Acta Biomed 2024; Vol. 95, N. 4: e2024092 DOI: 10.23750/abm.v95i4.15635

Original article

Diagnosis of tuberculosis in pleural effusion of lung tumor patients using adenosine deaminase test

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Abstract. *Background and aim:* Tuberculosis (TB) remains a global burden and presents challenges both in diagnosis and treatment, primarily when focusing on the association between pleural effusion, lung tumors, and TB. This study aimed to evaluate the efficacy of adenosine deaminase (ADA) as a non-invasive diagnostic tool for TB in pleural effusion among patients with lung tumors. Given the limitations of sputum culture, the study emphasizes the need for standardized diagnostic approaches, particularly in endemic regions such as Indonesia. *Methods:* The study includes 79 subjects with primary lung tumors and pleural effusion. Sample collection employed consecutive sampling, with pleural fluid samples obtained from hospitalized individuals. Laboratory tests were conducted using the ELISA method. Statistical analysis, using SPSS version 26, employed a descriptive approach to analyze the research data, with a level of statistical significance set at a *P* value of <0.05. *Results:* The study established an ADA cut-off of ≥34 IU/L for tuberculosis diagnosis, exhibiting excellent discrimination (AUC: 98.8%) and a sensitivity of 87.5% with 95.8% specificity. The positive and negative predictive values were 70% and 98.55%, respectively. These results support ADA's efficacy in predicting TB in lung tumor patients with pleural effusion, with considerations for potential biases in comorbid conditions and intensive TB treatment. *Conclusions:* ADA is a reliable diagnostic marker for TB in lung tumor patients with pleural effusion, underscoring its clinical utility in TB diagnosis. The findings emphasize ADA's significance in discriminating TB status, offering valuable insights for clinical decision-making in similar patient populations. (www.actabiomedica.it)

Key words: adenosine deaminase, lung tumors, pleural effusion, tuberculosis

Introduction

Tuberculosis (TB) has been a substantial global health burden, affecting around 9.9 million individuals worldwide, with 1-3 million fatalities reported in 2020. In Indonesia, the estimated TB prevalence in 2020 was 845,000 cases, resulting in 35,719 incidences and 139,477 deaths. Notably, disparities persist in diagnosis and treatment, with 28% of TB cases remaining undiagnosed and only 34% resulting in successful treatment (1,2).

Pleural effusion refers to the accumulation of fluid in the pleural cavity. This condition has diverse causes, including malignancies such as primary lung tumors or metastases. It occurs at 660 cases per 1,000,000, with 150,000 new cases per year in the United States and 100,000 in Europe (3,4). Among malignant pleural effusion cases, lung adenocarcinoma constitutes 29-37% (5). As reported by the National Cancer Center of China in 2015, lung cancer contributes to approximately a quarter of all cancer cases, with Non-small Cell Lung Carcinoma

(NSCLC) representing about 85% of lung cancer cases (6).

The simultaneous occurrence of TB and lung cancer is well-documented in various studies. Reportedly, 2.1% of cases occurred from 1990 to 2015 in Lithuania (7) and 4% of cases were observed from 2009 to 2014 in Turkey (8). TB significantly elevates the risk of developing lung cancer, with some studies indicating an increase of up to 11-fold (9–11). Conversely, the incidence of TB in patients with lung cancer was found to be 0.65%, 1.15%, and 1.38% over six months, one year, and two years, respectively (12). Notably, a cohort study found that the incidence of lung cancer in TB patients was much higher than in healthy control people (9).

Sputum culture stands as the gold standard for the diagnosis of TB. However, it diverges in pleural fluid examinations because the culture results are not readily accepted, primarily due to its lower sensitivity, which was reported in previous studies to be about 30%. Consequently, obtaining pleural tissue through needle biopsy, an invasive procedure, becomes imperative for a definitive diagnosis. Considering the associated risk of complications with such a procedure, a safer alternative is required, involving the use of biomarkers without a biopsy (13).

Adenosine deaminase (ADA) emerges as a biomarker that is suitable for diagnosing TB in pleural fluid, offering advantages such as quicker results, non-invasiveness, and cost-effectiveness (13–15). Reported cut-off values for ADA in pleural fluid from several studies range from 30 to 100 IU/L (16). Interestingly, different countries may show different cut-off values regardless of their tuberculosis prevalence rates (13,14,17–19).

Despite the existence of widely accepted ADA values, their application in the field often produces divergent results, particularly in endemic regions such as Indonesia. Notably, pleural effusion ranks among the most common clinical manifestations in patients with lung tumors, and previous data highlight an association between pulmonary TB and lung tumors. This association emphasizes the need for non-invasive diagnostic parameters obtained through pleural effusion to identify TB infection in lung tumors. Therefore, this study aimed to ascertain the value of ADA as a diagnostic tool for TB in pleural effusion among patients with lung tumors.

Materials and methods

Ethical approval

This research was approved by the Ethics Committee of Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. Based on recommendation letter Number: 695/UN4.6.4.5.31/PP36/2023, September 15th, 2023, and duration of the study approval from September 15th, 2023, to September 15th, 2024, protocol number: UH23080628.

Study population

The study included both outpatients and inpatients at Dr. Wahidin Sudirohusodo General Hospital, Indonesia, together with patients from affiliated hospitals who were diagnosed with a primary lung tumor accompanied by a pleural effusion. The research was conducted from October 2023 until the completion of sample collection. A total of 79 subjects meeting the specified inclusion and exclusion criteria constitute the study sample.

Inclusion criteria:

- Light criteria for pleural fluid suggest an exudative nature
- Identification of lung tumors through bronchoscopy and histopathological examinations
- Acid-Fast Bacilli (AFB)/Molecular Rapid Test (MRT) sputum examination results indicating positive or negative outcomes for the presence or absence of *Mycobacterium tuberculosis*

Exclusion criteria:

- Patients with lung metastasis or mediastinal tumors

Sample collection and preparation

Sample collection employed the consecutive sampling method on eligible patients. Pleural fluid samples were obtained from hospitalized individuals diagnosed with primary lung tumors and concurrent pleural

effusion who had completed consent forms for study participation. Laboratory tests were conducted at the Hasanuddin University Teaching Hospital's research facility (Indonesia). Aseptic techniques were employed, from cleansing the targeted site using an antiseptic solution. A fine needle, typically within the 20ml range, was inserted through the posterior thorax to access the pleural space. The initial gross examination encompassed a comprehensive assessment that involved the observation of various aspects, such as volume, color, turbidity, and the presence of flakes within the pleural fluid. This detailed examination provided a holistic understanding of the macroscopic characteristics of the collected pleural fluid samples. Subsequently, the pleural fluid was transferred to a centrifuge tube. Samples were centrifuged for 20 minutes at 1,000×g. The supernatant was collected and stored at -20 ˚C for later use.

Enzyme-linked Immunosorbent Assay (ELISA) analysis

The measurement of pleural fluid by ELISA method used the ELISA Kit for Adenosine Deaminase (ADA) Organism Species: *Homo sapiens* (Human) purchased from MyBioSource (San Diego, USA). The kit included a pre-coated, ready-to-use 96-well strip plate; plate sealer for 96 wells, standard; standard diluent; detection reagent A; detection reagent B; assay diluent A; assay diluent B; substrate solution; stop solution; and wash buffer.

First, all reagents, samples, and standards from the ELISA kit were prepared. Subsequently, 100µL of the standard or sample was added to each well, followed by an incubation period of one hour at 37˚C. Next, 100µL of prepared detection reagent A was added, and the mixture was incubated for an additional hour at 37˚C. Following a triple wash, 100µL of prepared detection reagent B was added, and the incubation continued for 30 minutes at 37˚C. After five wash cycles, 90µL of substrate solution was added, with an incubation period of 10-20 minutes at 37˚C. The reaction was halted by adding 50µL of stop solution, and the absorbance was quickly measured at 450nm. The standardized ELISA employed in this study has a detection range from 0.156 to 10 ng/mL and a sensitivity of less than 0.061 ng/mL, indicating a high sensitivity and excellent specificity for detecting ADA.

Statistical analysis

Data analysis utilized SPSS version 26, employing a descriptive approach to describe the characteristics of the research sample through calculation of means, standard deviations, Independent T-test, ANOVA, Chi-Square, and Fisher Exact test. Statistical significance was defined as a *P* value of <0.05.

Results and discussion

Study population

A total of 79 subjects, comprising 52 males (65.8%) and 27 females (34.2%), showed a diverse age range, with 51 individuals (64.6%) falling between 18 and 60 years, while 28 individuals (35.4%) were over 60 years old. In cases of hemorrhagic pleural effusion, positive AFB/MRT results were observed in 8 cases (10.2%), contrasting with negative findings in 71 cases (89.8%), as shown in Table 1.

Histopathological findings revealed that the majority of neoplasms were NSCLC, with 35 cases (44.3%) identified as adenocarcinoma, 7 cases (8.9%) as adenosquamous carcinoma, and 36 cases (45.6%) as squamous cell carcinoma. Additionally, a single case (1.3%) was attributed to Small Cell Lung Carcinoma (SCLC). These results align with the findings reported by Horton et al., indicating a predominant prevalence among males aged 20-54 years (20). Marcoa et al. consistently reported similar trends, highlighting a higher prevalence among males aged 20-59 years (21).

This study observed a predominance of NSCLC cases in stages III (43%), I (25.3%), II (15.2%), and IV (15.2%). In contrast, Suzuki et al. (2016) reported a higher prevalence of stage I (36.2%), IV (33.5%), III (23.7%), and II (6.6%) cases. Among the 79 patients, seven underwent chemotherapy, while 72 received supportive therapy alone. The comorbidities noted in the study included empyema (14%), congestive heart failure (CHF) (6.3%), chronic kidney disease (CKD) (3.8%), hypertension (10.1%), diabetes mellitus (DM) (2.5%), liver disease (7.6%), and a combination of TB and lung cancer (55.7%).

Table 1. Demographic and diagnostic characteristics of the study population

Variable	n	Percentage (%)
Age (years)		
18-60	51	64.6
> 60	28	35.4
Gender		
Male	52	65.8
Female	27	34.2
AFB/MRT†		
Positive	8	10.2
Negative	71	89.8
Histopathology result		
Adenocarcinoma	35	44.3
Adenosquamous carcinoma	7	8.8
Squamous cell carcinoma	36	45.6
Small cell carcinoma	1	1.3
Stage of Lung Cancer		
NSCLC¶ stage I	20	25.3
NSCLC stage II	12	15.2
NSCLC stage III	34	43
NSCLC stage IV	12	15.2
SCLC‡ limited stage	-	-
SCLC extensive stage	1	1.3
Therapy		
Chemotherapy	7	8.9
Best supportive care	72	91.1
Comorbidities		
Empyema/pneumonia	11	14
Rheumatoid arthritis	-	-
Systemic lupus erythematous	-	-
Congestive heart failure	5	6.3
Chronic kidney disease	3	3.8
Hypertension	8	10.1
Diabetes mellitus	2	2.5
Liver disease	6	7.6
No other comorbidity except only TB and lung cancer	44	55.7
Macroscopic Examination (Pleural Fluid)		
Volume (ml)		
>10	12	15.2
3-10	67	84.8
Color		
Straw-color	8	10.1
Bloodstained	68	86.1
Chylous	-	-
Purulent	3	3.8
Turbidity		
Exudate	79	100
Transudate	-	-
Flakes		
Yes	79	100
No	-	-
Microscopic Examination		
LDH§ (U/L)		
100-190	8	10.1
>190	71	89.9
Glucose (mg/dl)		
<200	69	87.3
>200	10	12.7
Protein (mg/dl)		
<3000	8	10.1
>3000	71	89.9

Notes: †: Acid-Fast Bacilli (AFB)/Molecular Rapid Test (MRT); §: Lactate Dehydrogenase; ¶: Non-small Cell Lung Carcinoma; ‡: Small Cell Lung Carcinoma.

Comparison of age, gender, AFB/MRT with ADA values

In the age analysis, patients within the 18-60 age range had a mean ADA value of 21.67 ± 12.7 IU/L, whereas samples with age >60 had a mean ADA of 20.90 ± 15.5 IU/L. Comparing these data sets revealed no significant difference in ADA values based on age categories (P = 0.828). Regarding gender, male samples showed a mean of 22.18 ± 15.63 IU/L, while females had a mean of 19.86 ± 9.17 IU/L; the comparison indicated no significant difference in ADA values between the genders (P = 0.479). In contrast, AFB/MRT

Table 2. Comparison of adenosine deaminase values across age, gender, and sputum examination in the study population

Variable	ADA† value in pleural fluid (IU/L)	*P* value
Age (years)		
18-60	21.66 ± 12.7	0.828
> 60	20.90 ± 15.5	
Gender		
Male	22.18 ± 15.63	0.479
Female	19.86 ± 9.17	
AFB/MRT§		
Positive	52.23 ± 15.20	<0.001
Negative	17.91 ± 8.16	

Notes: †: Adenosine deaminase; §: Acid-Fast Bacilli (AFB)/Molecular Rapid Test (MRT).

results displayed significant statistical differences, with positive results having a mean of 52.23 ± 15.20 IU/L and negative results with a mean of 17.91 ± 8.16 IU/L (P <0.001), as shown in Table 2.

In this study, we analyzed ADA values across different age groups (18-60 years and >60 years) and stratified by gender. The thorough examination showed no significant differences in mean ADA values within these categories. Our findings align with those of Huan et al., who reported no significant associations between age and gender with ADA values (22).

However, the AFB/MRT results revealed significant differences in mean ADA values between positive and negative outcomes (P < 0.001). This discrepancy can be attributed to our predominant use of MRT over AFB for TB diagnosis due to the higher sensitivities and specificities of MRT. A previous study reported that sensitivities and specificities of AFB were 48% and 84%, respectively, and for MRT were 94% and 92%, respectively (23). The use of MRT in pleural fluid at the Dr. Wahidin Sudirohusodo Hospital remains uncommon, with ADA being the preferred diagnostic tool. Additionally, a recent meta-analysis reported sensitivities and specificities for MRT in pleural fluid as 46.4% and 99.1%, respectively, while ADA demonstrated 92% sensitivity and 90% specificity, further endorsing the preference for ADA usage (24).

Table 3. The histopathological results and their correlation with tuberculosis

Histopathology result	TB† (+)	TB† (-)
Adenocarcinoma	4	31
Adenosquamous carcinoma	1	6
Squamous cell carcinoma	3	33
Small cell carcinoma	0	1

Notes: †: Tuberculosis.

Comparison of histopathological results with Tuberculosis (TB)

Histopathological examination is a valuable diagnostic tool for TB, carefully examining tissue specimens for characteristic morphological changes associated with the infection (Table 3). It helps to identify specific histopathological features indicative of TB, such as granulomas and caseating necrosis (25).

In this study, no statistically significant difference was found between tumor types and the occurrence of tuberculosis (TB) ($P = 0.932$). However, there was a tendency towards a higher incidence of NSCLC compared to SCLC. This observation is in line with previous research indicating a notable association of NSCLC with comorbid TB, highlighting a potential trend in the relationship between specific tumor subtypes and TB susceptibility (26).

Cut-off values for ADA, sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV)

In determining the cut-off value for this study, the receiver-operating characteristic (ROC) method was employed, pinpointing the intersection of sensitivity and specificity at the 67-point on the ROC curve. This intersection sets the cut-off at 34 IU/L when converted into ADA values, as shown in Figure 1.

Figure 2 visually presents the parameters at the cut-off value of 34 IU/L, with a sensitivity of 87.5%, a specificity of 95.8%, and a total area under the curve (AUC) coverage of 98.8%. The calculated result places the area under the ROC curve between 0.9 and 1.0, denoting excellent discrimination.

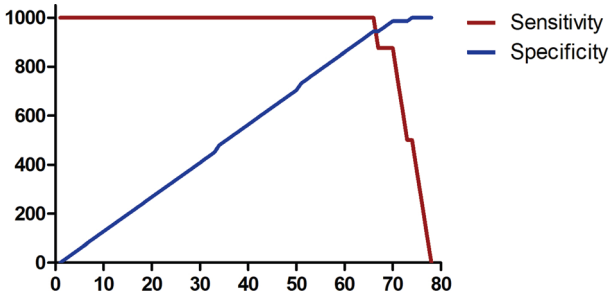

Figure 1. Cut-off values for adenosine deaminase.

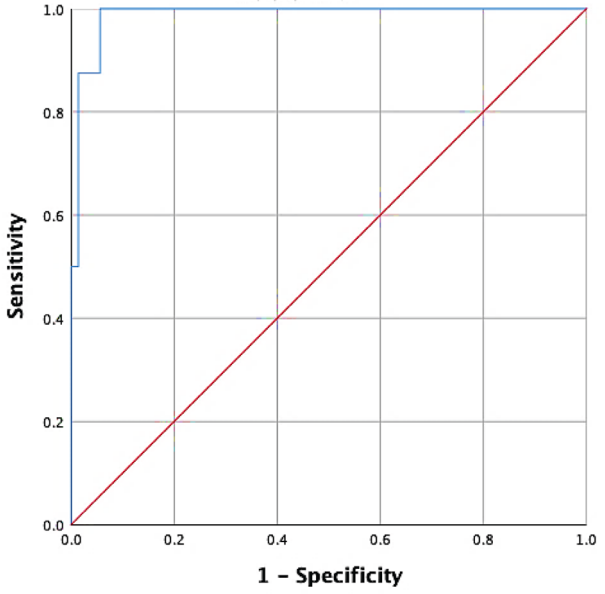

Figure 2. Receiver-operating curve of adenosine deaminase values.

The analysis proceeded by categorizing ADA values and examining their association with pleural effusion, considering both TB-positive and TB-negative cases. Within the study cohort, ten individuals exhibited ADA values ≥34 IU/L, with 7 of them (70%) presenting pleural effusion accompanied by TB, while three individuals demonstrated pleural effusion without TB (30%). In contrast, 69 individuals displayed ADA values <34 IU/L, with one person (1.45%) showing pleural effusion accompanied by TB and 68 individuals having pleural effusion without TB (98.55%). The observed relationship between ADA value categories and the incidence of pleural

Table 4. Sensitivity and specificity of adenosine deaminase values

ADA† values	Pleural effusion with TB§	Pleural effusion without TB§
≥ 34 (IU/L)	7 (87.5%)	3 (4.2%)
< 34 (IU/L)	1 (12.5%)	68 (95.8%)
Total	8 (100 %)	71 (100%)

Notes: †: Adenosine deaminase; §: Tuberculosis.

effusion with and without TB was statistically significant (P <0.001). In conclusion, the outcomes shown in Table 4 indicate that ADA values possess a sensitivity of 87.5%, specificity of 95.8%, PPV of 70%, and NPV of 98.55%.

This investigation established a diagnostic cut-off for ADA ≥34 IU/L in tuberculosis (TB) diagnosis among lung tumor patients with pleural effusion, yielding a sensitivity of 87.5% and specificity of 95.8%. These outcomes align with previous studies conducted by Piras et al., with an ADA cut-off of 30 IU/L demonstrating 100% sensitivity and specificity, and Villena et al. determined a cut-off of 33 IU/L with 90% sensitivity and 85% specificity (26,27). Additionally, Huan et al. identified a cut-off ≥29.6 IU/L with 97.6% sensitivity and 90.4% specificity (22).

The PPV and NPV in our study were 70% and 98.55%, respectively. These metrics indicate that an ADA value ≥34 IU/L accurately predicts TB in lung tumor patients, as a pathological value, with effusion in 70% of cases. Meanwhile, an ADA value <34 IU/L predicts non-TB with an accuracy of 98.55%. Notably, three cases of pleural effusion without TB exhibited ADA values ≥34 IU/L, attributable to comorbid conditions such as empyema and pneumonia during sample collection, introducing potential bias. Therefore, a comprehensive consideration of diverse conditions affecting ADA levels in such contexts is essential. Furthermore, one case of pleural effusion with TB demonstrated ADA values <34 IU/L, a phenomenon explained by the patient undergoing intensive TB treatment during sample collection.

As a summary of this research: 1) the mean pleural fluid ADA value was higher in lung tumors with TB infection, compared to those without TB infection; 2) the cut-off value of ADA in diagnosing TB in lung tumor patients with pleural effusion is ≥34 IU/L with a sensitivity of 87.5%, specificity of 95.8%, PPV of 70%, and NPV of 98.55%; and 3) there was no association between TB incidence rate and tumor type.

Conclusion

ADA is a reliable diagnostic marker for TB in lung tumor patients with pleural effusion, underscoring its clinical utility in TB diagnosis. This study established ADA ≥34 IU/L as a diagnostic cut-off for tuberculosis (TB) in lung tumor patients with pleural effusion, demonstrating robust sensitivity (87.5%) and specificity (95.8%). The findings emphasize ADA's significance in discriminating TB status, offering valuable insights for clinical decision-making in similar patient populations.

Acknowledgements: This research was supported by the Department of Internal Medicine, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia.

Ethics committee: This research was approved by the Ethics Committee of Biomedical Research on Humans, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia. Based on recommendation letter number: 695/UN4.6.4.5.31/PP36/2023, protocol number: UH23080628.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: MDF (concept, design, resources, materials, data collection and processing, analysis and interpretation, literature search, manuscript writing). MI (concept, design, supervision, analysis and interpretation, literature search). AS (concept, design, supervision, analysis and interpretation, literature search). SB (concept, design, critical review). SA (concept, design, critical review). AAZ (concept, design, analysis and interpretation, critical review).

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Received: 18 January 2024
Accepted: 8 March 2024
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