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The Utility of Pleural Fluid Lactate Dehydrogenase to Adenosine Deaminase Ratio in Pleural Tuberculosis

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Established Facts

- In high-burden settings, the diagnosis of pleural tuberculosis (TB) is frequently inferred in patients who present with lymphocytic exudative effusions and high adenosine deaminase (ADA) levels.
- Two recent small retrospective studies suggested that the lactate dehydrogenase (LDH)/ADA ratio is significantly lower in TB than in non-TB pleural effusions and that the LDH/ADA ratio may be useful in differentiating pleural TB from other pleural exudates.

Novel Insights

- In a large prospectively collected cohort of patients with suspected pleural tuberculosis (TB), the lactate dehydrogenase/adenosine deaminase ratio of the effusion was a valuable adjunct to support the diagnosis of pleural TB.

Keywords
Tuberculosis · Pleural effusions · Adenosine deaminase · Lactate dehydrogenase

Abstract
In high-burden settings, the diagnosis of pleural tuberculosis (TB) is frequently inferred in patients who present with lymphocyte predominant exudative effusions and high adenosine deaminase (ADA) levels. Two recent small retrospective studies suggested that the lactate dehydrogenase (LDH)/ADA ratio is significantly lower in TB than in non-TB pleural effusions and that the LDH/ADA ratio may be useful in differentiating pleural TB from other pleural exudates. We compared the pleural LDH/ADA ratios, ADA levels, and lymphocyte predominance of a prospectively collected cohort of patients with proven pleural TB (n = 160) to those with a definitive alternative diagnosis (n = 68). The mean pleural fluid LDH/ADA ratio was lower in patients with pleural TB than alternative diagnoses (6.2 vs. 34.3, $p < 0.001$). The area under the receiver operating characteristic curve was 0.92 ($p < 0.001$) for LDH/ADA ratio and 0.88 ($p < 0.001$) for an ADA ≥40 U/L alone. A ratio of ≤12.5 had the best overall diagnostic efficiency, while a ratio of ≤10 had a specificity of 90% and a positive predictive value of 95%, with a sensitivity of 78%, making it a clinically useful "rule in" value for pleural TB in

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high incidence settings. When comparing the LDH/ADA ratio to an ADA level ≥40 U/L in the presence of a lymphocyte predominant effusion, the latter performed better. When lymphocyte values are unavailable, our data suggest that the LDH/ADA ratio is valuable in distinguishing TB effusions from other pleural exudates.

Introduction

Tuberculosis (TB) is one of the commonest causes of pleural exudates globally [1–3]. The gold standard for the diagnosis of pleural TB remains the isolation of *Mycobacterium tuberculosis* from pleural fluid or pleural tissue by culture, microscopy, or nucleic acid amplification tests; or histology demonstrating caseating granulomas containing acid-fast bacilli [1, 3, 4]. Histology and/or culture of pleural tissue via medical thoracoscopy may have sensitivities up to 100%, but many high TB incidence regions have limited resources, lack of training and lack of infrastructure for routine thoracoscopy [5]. Moreover, *Mycobacterium tuberculosis* is often not cultured from pleural fluid aspirates in high-burden settings, given the paucibacillary nature of the disease [3, 5, 6]. Waiting for culture results can delay the initiation of treatment; therefore, the diagnosis is frequently inferred in patients who present with lymphocyte-predominant exudative pleural effusions in combination with a high adenosine deaminase (ADA) level [2–4, 7]. An additional test to support the probability of pleural TB is valuable, especially in situations where lymphocyte values may not be available.

Both interferon gamma and interleukin-27 have been found superior to ADA in the diagnosis of TB versus malignant pleural effusion, but the lack of commercially available assays and uncertainty regarding the ideal cutoff values still precludes its widespread use [1, 4]. ADA levels must be interpreted with caution in the absence of lymphocyte predominance, as it is nonspecific, often elevated in other pleural exudates, including malignancies (especially those of hematological origin), bacterial infections, empyema, and collagen vascular diseases (including systemic lupus erythematosus and rheumatoid arthritis) [2, 8].

Recent retrospective evidence from a very low TB incidence setting suggested that the lactate dehydrogenase (LDH)/ADA ratio in TB pleural effusion was significantly lower than in non-TB pleural effusions [9]. Likewise, a study from a higher incidence setting suggested that the LDH/ADA ratio could aid in differentiating tuberculous and parapneumonic pleural effusions [10].

The use of the pleural LDH/ADA ratio to differentiate pleural TB from other causes of pleural exudates has not been investigated in a large cohort. We, therefore, aimed to investigate its diagnostic accuracy in patients with a high pretest probability for pleural TB and compare it to that of isolated pleural ADA levels, to ADA levels in the context of a lymphocyte predominant exudate, and to the LDH/ADA ratio in the context of a lymphocyte predominant exudate.

Case Series

We searched an existing prospectively collected registry of patients with a high clinical probability of pleural TB who had presented to the Division of Pulmonology, Tygerberg Hospital, Cape Town, South Africa, between 2008 and 2018. Tygerberg Hospital renders a tertiary service to a population of approximately 3 million people, and is 1 of 2 academic referral centers in the city with high background incidence of TB (>500/100,000 population) [11].

We identified all patients with either a definitive diagnosis of pleural TB (with microbiological or histological confirmation) or a definitive alternative diagnosis. Cases categorized as "nonspecific chronic pleuritis" on histology had been subjected to medical thoracoscopy and followed up for at least 6 months to confirm lack of clinical and radiological progression [12]. Patients with undiagnosed exudates (no definitive tissue or microbiological diagnoses) or missing ADA or LDH data were excluded. The ADA was determined using the Giusti-Galanti method [6], and a lymphocyte predominant effusion (LPE) was defined as one with >75% lymphocytes and/or a lymphocyte/neutrophil ratio >0.75 [5].

The final diagnoses, demographic data, pleural fluid ADA, and LDH were documented, as well as whether or not the effusion was lymphocyte predominant. We compared (1) the LDH/ADA ratios, (2) the absolute ADA levels, (3) the presence of an ADA level ≥40 U/L, (4) the presence of LPEs with an LDH/ADA ratio ≤10, and (5) the presence of LPEs with an ADA level ≥40 U/L of patients with a definitive diagnosis of pleural TB to those with an alternate diagnosis.

Intergroup differences were analyzed statistically using SPSS® 17.0 (SPSS Inc., Chicago, IL, USA). Receiver operating characteristic (ROC) curves were used to identify the optimal cutoff points and to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each data point with 95% confidence intervals (CIs). Mann-Whitney tests were used for comparisons of the test results between independent groups. Pearson chi-square tests were used to compare categorical variables between groups. Statistical significance was set at $p < 0.05$.

Of 267 patients who had thoracocentesis performed at Tygerberg Hospital, 228 were included in the analysis (Table 1). Thirty-nine were excluded because of incomplete laboratory data, including no ADA and LDH performed ($n = 17$) and no ADA performed ($n = 7$), and undiagnosed exudates ($n = 15$). In total, 160 patients had confirmed pleural TB, and 68 had alternative diagnoses, including malignant pleural effusions ($n = 44$), chronic nonspecific

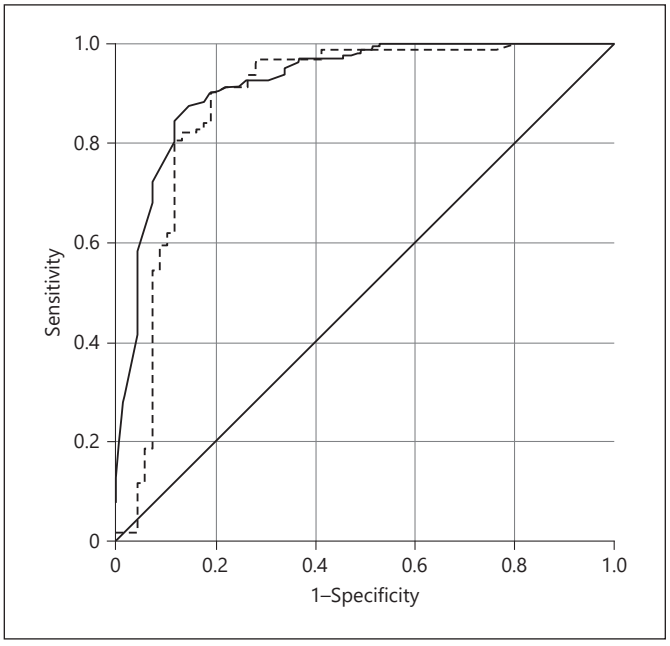

Fig. 1. ROC curve for the LDH/ADA ratio (solid line) and for an ADA ≥40 U/L alone (dashed line) in differentiating pleural TB from other pleural exudates. An AUC value of 0.92 (95% CI 88–96%, $p < 0.001$) was obtained using the pleural LDH/ADA as an indicator for pleural tuberculosis. A ratio of 12.5 had coordinates of 0.875 for sensitivity and 0.147 for 1-specificity, respectively, furthest away from random, making it the value with optimal sensitivity and specificity. An AUC value of 0.88 (95% CI 82–95%, $p < 0.001$) was obtained using the data for an ADA ≥40 U/L alone. ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; TB, tuberculosis; ADA, adenosine deaminase; LDH, lactate dehydrogenase.

pleuritis ($n = 18$), parapneumonic effusions (PPEs, $n = 4$), sarcoidosis ($n = 1$), and hydatid disease ($n = 1$).

Patients with confirmed pleural TB had significantly higher pleural ADA levels than those with alternative diagnoses (88.4 vs. 18.1 IU/L, $p < 0.001$), but comparable LDH levels (476.0 vs. 527.5 U/L, $p = 0.199$). The pleural fluid ratio of LDH/ADA was significantly lower in patients with pleural TB than alternative diagnoses (6.2 vs. 34.3, $p < 0.001$).

The ROC curve (Fig. 1) for the LDH/ADA ratio in differentiating pleural TB from other pleural exudates had an area under the curve of 0.92 (95% CI 88–96%, $p < 0.001$). A ratio of 12.5 was the value with the maximal combined sensitivity and specificity of 86 and 88%. It had a PPV of 94% and an NPV of 72%. A ratio of ≤10 had a higher specificity and PPV of 90 and 95%, respectively, with a sensitivity of 78% and NPV of 64%. A ratio of ≤7.5 had a specificity and PPV of 96 and 97%, respectively; however, the sensitivity at this value was reduced to 64% (Table 2). An ADA level ≥40 U/L alone had a specificity and PPV of 78 and 91%, respectively, in this cohort. The ROC curve for an ADA level ≥40 U/L (Fig. 1) in this population yielded an area under the curve of 0.88 (95% CI 82–95%, $p < 0.001$). The pleural fluid lymphocyte data were un-

Table 1. Comparison of demographics and laboratory findings between participants with TB pleural effusion and all other alternative diagnoses

	TB ($n = 160$)	All alternative diagnoses ($n = 68$)	MPE ($n = 44$)	CNSP ($n = 18$)	PPE ($n = 4$)	Hydatid disease ($n = 1$)	Sarcoidosis ($n = 1$)	p^*
Age, (mean, SD), years	34.2 (13.5)	55.3 (13.3)	59.1 (10.7)	49.2 (15.8)	54.0 (15.4)	40.0	35.0	<0.001
Male, *n* (%)	88 (55.0)	49 (72.1)	31 (70.5)	14 (77.8)	3 (75.0)	0	1	0.016
ADA, U/L	88.4 (62.8–115.5)	18.1 (12.7–36.3)	17.6 (12.7–27.6)	15.5 (8.7–36.3)	160.4 (73.1–196.7)	144.5	37.1	<0.001
LDH, U/L	476.0 (314.5–781.5)	527.5 (301.0–1,501.5)	735.5 (331.5–1,784.5)	367.5 (122.0–460.0)	7,782.0 (3,830.5–13,516.5)	14,404.0	1,132.0	0.199
LDH/ADA	6.20 (3.7–9.6)	34.3 (16.9–61.5)	41.1 (20.6–65.9)	16.3 (9.9–33.8)	49.3 (29.9–77.3)	99.7	30.5	<0.001

All values are represented as median and interquartile range unless otherwise stated. SD, standard deviation; TB, tuberculosis; MPE, malignant pleural effusion; CNSP, chronic non-specific pleuritis; PPE, parapneumonic effusion; ADA, adenosine deaminase; LDH, lactate dehydrogenase. * *p* values for pleural TB versus all alternative diagnoses.

Table 2. Diagnostic accuracy of selected pleural fluid LDH/ADA ratios, an LDH/ADA ratio of <10 with the presence of LPE, an ADA level ≥40 U/L, and of an ADA level ≥40 U/L in combination with the presence of an LPE, for TB pleural effusion

LDH/ADA	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
7.5	64% (57–72%)	96% (87–98%)	97% (91–99%)	53% (44–62%)
10.0	78% (71–84%)	90% (79–95%)	95% (89–98%)	64% (53–73%)
12.5	86% (79–90%)	88% (78–94%)	94% (89–97%)	72% (61–81%)
15.0[a]	91% (85–94%)	81% (69–89%)	92% (86–95%)	79% (67–87%)
16.2[a]	91% (85–95%)	76% (64–86%)	90% (84–94%)	79% (67–88%)
25.0	97% (92–99%)	62% (49–73%)	86% (79–90%)	89% (76–96%)
LDH/ADA with LPE[b]	73% (65–80%)	91% (80–97%)	96% (89–98%)	57% (46–67%)
ADA ≥40 U/L	90% (84–94%)	78% (66–87%)	91% (85–94%)	77% (65–86%)
ADA ≥40 U/L with LPE[b]	89% (82–93%)	95% (85–99%)	98% (97–99%)	77% (66–86%)

LDH, lactate dehydrogenase; ADA, adenosine deaminase; LPE, lymphocyte predominant effusion; PPV, positive predictive value; NPV, negative predictive value; TB, tuberculosis; CI, confidence interval. [a] Values suggested by Blakiston et al. [9] and Wang et al. [10], respectively. [b] Lymphocyte data available only in 140/160 patients with pleural TB and 58/68 with alternative diagnoses.

available in 30 patients for technical reasons, including degeneration of cells ($n = 29$) and not being requested ($n = 1$). In a subgroup analysis of participants where lymphocyte data were available, the LDH/ADA ratio in the presence of a LPE had a specificity and PPV of 91 and 96%, respectively. An ADA level ≥40 U/L in the presence of a LPE had a specificity and PPV of 95 and 98%, respectively.

Discussion

We found the pleural fluid LDH/ADA ratio to be a valuable adjunct in the diagnostic assessment of this large prospectively collected cohort of patients with a high pretest probability of pleural TB. While microbiological confirmation is always preferred, the LDH/ADA ratio could guide clinicians working in high TB incidence settings in initiating TB therapy. A ratio of ≤10 had a specificity of 90% and PPV of 95%, with a sensitivity of 78%, making it an easy-to-remember and clinically useful "rule in" value for pleural TB in high-incidence settings, superior to the use of pleural fluid ADA alone. Consistent with other studies, the combination of an ADA level ≥40 U/L with a lymphocyte predominant pleural effusion carried the highest specificity and PPV for pleural TB [6, 8, 13].

Combining the LDH/ADA ratio with a lymphocyte predominant pleural effusion performed similarly to the ratio alone. In practice, a pleural fluid lymphocyte count might be omitted from the initial thoracentesis, or be unavailable for technical or budgetary reasons. Should lymphocyte values be unavailable, our data suggest that the LDH/ADA ratio is preferable to a "standalone" ADA cutoff value in distinguishing TB effusions from other pleural exudates, and it may even be argued that an LDH/ADA ratio of ≤7.5 obviates the need to test for lymphocyte predominance. In some cases, this may save the patient a second thoracentesis. There is a plausible physiological explanation for the reliability of the LDH/ADA ratio in TB effusions. Both the LDH and the ADA will be raised in TB effusions, PPEs, and malignant effusions. However, the LDH tends to be raised proportionately more in parapneumonic and malignant effusions than in tuberculous effusions, and similarly, the ADA tends to be higher in tuberculous effusions than in the others. Thus, the ratios between the enzymes are more representative of the usual pattern of elevation in the pleural fluid than isolated values [2].

There is surprisingly little published data on the utility of the LDH/ADA ratio in suspected pleural TB. In a retrospective study of patients with pleural TB ($n = 72$) and PPEs ($n = 47$) performed in China, investigators found an LDH/ADA ratio ≤16.2 to be the statically optimal cutoff, with a sensitivity of 93% and specificity of 62% [10] In another report from New Zealand that included 57 patients with confirmed pleural TB, a ratio of ≤15 had a sensitivity of 89%, specificity of 85%, PPV of 17%, and NPV of almost 100% [9]. The contrast between the high NPV in the New Zealand study and the low NPVs obtained from our cohort is expected and reflects the markeddifference in the regional TB incidence rates between New Zealand and South Africa (<10 vs. >500 per 100,000) [11].

The high local TB burden potentially limits the applicability of our suggested cutoffs to similar high incidence

populations. Only studies from low-incidence settings would be able to suggest a cutoff with a high NPV that might be used to rule out pleural TB. Another limitation is the fact that only patients referred to a tertiary facility were included in this study.

In conclusion, we found the pleural fluid LDH/ADA ratio to be a valuable adjunct in the assessment of patients with suspected TB pleural effusion. It was superior to the pleural fluid ADA alone in differentiating TB pleural effusion from alternative etiologies, but less efficient than a raised ADA in the setting of a lymphocyte predominant pleural effusion.

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Statement of Ethics

This analysis of the registry was approved by the Stellenbosch University Health Research Ethics Committee (study number S19/05/087). Informed consent was obtained from all subjects prior to inclusion in the registry and all invasive procedures.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.B., J.A.S., A.H.D., E.M.I., and C.F.N.K. conceived and designed the study and collected all data. A.B. and C.F.N.K. prepared the manuscript, which was critically reviewed by all authors.

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