Title
Diagnostic Accuracy of Lactate Dehydrogenase/Adenosine Deaminase Ratio in Differentiating Tuberculous Pleural Effusion and Parapneumonic Effusion: A Systematic Review

Running title
LDH/ADA ratio for TB and parapneumonic effusions

Author list
Dr. Larry Ellee NYANTI\textsuperscript{a}, MRCP (first author)
E-mail: larrynyanti@ums.edu.my
ORCID: 0000-0002-5790-3919

Dr. Muhammad Aklil ABD RAHIM\textsuperscript{b}, DrPH (corresponding author)
E-mail: aklil@ums.edu.my
ORCID: 0000-0002-1087-4444

Dr. Nai-Chien HUAN\textsuperscript{c}, MRCP (collaborating author)
E-mail: naichien89@gmail.com
ORCID: 0000-0002-2671-4189
Affiliations

\(^a\)Medical Department, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia.

\(^b\)Department of Public Health Medicine, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia.

\(^c\)Department of Respiratory Medicine, Queen Elizabeth Hospital, PO Box 2029, 88586 Kota Kinabalu, Sabah, Malaysia.

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LEN: Conceptualization, data curation, formal analysis, methodology, writing-original draft, and writing-review & editing.

MAAR: Data curation, methodology, formal analysis, and writing-review & editing.

NCH: Conceptualization, methodology, writing-original draft, and writing-review & editing.

Authors’ declaration

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Corresponding author

Dr. Larry Ellee Nyanti

Mailing address: Medical Department, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400 Kota Kinabalu, Sabah, Malaysia.

Email: larrynyanti@ums.edu.my
Title: Diagnostic accuracy of lactate dehydrogenase/adenosine deaminase ratio in differentiating tuberculous and parapneumonic effusion: a systematic review

ABSTRACT

Background
Tuberculous pleural effusion (TPE) and parapneumonic effusion (PPE) are often difficult to differentiate owing to overlapping clinical features. Observational studies demonstrate that the ratio of lactate dehydrogenase to adenosine deaminase (LDH/ADA) is lower in TPE compared to PPE; but integrated analysis is warranted.

Methods
We conducted a systematic review to evaluate the diagnostic accuracy of LDH/ADA ratio in differentiating TPE and PPE. We explored the PUBMED and Scopus databases for studies evaluating LDH/ADA ratio in TPE and PPE.

Results
From a yield of 110 studies, five were included for systematic review. The cutoff value for LDH/ADA ratio in TPE ranged from <14.2 to <25. The studies demonstrated high heterogeneity, precluding meta-analysis. QUADAS-2 assessment revealed a high risk of bias in terms of patient selection and index test.

Conclusion
LDH/ADA ratio is a potentially useful parameter to differentiate between TPE and PPE. Based on the limited data, we recommend a LDH/ADA ratio cutoff value of <15 in differentiating TPE and PPE. However, more rigorous studies are needed to further validate this recommendation.

KEYWORDS: Lactate dehydrogenase, adenosine deaminase, tuberculous pleural effusion, parapneumonic effusion, diagnostic accuracy
Introduction

The definitive diagnosis of tuberculous pleural effusion (TPE) requires identification of Mycobacterium tuberculosis (MTB) in pleural tissue or fluid.\(^1\) In high TB prevalence regions, more than half of undiagnosed exudative pleural effusion is eventually diagnosed as TPE \(^2\). Owing to the low sensitivity of fluid mycobacterial culture, and medical thoracoscopy not being universally available, biomarkers such as adenosine deaminase (ADA) are often employed as rule out tools.\(^3\) Further complicating matters are that parapneumonic effusion (PPE) and tuberculous effusion (TPE) often present with similar symptoms and elevated ADA.\(^3\) As a standalone test, ADA may be raised in bacterial empyema as well, thus making it difficult to differentiate with tuberculous empyema.\(^4\) The observation that lactate dehydrogenase (LDH) is raised to different degrees in TPE and PPE raised interest in the idea of LDH/ADA ratio as a discriminative test, leading to the seminal 2017 study.\(^5\) However, there is no clear, definitive data on the diagnostic accuracy of the lactate dehydrogenase/adenosine deaminase ratio for this purpose. The rationale for the ratio is that 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.\(^6\)

Thus, a systematic review is needed to elucidate studies which looked at the role of LDH/ADA ratio in differentiating PPE from TPE. Our research question was: In adults with undiagnosed pleural effusion, what is the LDH/ADA ratio distinguishing between PPE and TPE. We evaluated the diagnostic accuracy of LDH/ADA ratio by measuring the summary diagnostic accuracy (sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values) of pleural fluid lactate dehydrogenase/adenosine deaminase ratio in differentiating tuberculous pleural effusion from parapneumonic effusion.
Methods

Data sources and search

We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We identified English-language studies, without temporal restriction or study type restriction, in Scopus and PubMed databases. Studies published from inception up until 31st October 2022 were included in the search criteria. Our search duration of the two databases lasted from 5th September 2022 until 31st October 2022. We used the following free text search terms on PubMed: “tuberculosis” and its MESH terms, AND “adenosine deaminase” and its MESH terms, AND “Lactate Dehydrogenase” and its MESH terms. We modified the search terms to suit the SCOPUS search algorithm. This systematic review was registered in the PROSPERO database under CRD42022359917.

Study selection and eligibility criteria

We included studies of adult patients having both tuberculous and parapneumonic pleural effusions which reported on diagnostic performance of pleural fluid lactate dehydrogenase/adenosine deaminase ratio. Observational studies (cross-sectional, cohort and case-control studies) were included. The study titles and abstracts were screened by two review authors to determine if the study fulfilled eligibility criteria. The two review authors independently evaluated the risk of bias in the eligible studies based on the Quality Assessment of Diagnostic Accuracy Studies Tool 2 (QUADAS 2). Any disagreement between the two review authors over the eligibility of any studies were resolved through discussion with a third review author. We reviewed full-text publications to identify studies for inclusion in the analysis after the reviewers agreed that the cited publication met the eligibility criteria, and all disagreements were resolved. Information regarding the study design, methodology, participant demographics, baseline characteristics, and measures of effects were extracted from the studies and data was recorded in an Excel spreadsheet.
Outcomes of interest

The main outcomes were summary diagnostic accuracy (sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values) of pleural fluid lactate dehydrogenase/adenosine deaminase ratio in differentiating tuberculous pleural effusion from parapneumonic effusion.

Statistical analysis (data synthesis and analysis)

We derived summary diagnostic accuracy estimates from all the studies. MetaDiSc version 1.4 was used to analyze and derive a summary estimate of diagnostic accuracy of LDH/ADA ratio.\[^9\] Pooling estimates by random effects model were derived using the DerSimonian-Laird method. Chi-square test was used to determine significant heterogeneity with alpha set at 0.1 whereby P values of < 0.1 indicated significant difference with the null. I^2 was used to estimate and quantify the degree of heterogeneity. The I^2 value ranges from 0 to 100%, with 75% or more expressing high degree of heterogeneity.\[^10\]
Results

Study selection and characteristics of the selected studies

Based on the electronic database search, 110 studies were found, 8 of which were excluded as duplicates (Figure 1). 59 studies were excluded based on their title and abstract. The remaining 43 studies were subjected to full-text assessment. One study was not retrievable. We excluded 35 of these studies because they did not mention LDH/ADA ratio (n=24), absence of tuberculous pleural effusion or parapneumonic effusion (n=12), and absence of accuracy testing (n=1). Finally, a total of five studies were deemed eligible for the systematic review, encompassing a total of 2,407 patients (Figure 1). These studies were published between 2017 and 2022. All of the five studies were observational, single-centre studies, and only one was a prospective study.\(^\text{[6]}\) The studies were conducted in South Africa, New Zealand, Taiwan, and China.\(^\text{[4-6,11,12]}\) There were no randomized control trials. Of note, one of the studies only recruited patients with ADA value >40 U/L.\(^\text{[12]}\) Criteria for TPE was consistent in all but one study, which only included TB culture-positive samples.\(^\text{[11]}\) Meanwhile, criteria for PPE differed between studies; one study did not explicitly state the PPE criteria.\(^\text{[6]}\) Variation in PPE criteria included a documented clinical diagnosis in the absence of alternative causes\(^\text{[11]}\), positive pleural or sputum culture with preceding clinical pulmonary infection\(^\text{[12]}\), clinical pulmonary infection in absence of TPE\(^\text{[4,5]}\). The characteristics of the included studies and their patients are presented in Table 1.

ADA assays

Varying ADA assays were used, such as Giusti-Galanti method and the Diazyme method.\(^\text{[6,11]}\) ADA assay used in the remaining two studies was not detailed.

Role of LDH/ADA in differentiating PPE and TPE

Cited LDH/ADA ratio cutoff values for TPE differed in each study, ranging from <7.5 (sensitivity: 64%; specificity: 96%) in a South African cohort\(^\text{[6]}\), to <25 (sensitivity: 97%; specificity: 62%) in a South African
cohort\textsuperscript{[6]} sensitivity: 100%; specificity: 61.6% in a New Zealand cohort\textsuperscript{[111]}. PPV was much lower (ranging 8.5-57.3 at cutoff values of $<15$ to $<25$, with ADA $>15$ or $>30$) but NPV was high (99.5-100) in the New Zealand cohort, where TB prevalence is very low.\textsuperscript{[111]} Specific cut-off values for PPE ranged at $>14.5$ (sensitivity: 79.9%; specificity: 78.5%) in the Taiwanese cohort.\textsuperscript{[12]} LDH/ADA ratio was found to be superior compared to ADA alone in differentiating TPE from alternative diagnoses (area under the receiver operating characteristic curve 0.92 (p < 0.001) versus 0.88 (p < 0.001)),\textsuperscript{[6,12]} while other studies demonstrated non-inferiority.\textsuperscript{[111]} However, LDH/ADA ratio had less positive and negative predictive values than ADA alone in a setting of lymphocyte-predominant pleural effusion.\textsuperscript{[6]} In studies which employed multiple cutoff values, PPV and sensitivity increased as the LDH/ADA ratio cutoff values decreased, while NPV and specificity decreased accordingly. LDH/ADA ratio is significantly lower in TPE than PPE.\textsuperscript{[5]} Detailed information can be found in Table 2.

**Additional value of ADA or lymphocyte-predominance in combination with LDH/ADA ratio**

When compared to LDH/ADA ratio alone, no difference was found with combined LDH/ADA ratio and lymphocyte-predominance, with the authors proposing that a ratio $<7.5$ precludes the need for fluid lymphocyte testing.\textsuperscript{[6]} Combined LDH/ADA and elevated fluid ADA increased specificity and PPV,\textsuperscript{[111]} while a combination of LDH/ADA, ADA, serum albumin, serum LDH, pleural fluid LDH/total protein provided a 100% sensitivity and 98.7% specificity.\textsuperscript{[4]} More details on this can be found in Table 2. Median values for ADA, LDH and LDH/ADA ratios are detailed in Table 3.

**Risk of bias assessment (QUADAS-2)**

Selection bias was high for all the studies identified, as convenience sampling was used in all five studies. None of the studies were randomized. A summary table of risk of bias assessments is described in detail in Supplementary Table 1.
Domain: Patient selection

Patient selection was conducted via convenience sampling from a database or registry, lab samples, or consecutive patients presenting to a healthcare center. In all studies, none of the sampling methods were randomized.

Inclusion and exclusion criteria varied greatly between the studies. One study included all exudative pleural effusions, one study included both exudative and transudative effusions, and one study included only effusions with ADA levels above 40. The remaining three studies were conducted on patients with an established diagnosis. Most studies excluded subjects with incomplete clinical data. Two studies did not define their exclusion criteria. One study excluded undiagnosed exudates. Risk of bias for patient selection was high in all studies and may have led to underestimation of diagnostic accuracy.

Domain: Index test

In all studies, LDH/ADA ratio was interpreted with knowledge of the reference standards, as they assessed patients with a known diagnosis based on reference standard to compare their respective LDH/ADA ratios. LDH/ADA ratio was assessed retrospectively, after the diagnosis was made, hence there was high risk of bias.

Of note, the studies had varying analysis groups. One study subclassified PPE into uncomplicated and complicated groups and included two categories not found in other studies - connective tissue disease-related effusion and chronic, non-specific pleuritis. A few studies had preset LDH/ADA ratio thresholds. The New Zealand cohort used a ratio <25 and <15; these values were determined based on historical data from an internal audit conducted at the study site, but threshold was determined after data collection. Receiver operating characteristic (ROC) curves were used to identify the optimal cutoff points in other studies. Two studies excluded patients with an ADA level of below 40. This may have led to overestimated test performance.
Reference standard

Parapneumonic effusion was explicitly defined in all but one study.\textsuperscript{6} Meanwhile, pleural TB was consistently defined in all studies. The authors have low concerns regarding both whether the reference standard is likely to correctly classify the target condition and whether the target condition will not match the review question. This is because in all studies, LDH/ADA ratios were calculated and interpreted retrospectively in patients with already known diagnosis, hence there is no risk of bias.

Flow and timing

There were no concerns regarding verification bias, as all studies retrieved ADA and LDH samples in the same pleural fluid sampling time frame. Not all (only 68.7\%) of the pleural fluid samples in one study were cultured for TB, as the practice in the center was only to culture those with ADA >15.\textsuperscript{11} A few studies had significant exclusion of patients. In one study, 39 out of 267 patients were excluded from analysis due to missing data (n=24) or undiagnosed effusion (n=15).\textsuperscript{6} In another study, 42 patients of 353 patients were excluded from analysis due to missing data.\textsuperscript{12} Some studies had no described exclusions while two studies mentioned excluding patients who did not fulfill inclusion criteria but did not mention how many patients were excluded.\textsuperscript{4} A summary of all studies can be viewed in Table 1.
**Discussion**

Overall, the studies demonstrated high heterogeneity in terms of methodology and clinical characteristics. This heterogeneity was statistically significant as well, as evidenced by chi-square value for between-studies heterogeneity of 140.59 (P < 0.001) for sensitivity and 1226.87 (P < 0.001) for specificity (data not shown). Furthermore, using $I^2$ statistics, heterogeneity was also quantified to be 87.9% and 98.6% respectively (data not shown). We have considered that even if statistical heterogeneity were to be improved by sub-group analyses, the vastly different and heterogeneous nature of the methodologies and clinical characteristics of the studies rendered meta-analysis as fundamentally unsuitable and invalid. Thus, meta-analysis was not done and is not presented in this study.

While data analysis suggests that pleural fluid LDH/ADA ratio is significantly lower in TPE compared to PPE, the optimal cut-off value to differentiate TPE and PPE remains undefined and is most likely influenced by various confounding factors. Various ratios of between 14.2 to 16.2 have been suggested, each with varying levels of sensitivity and specificity. Potential causes of heterogeneity in cutoff values include differing study designs and laboratory thresholds or clinical factors - which may be summed up by the agent-host-environment triad, whereby agent factors include TB incidence and strain, host factors include genetic variability and susceptibility, and environment factors include climate, living conditions, and geographical differences. TB incidences differ the most between Beukes and Blakiston (TB incidence of >500/100,000 in South Africa versus 6.4/100,000 in New Zealand).\(^6,11\), while for the three other studies, TB incidences ranged from 21.7 to 103.5/100,000.\(^4,5,12-16\) In areas with low tuberculosis burden, pleural fluid LDH/ADA ratio cut-off value with a high NPV might be sufficient to rule out TPE. However, this broad interpretation does not account for the variable thresholds used in different individual studies. To further complicate matters, it is known that different ADA assays may cause slightly different results – for example, Giusti method has a positive bias compared to non-Giusti Diazyme method.\(^13\)
Although current strength of evidence is weak, a low pleural fluid LDH/ADA ratio may alert the astute clinician to the diagnosis of TPE. It is probably appropriate to consider empirical treatment for TPE in these patients, especially in high tuberculosis prevalence areas and if other clinical, radiological and laboratory parameters are consistent with TPE. This option is attractive in resource-limited settings, among patients who were not keen for further invasive tests or among patients with small amounts of pleural effusion or dense septations rendering medical thoracoscopy difficult to perform. Nevertheless, it is vital to exercise caution due to chances of misclassifying non-TPE among patients with true TPE. The availability of pleural fluid ADA should not deter healthcare members from offering other standard-of-care tests such as Abram’s needle pleural biopsy or medical thoracoscopy whenever available. The current evidence is insufficient to recommend the use of LDH/ADA ratio for neutrophil-predominant exudative effusion, and further studies are needed in this area. Other parameters like the pleural fluid adenosine deaminase/serum C-reactive protein ratio may facilitate differentiating between the two.\(^{[17]}\)

Data from the two largest studies, which also encompass two geographical areas of highest and lowest TB prevalence (South Africa, New Zealand) out of the five studies seem to suggest a LDH/ADA ratio cutoff of <15 as having the optimal PPV to differentiate TPE from PPE.\(^{[6,11]}\) One caveat to this recommendation is that PPV is optimal at an ADA value of >30.\(^{[11]}\) This recommendation is not meant to be intransigent; moving forward, studies with more rigorous methodology and larger sample sizes should be conducted. It would not be surprising to have geographical-specific or population-specific values in the future.

LDH/ADA ratio value is probably <15 (we all need to agree on this). In Beukes study (highest TB incidence) PPV is 92.0 and NPV is 79.0, and in Blakiston study (lowest TB incidence) PPV is 17.3 and NPV is 99.5 (PPV improved significantly if LDH/ADA paired with ADA>30). Moving forward, more studies with better methodological quality and larger study populations should be conducted.

Our systematic review is not without limitations. First, the analysis was restricted to articles published in English language, thus non-English studies may have been missed out. The quality of most studies was
suboptimal owing to their retrospective, single-center design. None of the studies were randomized. Also, the differing TB incidences suggest differing prevalence and by extension pre-test probabilities as well, affecting PPVs and NPVs. Although sensitivity and specificity are the inherent values of the tool itself and not affected by disease prevalence, the utility of LDH/ADA ratio to differentiate between tuberculous and parapneumonic effusions should be viewed from the perspective of clinical decision making, and thus robust PPV and NPV values are more useful. This accentuates the limitation further. Several biases may have occurred in these studies, such as confirmation bias due to diagnosis or suspicion of tuberculosis being influenced by ADA results. One study included patients with transudative effusions, which despite potentially improving specificity estimates, would contribute to increased heterogeneity.[11] Last but not least, none of the studies included in our review performed external or temporal validation.

**Conclusion**

LDH/ADA ratio is significantly lower in TPE compared to PPE, and may be employed in clinical encounters where medical thoracoscopy is contraindicated or unavailable, or when emergent decisions on commencement of anti-tuberculous treatment are warranted due to clinical urgency or public health concerns, such as outbreaks. Contemporary evidence suggests an LDH/ADA ratio cutoff value of <15 appears useful in differentiating TPE and PPE. Nevertheless, the interpretation of LDH/ADA ratio requires the clinician to evaluate the pretest probability of tuberculosis. Rigorous studies with improved designs integrating randomization, standardization of ADA assays, and studies which limit biases, are needed in the future.
References


Table 1: Summary table of included studies.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Country</th>
<th>Design &amp; Incidence of TB</th>
<th>Sample size</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Classification of effusion</th>
<th>Criteria for TPE</th>
<th>Criteria for PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beukes (2021)</td>
<td>South Africa</td>
<td>Prospective, TB incidence: 500/100,000</td>
<td>228</td>
<td>(i) Confirmed TPE</td>
<td>(i) Undiagnosed ed TPE</td>
<td>(ii) Chronic non-specific pleuritis</td>
<td>(i) Microbiological confirmation</td>
<td>(i) Not stated</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(ii) Confirmed chronic non-specific exudates</td>
<td>(ii) Missing ADA/LDH data</td>
<td>(iii) MPE</td>
<td>(iv) PPE of TPE</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(iii) Confirmed MPE</td>
<td>(v) ADA/LDH data</td>
<td>(v) Miscellaneous</td>
<td>(i) Microbiological confirmation</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(iv) Confirmed PPE</td>
<td></td>
<td></td>
<td>(i) Not stated</td>
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<tr>
<td>Blakiston (2018)</td>
<td>New Zealand</td>
<td>Retrospective, TB incidence: 6.4/100,000</td>
<td>1,637</td>
<td>(i) Age at least 15 years</td>
<td>(i) Duplicate samples</td>
<td>(ii) Non-TPE culture</td>
<td>(i) Documented clinical diagnosis</td>
<td>(ii) Absence of an alternative cause</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(ii) Exudative effusion or unknown nature</td>
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<td></td>
<td>(i) Non-TPE culture</td>
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<td></td>
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<td></td>
<td>(iii) Transudative effusion</td>
<td></td>
<td></td>
<td>(ii) Absence of an alternative cause</td>
<td></td>
</tr>
<tr>
<td>Ho (2022)</td>
<td>Taiwan</td>
<td>Retrospective, TB incidence: 43.9/100,000</td>
<td>311</td>
<td>(i) First-time thoracentesis for undiagnosed effusion</td>
<td>(i) Incomplete data</td>
<td>(ii) MPE culture</td>
<td>(i) Positive culture</td>
<td>(i) Preceding pneumonia, bronchiectasis, lung abscess and positive pleural sputum culture</td>
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<tr>
<td>Author</td>
<td>Country</td>
<td>Study Design</td>
<td>No.</td>
<td>Effusion Type</td>
<td>Confirmation</td>
<td>Response to TB Therapy</td>
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<tr>
<td>Lin</td>
<td>China</td>
<td>Retrospective</td>
<td>112</td>
<td>(i) Exudative effusion</td>
<td>Not stated</td>
<td>(i) TPE (ii) MPE (iii) UPPE (iv) CPPE (v) CTD-effusion</td>
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<td></td>
<td>Microbiological or histological confirmation of TPE</td>
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<td></td>
<td></td>
<td></td>
<td>(ii) Clinical response to anti-tuberculous therapy</td>
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<td></td>
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<tr>
<td>Wang</td>
<td>China</td>
<td>Retrospective</td>
<td>119</td>
<td>(i) Confirmed TPE</td>
<td>Not stated</td>
<td>(i) TPE (ii) PPE</td>
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<td></td>
<td></td>
<td></td>
<td>(i) Histological confirmation</td>
<td></td>
<td>(i) Exudative effusions associated with bacterial pneumonia, lung abscess,</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(ii) Clinical response to anti-tuberculous therapy</td>
<td></td>
<td>(ii) Absence of MTB in pleural fluid</td>
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<td></td>
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<td></td>
<td>(iii) Absence of TB No/minimal pleural effusion in last 12 months</td>
<td></td>
<td>(iii) Absence of TB No/minimal pleural effusion in last 12 months</td>
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<td></td>
<td>(iv) Remission and recovery for at least 3 months at follow-up</td>
<td></td>
<td>(iv) Remission and recovery for at least 3 months at follow-up</td>
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</tr>
</tbody>
</table>

*TPE: tuberculous pleural effusion, PPE: parapneumonic effusion

† LDH: lactate dehydrogenase, ADA: adenosine deaminase
Table 2: Cutoff values of LDH/ADA ratio and their diagnostic accuracy values.

<table>
<thead>
<tr>
<th>First author</th>
<th>Cutoff value of LDH/ADA ratio for TPE</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>*LR+</th>
<th>*LR-</th>
<th>‡PPV</th>
<th>‡NPV</th>
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<tbody>
<tr>
<td>Beukes (2021)</td>
<td>&lt;25</td>
<td>97</td>
<td>62</td>
<td>2.6</td>
<td>0.1</td>
<td>86</td>
<td>89</td>
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<tr>
<td></td>
<td>&lt;16.2</td>
<td>91</td>
<td>76</td>
<td>3.8</td>
<td>0.1</td>
<td>90</td>
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<td>91</td>
<td>81</td>
<td>4.8</td>
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<td>79</td>
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<td>&lt;12.5</td>
<td>86</td>
<td>88</td>
<td>7.2</td>
<td>0.2</td>
<td>94</td>
<td>72</td>
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<td>Beukes (2021)</td>
<td>&lt;10</td>
<td>78</td>
<td>90</td>
<td>7.8</td>
<td>0.2</td>
<td>95</td>
<td>64</td>
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<td></td>
<td>&lt;7.5</td>
<td>64</td>
<td>96</td>
<td>16.0</td>
<td>0.4</td>
<td>97</td>
<td>53</td>
</tr>
<tr>
<td>Blakiston (2018)</td>
<td>&lt;25</td>
<td>100.0</td>
<td>61.6</td>
<td>2.6</td>
<td>0.0</td>
<td>8.5</td>
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<tr>
<td></td>
<td>&lt;15</td>
<td>89.1</td>
<td>85</td>
<td>5.9</td>
<td>0.1</td>
<td>17.3</td>
<td>99.5</td>
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<td></td>
<td>&lt;15 and ADA&gt;30</td>
<td>85.5</td>
<td>97.8</td>
<td>38.9</td>
<td>0.2</td>
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<td>&lt;25 and ADA&gt;30</td>
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<td>Blakiston (2018)</td>
<td>&lt;15 and ADA&gt;15</td>
<td>89.1</td>
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<td>&lt;25 and ADA&gt;15</td>
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<td>Ho (2022)</td>
<td>&lt;14.2</td>
<td>90.4</td>
<td>74.2</td>
<td>3.5</td>
<td>0.1</td>
<td>70.2</td>
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<td>&gt;14.5 for PPE</td>
<td>79.9</td>
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<td>3.7</td>
<td>75</td>
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<td>Lin (2021)</td>
<td>&lt;29.61 for TPE</td>
<td>100.0</td>
<td>98.7</td>
<td>76.9</td>
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<td>97.1</td>
<td>100.0</td>
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<td>Wang (2017)</td>
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<td>93.1</td>
<td>13.5</td>
<td>0.5</td>
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*LR+: positive likelihood ratio, LR-: negative likelihood ratio
‡PPV: positive predictive value, NPV: negative predictive value

LDH: lactate dehydrogenase. ADA: adenosine deaminase. TPE: tuberculous pleural effusion. PPE: parapneumonic effusion
<table>
<thead>
<tr>
<th>First author</th>
<th>Median pleural fluid LDH, U/L (IQR)</th>
<th>Median pleural fluid ADA, U/L (IQR)</th>
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<td>PPE</td>
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<td>Beukes</td>
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<td>UPPE: 260 (156-478)</td>
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<td>Ho*</td>
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<td>UPPE: 277 (68-1169)</td>
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<td>Wang</td>
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<td>4037 (103-48730)</td>
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*inclusion criteria of ADA >40 U/L
LDH: lactate dehydrogenase. ADA: adenosine deaminase. TPE: tuberculous pleural effusion. PPE: parapneumonic effusion
UPPE: uncomplicated parapneumonic effusion. CPPE: complicated parapneumonic effusion.
Figure caption

Figure 1: PRISMA flowchart detailing identification of studies for review inclusion.

Footnote for figure 1: LDH/ADA: lactate dehydrogenase/adenosine deaminase. TPE: tuberculous pleural effusion. PPE: parapneumonic effusion.