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Research Article

Comparative Evaluation of Pleural Fluid Adenosine Deaminase (Ada) Versus Lactate Dehydrogenase/Adenosine Deaminase (Ldh/Ada) Ratio for Distinguishing Tubercular From Non-Tubercular Pleural Effusions

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A B S T R A C T

Introduction: Pleural effusion is a frequently encountered clinical condition with varied aetiologies, including tuberculosis, malignancy, and bacterial infections. While pleural fluid adenosine deaminase (ADA) is a commonly used marker for diagnosing tuberculous pleural effusion (TPE), its diagnostic specificity may be limited in cases with elevated ADA levels. The lactate dehydrogenase to adenosine deaminase (LDH/ADA) ratio in pleural fluid has recently emerged as a promising marker for differentiating TPE from non-tuberculous pleural effusion (NTPE).

Materials and Methods: This retrospective study included 80 patients with pleural effusion and pleural fluid ADA ≥40 IU/L who underwent diagnostic thoracentesis at a tertiary care centre. Patients were categorised into TPE and NTPE groups based on microbiological, cytological, and clinical response criteria. Demographic, clinical, and pleural fluid biochemical data including LDH and ADA were analysed.

Results: Of the 80 patients, 40 had TPE and 40 had NTPE. The median LDH/ADA ratio was significantly lower in TPE (5.46) than in NTPE (39.82). A cutoff of 13.9 for the LDH/ADA ratio showed 76.5% sensitivity and 91.2% specificity for diagnosing TPE (AUC: 0.87).

Conclusion: The pleural fluid LDH/ADA ratio is a reliable and superior diagnostic tool compared to ADA alone in distinguishing TPE from NTPE in patients with elevated ADA. It offers enhanced specificity and can aid clinical decision-making in TB-endemic settings.

Keywords: Tuberculous pleural effusion (TPE), Non-tuberculous pleural effusion (NTPE), Adenosine deaminase (ADA), Lactate dehydrogenase (LDH)

Introduction

Pleural effusion refers to an abnormal accumulation of fluid within the pleural cavity, and it can arise from numerous underlying pathological conditions. These conditions encompass infectious diseases like pulmonary tuberculosis, inflammatory disorders such as pneumonia, cardiac diseases like heart failure, and malignancies involving pleural surfaces.[1,2] Due to the broad spectrum of possible causes, accurate identification of the specific aetiology of pleural effusion represents a significant clinical challenge, necessitating reliable diagnostic tools and biomarkers.

One widely adopted diagnostic approach involves the application of Light's criteria, which are primarily utilised to classify pleural effusions as either exudative or transudative based on biochemical analysis. Although Light's criteria effectively distinguish exudative pleural effusions from transudative ones, they do not specifically identify the underlying disease causing the effusion.[3] Consequently, further differentiation among various types of exudative effusions, particularly between tuberculous pleural effusion (TPE) and other non-tuberculous effusions, remains critically important yet diagnostically challenging.

Among the various aetiologies of exudative pleural effusions, tuberculous pleural effusion (TPE) is especially significant, predominantly in regions with a high incidence of tuberculosis (TB). The diagnosis of TPE often relies upon integrating multiple clinical, radiological, and laboratory parameters. Within laboratory assessments, the biochemical evaluation of pleural fluid has emerged as a key diagnostic component. Specifically, pleural fluid adenosine deaminase (ADA) activity is widely recognized as an important diagnostic biomarker due to its strong association with active tuberculosis. ADA is an ensyme involved prominently in purine metabolism, and elevated ADA activity in pleural fluid typically suggests an ongoing inflammatory response characteristic of tuberculous infection. However, despite its general reliability, the diagnostic accuracy of ADA levels, including optimal cutoff thresholds, varies considerably across different geographic regions and patient populations depending on local TB prevalence and other epidemiological factors.[4,5,6,7]

In addition to ADA, another biochemical parameter, lactate dehydrogenase (LDH), present in pleural fluid, has been studied for its diagnostic potential. Recently, the ratio of LDH to ADA in pleural fluid has emerged as a potentially valuable diagnostic marker. This LDH-to-ADA ratio offers a comparative ensymatic measure that may provide additional diagnostic clarity, particularly when ADA levels are borderline or ambiguous and fail to decisively differentiate TPE from non-tubercular pleural effusions. The rationale behind using the LDH-to-ADA ratio is to enhance diagnostic specificity by combining two biochemical parameters, potentially improving clinicians' ability to discriminate among pleural effusions with differing aetiologies.[8,9,10]

Despite this growing interest, there remains a paucity of robust studies examining the clinical efficacy and reliability of the pleural fluid LDH-to-ADA ratio in differentiating TPE from other types of pleural effusions. Consequently, further evaluation is necessary to clearly define its diagnostic role. Considering these knowledge gaps, the current study has been designed with the primary aim of investigating the effectiveness of the LDH-to-ADA ratio in pleural fluid as a diagnostic biomarker. Specifically, this study seeks to assess the utility of this biochemical ratio in accurately distinguishing tuberculous pleural effusions from non-tuberculous effusions, particularly in clinical scenarios where ADA levels alone are elevated but insufficiently conclusive for establishing a definitive diagnosis.

Materials and Methods

Ethical Approval

This was a retrospective study.

Patient Selection and Data Collection

The study population consisted of patients who underwent an initial diagnostic thoracentesis procedure for pleural effusions at KIMS Hospital and Research Centre, Bengaluru. Relevant clinical and laboratory data were retrospectively extracted from the patients' medical records. Collected information encompassed demographic characteristics, including age and gender, along with detailed laboratory measurements of pleural fluid parameters such as total and differential white blood cell (WBC) counts, pleural fluid adenosine deaminase (ADA), and lactate dehydrogenase (LDH) levels. Additionally, data pertinent to clinical diagnoses distinguishing between tuberculous and non-tuberculous aetiologies of pleural effusion were obtained.

Patients were eligible for inclusion if their pleural fluid ADA measurements were at least 40 U/L. Exclusion criteria encompassed cases where pleural fluid WBC counts and differential counts were incomplete or unavailable from medical records.

For identifying cases of tuberculous pleural effusion (TPE), the study included patients who had confirmed diagnoses based on laboratory evidence of Mycobacterium tuberculosis infection obtained from sputum, pleural fluid, or tissue biopsy samples. Additionally, documented clinical improvement following initiation of anti-tuberculosis therapy was required to confirm the diagnosis of TPE.

In contrast, non-tubercular pleural effusions (non-TPE) were classified based on specific underlying aetiologies. Malignant pleural effusions (MPE) were defined by the presence of previously confirmed malignancy (either

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primary lung carcinoma or metastatic disease involving the lung) identified through histopathological analysis of biopsy specimens or cytological evidence of malignant cells in pleural fluid samples. This diagnostic confirmation ensured accurate attribution of pleural effusions to underlying malignancy in these cases.

Furthermore, pleural effusions resulting from bacterial infections such as pneumonia, bronchiectasis, or pulmonary abscesses were classified as parapneumonic effusions (PPE). The categorization into PPE required positive bacterial cultures from either sputum or pleural fluid specimens to substantiate the diagnosis of bacterial infection and to clearly differentiate these cases from other aetiologies.

Patients whose pleural effusions did not meet the diagnostic criteria for either malignant or infectious aetiologies as outlined above were subsequently classified as idiopathic effusions.

Statistical Analysis

Continuous variables in the analysis were summarized using median values and corresponding interquartile ranges (IQR), whereas categorical variables were represented as frequencies and percentages within each diagnostic category. Statistical comparisons among different pleural effusion groups were conducted using appropriate statistical tests, including the Kruskal–Wallis test for continuous data, Pearson's Chi-square test, and Fisher's exact test for categorical data.

Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic performance, including sensitivity, specificity, and determination of optimal cutoff points, by calculating the area under the curve (AUC). To assess the strength of diagnostic association, odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated. Further, binary logistic regression analysis was conducted to adjust for potential confounding factors such as patient age, gender, total WBC count, and the proportion of lymphocytes in pleural fluid.

A two-tailed P-value of less than 0.05 was defined as statistically significant. All statistical evaluations and analyses were performed using SPSS (Statistical Package for Social Sciences) version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, a total of 80 patients underwent their initial thoracentesis and exhibited pleural fluid ADA levels ≥40 IU/L. The demographic and biochemical characteristics of the patients categorized by diagnosis are outlined in Table 1. Of these, 40 patients were classified as having tuberculous pleural effusion (TPE), while the remaining 40 were classified as having non-tuberculous pleural effusion (NTPE).

As illustrated in Figures 1 and 2, ROC analysis demonstrated superior diagnostic performance of the pleural fluid LDH-to-ADA ratio compared to ADA alone for distinguishing TPE from NTPE. For identifying TPE patients, the LDH-to-ADA ratio exhibited an area under the curve (AUC) of 0.87 at an optimal cutoff value of 13.9, with a sensitivity of 76.5% and specificity of 91.2%. Similarly, in differentiating NTPE, the LDH-to-ADA ratio showed an AUC of 0.89 at a cutoff value of 14.5, achieving a sensitivity of 81.3% and specificity of 78.6%.

The selected cutoff points for the pleural fluid LDH-to-ADA ratio were then utilized to calculate crude odds ratios (ORs) to estimate the likelihood of TPE and NTPE. Adjusted odds ratios were also determined using multivariate logistic regression, accounting for confounders such as patient age, gender, total white blood cell count, and the percentage of lymphocytes present in the pleural fluid. These adjusted analyses revealed that the pleural fluid LDH-to-ADA ratio significantly correlated with the identification of both TPE and NTPE aetiologies.

These adjusted and unadjusted results emphasise the robust diagnostic utility of the pleural fluid LDH-to-ADA ratio for accurately distinguishing between TPE and NTPE.

Table 1.Demographic and laboratory characteristics of patients categorised by diagnosis

Variables	TPE (n=40)	NTPE (n=40)
Mean Age (years)	66	59
Sex (male/female)	28/12	29/11
LDH (U/L), median	355	2150
ADA (U/L), median	65	62
LDH-to-ADA ratio, median	5.46	39.82
White cell count (/µL), median	1480	6250
Percentage lymphocytes (%), median	74	9
Lymphocyte count (/µL), median	1105	770

(Data presented as number or median; LDH: Lactate Dehydrogenase, ADA: Adenosine Deaminase, TPE: Tuberculous Pleural Effusion, NTPE: Non-Tuberculous Pleural Effusion)

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Table 2.ROC Analysis for Pleural Fluid LDH-to-ADA Ratio

Condition	Test	Cutoff Value	AUC	Sensitivity	Specificity
Tuberculous Pleural Effusion (TPE)	LDH-to-ADA Ratio	13.9	0.87	76.5%	91.2%
Non-Tuberculous Pleural Effusion (NTPE)	LDH-to-ADA Ratio	14.5	0.89	81.3%	78.6%

Table 3.Cut-off values of pleural fluid LDH-to-ADA ratio for differentiating pleural effusion etiologies

Variables	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Ratio <13.9 for TPE	27.3 (13.8–53.9)	<0.001	9.4 (4.1–20.8)	<0.001
Ratio >14.5 for NTPE	13.6 (7.5–25.8)	<0.001	5.2 (2.6–11.1)	<0.001

Discussion

This study primarily demonstrated that the pleural fluid LDH-to-ADA ratio outperformed pleural fluid ADA levels alone in distinguishing between tuberculous pleural effusion (TPE) and non-tuberculous pleural effusion (NTPE), especially in cases where ADA levels were elevated. Among the 80 patients included, 40 were diagnosed with TPE and 40 with NTPE, all of whom had pleural fluid ADA levels ≥40 IU/L. The median LDH-to-ADA ratio in the TPE group was 5.46, which was significantly lower than the NTPE group, which had a median ratio of 39.82. ROC analysis in our study revealed that a pleural fluid LDH-to-ADA ratio cutoff of 13.9 yielded an area under the curve (AUC) of 0.87, with a sensitivity of 76.5% and specificity of 91.2% for diagnosing TPE. Similarly, in distinguishing NTPE, a cutoff of 14.5 showed an AUC of 0.89, with a sensitivity of 81.3% and specificity of 78.6%. These findings highlight the superior diagnostic performance of the LDH-to-ADA ratio in pleural effusion evaluation when ADA levels alone may not be definitive.[11]

ADA is an enzyme involved in purine metabolism and is particularly elevated in T-cell–rich environments, making it a widely studied biomarker for TPE. However, its diagnostic value can vary based on regional disease prevalence. In a study from Serbia involving 54 patients, a pleural ADA cutoff of 49 U/L demonstrated a sensitivity of 89.2% and a specificity of 70.4%. A much larger study from Spain that included 2,104 patients reported a sensitivity of 93% and specificity of 90% using a cutoff of 35 U/L. Similarly, a Japanese study involving 435 patients found that an ADA level above 36 U/L had 85.5% sensitivity and 86.5% specificity for diagnosing TPE. These variations reflect the influence of regional tuberculosis prevalence on ADA performance. In our study, the median ADA levels were 65 U/L in the TPE group and 62 U/L in the NTPE group, indicating significant overlap and thus limiting the discriminatory power of ADA alone in high-ADA cases.

Interestingly, although NTPE is typically associated with lower ADA levels—particularly in malignant pleural effusion (MPE)[6,12,13]-elevated ADA levels have been reported in certain malignancies such as lung cancer, lymphoma, mesothelioma, and hematologic cancers.[6] This overlap can confound diagnosis, further emphasising the need for a more reliable marker. Recent studies have highlighted the utility of the pleural fluid LDH-to-ADA ratio in this context. One retrospective study reported that a ratio below 15 demonstrated 89.1% sensitivity and 84.8% specificity for identifying TPE.[14] Another study using a cutoff of 16.2 found sensitivity and specificity to be 93.6% and 93.1%, respectively. Yet another study showed that a cutoff of 10 or less achieved 78% sensitivity and 90% specificity for differentiating TPE from other pleural effusions. These findings align closely with our study, which showed that a cutoff of 13.9 had comparable sensitivity (76.5%) and even higher specificity (91.2%) for diagnosing TPE. For NTPE, our chosen cutoff of 14.5 yielded 81.3% sensitivity and 78.6% specificity, underscoring the ratio's value as a discriminatory tool in both directions.[9]

Additionally, our study revealed strong statistical associations between the LDH-to-ADA ratio and pleural effusion aetiology. The crude odds ratio for identifying TPE at a ratio <13.9 was 27.3 (95% CI: 13.8–53.9; p<0.001), while the adjusted odds ratio, after controlling for confounders such as age, gender, total white cell count, and lymphocyte percentage, remained significant at 9.4 (95% CI: 4.1–20.8; p<0.001). Likewise, a ratio >14.5 was associated with a crude OR of 13.6 and adjusted OR of 5.2 for NTPE, both with p-values <0.001. These findings provide robust statistical support for the use of this ratio as an independent predictor of pleural effusion type.[15]

Our study's strength lies in its focus on patients with elevated ADA levels (≥40 IU/L), a group in which ADA-based differentiation becomes more challenging. Despite elevated ADA values, the lymphocyte percentage was markedly higher in TPE cases (median 74%) compared to NTPE (9%), and the total white blood cell count was lower in TPE (1480/µL) versus NTPE (6250/µL). However, among all parameters, the LDH-to-ADA ratio consistently showed the highest discriminative ability.

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Nonetheless, the interpretation of our findings should be tempered by several limitations. This was a retrospective, single-centre study, which may introduce selection and information bias due to reliance on medical records. Moreover, the inclusion criterion of ADA ≥40 U/L limits the generalizability of the findings to cases with lower ADA levels. Finally, the relatively small sample size (n=80) necessitates further validation through multicentric prospective studies.

In conclusion, our study reaffirms that the pleural fluid LDH-to-ADA ratio is a more effective diagnostic marker than ADA alone in differentiating between TPE and NTPE, especially in patients with elevated ADA levels. It offers high specificity and robust predictive value, making it a useful and practical tool for clinicians managing pleural effusions, particularly in tuberculosis-endemic and resource-limited settings.

Conclusion

This study demonstrated that the pleural fluid LDH-to-ADA ratio is a highly effective diagnostic marker for distinguishing between tuberculous and non-tuberculous pleural effusions in patients with elevated ADA levels (≥40 IU/L). Compared to ADA alone, the LDH-to-ADA ratio exhibited superior diagnostic performance, with high sensitivity and specificity values at optimal cutoff points. A ratio below 13.9 was strongly associated with tuberculous pleural effusion, while a ratio above 14.5 significantly predicted non-tuberculous etiologies. Both crude and adjusted odds ratios confirmed the strong diagnostic correlation, even after accounting for potential confounders such as age, sex, total leukocyte count, and lymphocyte percentage. These findings underscore the clinical utility of the LDH-to-ADA ratio as a simple, cost-effective, and reliable tool for improving diagnostic accuracy in patients with pleural effusion.

Limitations

This study had several limitations that should be acknowledged. First, it was a retrospective and single-centre analysis, which may introduce selection and information biases and limit the generalisability of the findings to broader populations. Second, the sample size was relatively small (n=80), reducing the statistical power and potentially limiting the robustness of subgroup analyses. Third, the study included only patients with elevated pleural fluid ADA levels (≥40 IU/L), thereby excluding cases with lower ADA values where diagnostic differentiation may be even more challenging. As a result, the findings may not be applicable to all cases of pleural effusion. Additionally, reliance on medical records may have led to incomplete data capture or inconsistencies in documentation. Finally, microbiological confirmation of tuberculosis was not available in all TPE cases, and clinical response to anti-tubercular therapy was used as part of the diagnostic criteria, which could have introduced diagnostic bias.

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