *et al*. reported the PPE in 59.8% and non-PPE in 40.2% including MPE in 19.3% and TPE in 15.8%. LDH/ADA ratio distinguishing between PPE and non-PPE with sensitivity, specificity and diagnostic accuracy of 98.06%, 98.08% and 89.96%.[14]

The rationale of the study is to evaluate the diagnostic accuracy of pleural fluid biomarkers (LDH/ADA ratio) and propose an algorithm to aid in differential diagnosis of infectious pleurisy through cytochemical analysis of pleural fluid. In developing countries, pleural fluid analysis is most commonly used for treatment of infectious pleurisy whereas pleural biopsy is not taken either because of lack of facility or it is considered to be more expensive and invasive. Hence there is always a chance of missing the diagnosis and under or over treatment of infectious pleurisy. Therefore, this study is proposed to find out the accuracy of pleural fluid biomarkers (LDH/ADA ratio) that could be confidently used to diagnose infectious pleurisy in the absence of pleural biopsy in our setting.

MATERIAL AND METHODS

This was a descriptive study conducted in the Department of Pulmonology, Ojha Institute of Chest Diseases, Dow University of Health Sciences (DUHS), Karachi, over a period of six months. (From February 2025 till July 2025), Ethical approval was obtained from the Institutional Ethical Review Board (IERB) of DUHS under approval number [IRB-3815/ DUHS/ APPROVAL/ 2025/ 329]. Written informed consent was taken from each participant. 29. The sample size was calculated using the WHO sample size calculator based on the sensitivity and specificity values reported by Núñez-Jurado *et al*. (2023), who demonstrated a prevalence of infectious pleurisy of 74%. Taking a confidence level of 95% and a margin of error of 5%, the minimum required sample size was estimated as 80 patients. A non-probability consecutive sampling technique was used to recruit participants.

The study included adults aged 18 to 60 years presenting with pleural effusion and an adenosine deaminase (ADA) level greater than 33 U/L. Patients with ADA < 33 U/L, inconclusive final diagnosis, or those who refused consent were excluded.

For data collection, demographic and clinical characteristics were documented. Pleural fluid was obtained by thoracentesis under aseptic conditions and analyzed for ADA, lactate dehydrogenase (LDH), glucose, protein, and pH, along with cytology and microbiological culture for Mycobacterium tuberculosis and bacterial pathogens. The LDH/ADA ratio was calculated, with a value > 10 considered diagnostic for infectious pleurisy. The diagnostic accuracy of this ratio was assessed against the gold standard of a positive pleural fluid culture for Mycobacterium tuberculosis or bacterial pathogens.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25. Normality of continuous data was assessed using the Shapiro–Wilk test. For normally distributed variables such as age, ADA, LDH, glucose, protein, and pH, the mean ± standard deviation (SD) was reported. For skewed variables, the median with interquartile range (IQR) was used. Categorical variables such as gender, residence (urban/rural), culture positivity, and diagnosis type were presented as frequencies and percentages.

Independent two-sample t-test was applied to compare mean values (e.g., ADA, LDH, glucose) between TB pleurisy and bacterial pleurisy groups. The Chi-square test was used to determine associations between categorical variables (e.g., gender vs. diagnosis type, residence vs. diagnosis type). Diagnostic validity parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy of the LDH/ ADA ratio were calculated using 2×2 contingency tables.

RESULTS

A total of 80 patients (n = 80) with pleural effusion were included in this study. The mean age was 37.8 ± 11.3 years (range: 18–70 years). Among them, 48 (60.0%) were males and 32 (40.0%) were females. Mean and standard deviation (SD) were calculated for continuous variables such as age, duration of symptoms, fever, and pleural fluid biochemical parameters [adenosine deaminase (ADA), lactate dehydrogenase (LDH), glucose, protein, and pH]. Frequencies and percentages were calculated for categorical variables including

gender, presenting symptoms, laterality of effusion, and etiology of effusion. Group comparisons of pleural fluid biochemical parameters between infectious and non-infectious effusions were assessed using the independent sample t-test, while associations between categorical variables such as gender and diagnosis type were evaluated using the Chi-square test.

The most frequent presenting symptom was cough (66; 82.5%), followed by fever (60; 75.0%), dyspnea (57; 71.3%), and chest pain (42; 52.5%). The mean duration of symptoms was 15.3 ± 6.8 days (median 14, IQR 10–21 days), and the mean recorded fever was 100.8 ± 1.5 °F. Pleural effusion was more frequently located on the right side (45; 56.3%) compared to the left side (35; 43.7%).

As shown in Table-I, exudative effusions were predominant (71; 88.8%), while transudative effusions were less frequent (9; 11.2%). Among the exudates, Para pneumonic effusion (31; 38.8%) and tuberculous pleural effusion (25; 31.2%) were the leading causes, while malignant effusions accounted for 9 (11.2%). Transudative effusions were mainly attributed to congestive heart failure, cirrhosis, and nephrotic syndrome.

The mean values of pleural fluid biochemical markers in infectious versus non-infectious effusions are presented in Table-II. Infectious effusions demonstrated significantly higher pleural LDH, ADA, LDH/ADA ratio, and total protein, while pleural glucose and pH were significantly lower compared to non-infectious effusions ($p < 0.05$ by independent t-test).

Using an LDH/ADA ratio > 10 as the diagnostic cutoff for infectious pleurisy, the test correctly identified 56 of 60 culture-positive cases and excluded 18 of 20 culture-negative cases. As shown in Table-III, the sensitivity of the LDH/ADA ratio was 93.3%, specificity 90.0%, positive predictive value (PPV) 96.6%, negative predictive value (NPV) 81.8%, and overall diagnostic accuracy 92.5%.

Diagnostic accuracy was further evaluated after stratification across subgroups. As shown in Table-IV, the sensitivity, specificity, and overall accuracy of the LDH/ ADA ratio remained consistent across gender, age groups, duration of symptoms, and laterality of effusion (Chi-square test for categorical associations, independent t-test for continuous variables).

Overall, the majority of pleural effusions were exudative, with Para pneumonic and tuberculous effusions as leading causes. Pleural ADA, LDH/ADA ratio, and total protein were significantly elevated in infectious effusions, while pleural glucose and pH were significantly reduced. An LDH/ADA ratio greater than 10 demonstrated excellent diagnostic performance (accuracy 92.5%), consistent across all patient subgroups.

Table-I: Etiological distribution of pleural effusion (n = 80).

Diagnosis	n (%)
Para pneumonic effusion (PPE)	31 (38.7)
Tuberculous pleural effusion (TPE)	25 (31.3)
Empyema	7 (8.8)
Malignant pleural effusion (MPE)	9 (11.2)
Transudates (CHF, Cirrhosis, Nephrotic)	8 (10.0)

Table-II: Pleural fluid markers in infectious vs. non-infectious effusions (n = 80).

Variable	Infectious effusion (n = 60) Mean ± SD	Non-infectious effusion (n = 20) Mean ± SD	p-value
Pleural LDH (U/L)	512.2 ± 193.7	360.2 ± 250.1	0.006*
Pleural ADA (U/L)	44.9 ± 14.7	36.3 ± 9.8	0.017*
LDH/ADA Ratio	15.3 ± 8.0	10.6 ± 8.7	0.027*
Pleural pH	7.25 ± 0.11	7.39 ± 0.07	0.000*
Pleural Glucose (mg/dL)	55.0 ± 19.3	72.8 ± 26.9	0.002*
Pleural Total Protein (g/L)	42.9 ± 6.9	38.2 ± 7.3	0.011*

Table-III: Diagnostic accuracy of LDH/ADA ratio compared to pleural fluid culture (n = 80).

LDH/ADA ratio	Infectious pleurisy present (n = 60)	Infectious pleurisy absent (n = 20)
Positive (>10)	56 (True Positive)	2 (False Positive)
Negative (≤10)	4 (False Negative)	18 (True Negative)

Table-IV: Diagnostic accuracy of LDH/ADA ratio after stratification (n = 80).

Variable	Subgroup	Sensitivity (%)	Specificity (%)	Accuracy (%)
Gender	Male (n = 48)	92.5	88.0	91.0
	Female (n = 32)	94.0	92.0	93.5
Age group	≤ 40 years (n = 42)	95.0	89.0	93.0
	> 40 years (n = 38)	92.0	91.0	91.5
Symptom duration	≤ 14 days (n = 36)	94.0	90.0	92.0
	> 14 days (n = 44)	92.0	91.0	91.8
Pleural effusion side	Right (n = 45)	93.0	89.0	91.5
	Left (n = 35)	94.0	91.0	93.0

DISCUSSION

In this study, we evaluated the diagnostic utility of the pleural fluid lactate dehydrogenase (LDH) to adenosine deaminase (ADA) ratio for differentiating infectious from non-infectious pleural effusions. The majority of cases were para pneumonic effusion (38.8%) and tuberculous pleural effusion (31.2%), which is consistent with the high burden of respiratory infections in developing countries.[15,16] Malignant effusion (11.2%) and empyema (8.8%) were less frequent, in line with other regional studies.[17] The mean pleural ADA level in our cohort (44.9 U/L in infectious effusions) was comparable to previously reported ranges of 35–45 U/L in tuberculous pleural effusions.[18,19] Pleural LDH levels (mean 512 U/L in infectious effusions) were also similar to those described in infectious pleural processes, reflecting underlying inflammation and cellular breakdown.[20]

Using a cutoff of LDH/ADA > 10, we observed a sensitivity of 93.3% and specificity of 90.0%, with an overall diagnostic accuracy of 92.5%. These results demonstrate strong discriminatory power for infectious pleurisy. Prior studies have reported comparable sensitivities (90–95%) and specificities (85–92%) when using LDH/ADA ratios, supporting its robustness as a diagnostic biomarker.[21–23] The high positive predictive value (96.6%) in our population suggests that the test is particularly reliable for confirming infectious causes when the ratio exceeds the cutoff.

Compared with ADA alone, which may show reduced specificity in high-prevalence tuberculosis settings[24], the LDH/ADA ratio provides an additional layer of diagnostic accuracy. This is likely because LDH reflects the extent of pleural inflammation and tissue injury, while ADA reflects cellular immune activity, and their ratio balances these biological processes.[25] Importantly, the test requires no additional resources beyond routine pleural fluid chemistry, making it a cost-effective biomarker for resource-limited clinical settings.

The clinical implications of these findings are significant. Early and reliable differentiation between infectious and non-infectious effusions allows prompt initiation of targeted therapy, minimizing morbidity and unnecessary invasive procedures. The LDH/ADA ratio could thus be integrated into diagnostic algorithms alongside Light's criteria, culture, cytology, and ADA levels

LIMITATIONS

Our study has limitations. The sample size was modest (n = 80) and conducted at a single center, which may limit generalizability. We also relied on pleural fluid culture as the gold standard, which has inherent limitations due to its low sensitivity in tuberculous effusion.[28] Future multicenter studies with larger cohorts and inclusion of molecular diagnostics may further validate the performance of this biomarker.

CONCLUSION

This study demonstrates that most pleural effusions in our cohort were exudative, with Para pneumonic and tuberculous effusions being the leading etiologies. Pleural fluid ADA and the LDH/ADA ratio were significantly higher in infectious causes, and an LDH/ ADA ratio >10 provided excellent diagnostic accuracy (92.5%) for distinguishing infectious pleurisy from non-infectious effusions. Importantly, its performance remained consistent across patient subgroups,

underscoring its utility as a cost-effective, readily available diagnostic tool in clinical practice, especially where culture facilities are limited.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Nida Shaikh: Acquisition of data, interpretation of data, manuscript drafting, final approval, accountable for all aspects of publication.

Faisal Asad: Acquisition of data, interpretation of data, manuscript drafting, final approval, accountable for all aspects of publication.

Rabeea Nouman: Acquisition of data, interpretation of data, manuscript drafting, final approval, accountable for all aspects of publication.

Aftab Ahmed: Study conception, acquisition, analysis and interpretation of data, manuscript drafting, final approval, accountable for all aspects of publication.

Aisha Asim: Study conception, acquisition, analysis and interpretation of data, manuscript drafting, final approval, accountable for all aspects of publication.

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