Jurnal Impresi Indonesia (JII)
p-ISSN: 2828-1284 e-ISSN: 2810-062x
website: https: //rivierapublishing.id/JII/ index.php / jii /index

Profile of Pleural Fluid Adenosine Deaminase and Protein Levels in Tuberculous Pleural Effusion at Adam Malik Hospital Indonesia

Marisi Ester Nova Sihite, Syamsul Bihar*
Universitas Sumatera Utara, Indonesia
Email: marisiesternovasihite@gmail.com, syamsul.bihar@usu.ac.id*

Keywords
adenosine deaminase, Pleural effusion, pleural fluid protein

Abstract
Tuberculosis remains one of the most prevalent infectious diseases worldwide. In addition to affecting the lungs, *Mycobacterium tuberculosis* infection can also cause extrapulmonary tuberculosis, including *pleural effusion*. Diagnosing *tuberculous pleural effusion* presents a clinical challenge due to nonspecific symptoms and limitations of conventional diagnostic methods. Biomarker testing, such as measuring Adenosine Deaminase levels in pleural fluid, has been widely used as a diagnostic method due to its high sensitivity and specificity in distinguishing *tuberculous pleural effusion* from other causes. This study aims to analyze Adenosine Deaminase levels and pleural fluid protein levels in patients with *pleural effusion*. A descriptive study with a cross-sectional approach was conducted on thirty-five samples that met the inclusion criteria. The results showed that the mean Adenosine Deaminase level was 61.97 U/L, with a standard deviation of 58.314 and a median value of 41 U/L. The mean pleural fluid protein level was 4.5 g/dL, with a standard deviation of 1.56 and a median value of 4.31 g/dL. The analysis revealed significant differences in Adenosine Deaminase and pleural fluid protein levels based on nutritional status, comorbid diseases, and bacteriological examination results.

INTRODUCTION

Tuberculosis (TB) remains a significant global health issue, with a high incidence rate in developing countries, including Indonesia (Chakaya et al., 2021; Noviyani et al., 2021; Wedari et al., 2021). This disease, caused by Mycobacterium tuberculosis, can affect various organs but most commonly involves the lungs (Light, 2013). One of the frequent complications is tuberculous pleural effusion, which occurs due to an immunological reaction to TB infection in the pleura (Antonangelo et al., 2019). The incidence of tuberculous pleural effusion varies based on the prevalence of TB in a region, with higher occurrence rates in endemic areas (Arega et al., 2020). Diagnosing tuberculous pleural effusion is often challenging due to its nonspecific manifestations and the limited availability of highly accurate diagnostic methods (Rahman et al., 2004).

Although various diagnostic modalities are available, identifying tuberculous pleural effusion still requires a multidisciplinary approach (Antonangelo et al., 2019; Jany & Welte, 2019; Rea et al., 2021). Microbiological examinations have low sensitivity, while molecular-based methods are not always accessible in healthcare facilities with limited resources (Huan et al.,

2021). Therefore, biochemical parameters such as Adenosine Deaminase (ADA) and protein levels in pleural fluid have been extensively studied as alternative diagnostic markers (Aggarwal et al., 2019). Previous studies have shown that pleural ADA levels have high diagnostic accuracy in differentiating tuberculous pleural effusion from other causes (Gao et al., 2023). Additionally, pleural fluid protein levels play a role in determining the type of pleural effusion, whether transudate or exudate, and have potential as an additional marker in evaluating tuberculous pleural effusion (Chiner et al., 2021). However, studies specifically analyzing the relationship between ADA and pleural fluid protein levels in diagnosing tuberculous pleural effusion remain limited (Zeng et al., 2022).

Addressing this knowledge gap, this study aims to analyze the levels of ADA and pleural fluid protein in patients with tuberculous pleural effusion at Adam Malik Hospital in 2024. This analysis is expected to provide additional insights into the role of these two parameters in improving the diagnostic accuracy of tuberculous pleural effusion (Alsayed & Gunosewoyo, 2023). Thus, the findings of this study are anticipated to serve as a foundation for developing more effective diagnostic methods, particularly in clinical settings with limited access to molecular or mycobacterial culture diagnostic facilities (Flinn & Gennery, 2018).

RESEARCH METHOD

This study employed a descriptive research design with a cross-sectional approach to compare pleural fluid Adenosine Deaminase (ADA) and protein levels in diagnosing pleural effusion caused by pulmonary tuberculosis. Data were analyzed to determine the sensitivity, specificity, and accuracy of these two parameters. The study was conducted at the Department of Pulmonology and Respiratory Medicine, Adam Malik Hospital Medan, from July to December 2024, using primary data from laboratory examinations of pleural fluid ADA and protein levels.

The subjects were inpatients suspected of having tuberculous pleural effusion. Inclusion criteria were patients aged 18 years or older with clinical symptoms and chest radiographs indicating mild to massive pleural effusion suitable for thoracentesis, with active tuberculosis lesions, and who consented to participate. Exclusion criteria were patients with coagulation disorders, coexisting lung cancer or pneumonia, confirmed non-tuberculous pleural effusion, or transudative effusion based on pleural fluid chemistry analysis. The sample size was calculated using Lemeshow's formula, with a minimum of 34 subjects.

Pleural fluid samples were obtained through thoracentesis. A total of 20 cc of fluid was collected and divided equally: 10 cc for protein analysis at Adam Malik Hospital's clinical pathology laboratory and 10 cc for ADA analysis at Pramita Laboratory. Thoracentesis was performed by a pulmonary specialist or a trained resident. The procedure used standard sterile equipment including thoracentesis sets, syringes, a three-way stopcock, sterile gloves, gauze, alcohol swabs, and povidone-iodine.

Data analysis was performed using SPSS software. Descriptive statistics summarized subject characteristics, while the Chi-Square test and Pearson correlation assessed the relationships and correlations between ADA and pleural fluid protein levels in tuberculous pleural effusion.

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, prior to the study. Participants received detailed explanations of the study procedures, benefits, and potential risks before providing informed consent.

RESULTS AND DISCUSSION

Table 1. Characteristics of Study Subjects

Characteristic		Total	
		(n)	(%)
Age	<30 years	5	14.3
	30-39 years	7	20.0
	40-49 years	6	17.1
	50-59 years	9	25.7
	>60 years	8	22.9
Gender	Male	24	68.6
	Female	11	31.4
Sputum	C1	4	11.4
Cytology	C2	31	88.6
	C3	0	0
	C4	0	0
	C5	0	0
Molecular Rapid Test	MTB Rif Sen / Rif Res	16	45.7
	MTB Negative	19	54.
Nutritional Status	Normal Nutrition	13	37.1
	Mild-Moderate Malnutrition	14	40
	Severe Malnutrition	8	22.9
Comorbid	No comorbidities	9	25.7
Conditions	HIV	5	14.3
	Congestive Heart Failure	5	14.3
	Diabetes Mellitus Type 2	4	11.4
	Electrolyte Imbalance	4	11.4
	Chronic Obstructive Pulmonary Disease (COPD)	3	8.6
	Chronic Kidney Disease (CKD)	5	14.3

The demographic and clinical characteristics of the subjects showed a varied age distribution, with the majority falling within the 50–59 age group (25.7%) and those over 60 years old (22.9%). Most subjects were male (68.6%). Based on sputum cytology, the majority were classified as C2 (88.6%), while no cases were found in categories C3–C5. The results of the Rapid Molecular Test (Tes Cepat Molekuler, TCM) indicated that Mycobacterium tuberculosis (MTB) was detected in 45.7% of subjects, with either sensitivity or resistance to rifampicin, while 54.3% tested negative.

Regarding nutritional status, 40% of subjects experienced mild-to-moderate malnutrition, while 22.9% had severe malnutrition. A total of 25.7% of subjects had no comorbidities, while the most common comorbid conditions were HIV (14.3%), congestive heart failure (14.3%), and chronic kidney disease (14.3%), followed by type 2 diabetes mellitus

(11.4%), electrolyte imbalance (11.4%), and chronic obstructive pulmonary disease (COPD) (8.6%).

Table 2. Mean Levels of Adenosine Deaminase (ADA)

	n	Mean ± SD	Median (min-max)
ADA Levels	35	61.97 ± 58.314	41 (3 - 200)

The measurement of pleural fluid Adenosine Deaminase in 35 samples showed a mean value of 61.97 g/L with a standard deviation of 58.314 g/L, indicating considerable variation in protein levels among samples. The median ADA level in pleural fluid was 41 g/L, with a range from 3 g/L to 200 g/L.

Table 3. ADA Levels Based on Pleural Fluid Cytology

	ADA Levels		
Pleural Fluid Cytology	**>43**	**<43**	**Total**
C1	3	1	4
C2	14	17	31
Total	17	18	35

Descriptive analysis showed that out of 35 pleural fluid samples, 17 samples had Adenosine Deaminase (ADA) levels >43, while 18 samples had ADA levels <43. In the C1 cytology group, 3 samples had ADA levels >43, and 1 sample had ADA levels <43. Meanwhile, in the C2 cytology group, 14 samples had ADA levels >43, and 17 samples had ADA levels <43. These findings illustrate the distribution of ADA levels based on pleural fluid cytology classification.

Table 4. ADA Levels Based on Comorbidities

	ADA Levels		
Comorbidities	**>43**	**<43**	**Total**
Without Comorbidities	8	1	9
HIV	2	3	5
Chronic Obstructive Pulmonary Disease (COPD)	1	2	3
Diabetes Mellitus Type 2	1	3	4
Electrolyte Imbalance	2	2	4
Congestive Heart Failure	2	3	5
Chronic Kidney Disease (CKD)	1	4	5
Total	17	18	35

Among the 35 samples, 17 patients (48.6%) had ADA levels >43, while 18 patients (51.4%) had ADA levels <43. Patients without comorbidities predominantly had ADA levels >43 (8 out of 9 patients). Among patients with comorbidities, most cases with HIV, Chronic Obstructive Pulmonary Disease (COPD), Diabetes Mellitus Type 2, Congestive Heart Failure (CHF), and Chronic Kidney Disease (CKD) tended to have ADA levels <43. These findings suggest variability in ADA levels based on the presence and type of comorbidities associated with tuberculous pleural effusion.

Table 5. ADA Levels Based on Nutritional Status

	ADA Levels		
Nutritional Status	**>43**	**<43**	**Total**
Good Nutrition	4	9	13
Mild-Moderate Malnutrition	10	4	14

Severe Malnutrition	3	5	8
Total	17	18	35

Descriptive analysis showed that among the 35 samples, ADA levels >43 were more frequently found in patients with mild-moderate malnutrition (10 patients) compared to those with good nutrition (4 patients) and severe malnutrition (3 patients). Meanwhile, ADA levels <43 were more commonly observed in patients with good nutrition (9 patients) and severe malnutrition (5 patients) compared to those with mild-moderate malnutrition (4 patients). Overall, the distribution of ADA levels was relatively balanced between the >43 group (17 patients) and the <43 group (18 patients).

Table 6. ADA Levels Based on Molecular Rapid Test

	ADA Levels		
Molecular Rapid Test Result	**>43**	**<43**	**Total**
MTB Rifampicin Sensitive/Resistant	13	6	19
MTB Negative	4	12	16
Total	17	18	35

Based on descriptive analysis, out of 35 samples, 19 samples tested positive for Mycobacterium tuberculosis with rifampicin-sensitive or rifampicin-resistant results using the Molecular Rapid Test method, where 13 samples had ADA levels >43 and 6 samples had ADA levels <43. Meanwhile, 16 samples showed negative MTB results on Molecular Rapid Test, with 4 samples having ADA levels >43 and 12 samples having ADA levels <43. These findings suggest that the majority of patients with MTB-positive results tend to have higher ADA levels compared to those with MTB-negative results.

Table 7. Paired T-Test of Respondent Characteristics and ADA Levels

	Paired T-Test (ADA)		
	t	*df*	*Sig.*
Pleural Fluid Cytology	*-6.090*	*34*	*.000**
Comorbid Disease	*-5.884*	*34*	*.000**
Nutritional Status	*-6.099*	*34*	*.000**
Molecular Rapid Test Result	*-6.147*	*34*	*.000**

The paired t-test results indicate a significant difference between Adenosine Deaminase (ADA) levels and several respondent characteristics, including pleural fluid cytology, comorbid diseases, nutritional status, and the Molecular Rapid Test results. All variables show a significant value (Sig.) of 0.000, which is below the 0.05 threshold, indicating a statistically significant association. The negative t-values for all variables suggest a substantial mean difference between the groups compared. These findings reinforce factors such as pleural fluid cytology status, the presence of comorbidities, patient nutritional status, and Mycobacterium tuberculosis detection through Molecular Rapid Test influence ADA levels in pleural fluid.

Table 8. Distribution of Mean Pleural Fluid Protein Levels

Pleural Fluid Protein	**n**	**Mean ± SD**	**Median (min-max)**
	35	4.55 ± 1.56	4.31 (1.20 - 8.00)

Pleural fluid protein in 35 patients showed a mean pleural fluid protein level of 4.55 with a standard deviation (SD) of 1.56. This indicates that most values are clustered around the mean, but a considerable variation exists, as reflected by the relatively high standard deviation.

The median value for this dataset is 4.31, meaning half of the patients with pleural fluid protein below or equal to 4.31, while the other half have values above it. The range of values (1.20 – 8.00) indicates a broad variation in pleural fluid protein levels among the patients.

Table 9. Pleural Protein Levels Based on Pleural Fluid Cytology

	Pleural Fluid Protein Levels		
Pleural Fluid Cytology	**>4.31**	**<4.31**	**Total**
C1	3	1	4
C2	14	17	31
Total	17	18	35

Descriptive analysis shows that out of 35 samples, 17 samples had pleural fluid protein levels >4.31 g/dL, while 18 samples had levels <4.31 g/dL. In the C1 cytology category, 3 samples had protein levels >4.31 g/dL, while 1 sample had levels <4.31 g/dL. In the C2 category, 14 samples had protein levels >4.31 g/dL, and 17 samples had levels <4.31 g/dL. This distribution illustrates the relationship between pleural fluid cytology results and pleural protein levels.

Table 10. Pleural Protein Levels Based on Comorbidities

	Pleural Fluid Protein Levels		
Comorbidities	**>4.31**	**<4.31**	**Total**
Without Comorbidities	7	2	9
HIV	0	55	5
Chronic Obstructive Pulmonary Disease (COPD)	1	22	3
Diabetes Mellitus Type 2	1	23	4
Electrolyte Imbalance	2	2	4
Congestive Heart Failure	3	2	5
Chronic Kidney Disease (CKD)	3	2	5
Total	17	18	35

Among 35 patients with tuberculosis-related pleural effusion, 17 had pleural fluid protein levels >4.31 g/dL, while 18 had levels <4.31 g/dL. Patients without comorbidities were more likely to have protein levels >4.31 g/dL (7 out of 9 patients). Conversely, the majority of patients with HIV (5 out of 5), COPD (2 out of 3), and Type 2 Diabetes Mellitus (3 out of 4) had protein levels <4.31 g/dL. Electrolyte imbalance, congestive heart failure (CHF), and chronic kidney disease (CKD) showed a more balanced distribution between the two protein level categories.

Table 11: Pleural Protein Levels Based on Nutritional Status

	Pleural Fluid Protein Levels		
Nutritional Status	**>4.31**	**<4.31**	**Total**
Good Nutrition	7	6	13
Mild-Moderate Malnutrition	8	6	14
Severe Malnutrition	2	6	8
Total	17	18	35

Among the 35 patients with tuberculosis-related pleural effusion, 17 had pleural fluid protein levels greater than 4.31 g/dL, while 18 had levels below this threshold. Patients without comorbidities were more likely to have protein levels above 4.31 g/dL (7 out of 9). In contrast, the majority of patients with HIV (5 out of 5), COPD (2 out of 3), and Type 2 Diabetes Mellitus (3 out of 4) had protein levels below 4.31 g/dL. Meanwhile, patients with electrolyte imbalance, congestive heart failure (CHF), and chronic kidney disease (CKD) exhibited a more balanced distribution between the two protein level categories.

Table 12. Pleural Protein Levels Based on Molecular Rapid Test Results

Molecular Rapid Test Result	Pleural Fluid Protein Levels		Total
	>4.31	<4.31	
MTB Rifampicin Sensitive/Resistant	**6**	**10**	**16**
MTB Negative	**11**	**8**	**19**
Total	**17**	**18**	**35**

Among the 35 patients, 17 had pleural fluid protein levels >4.31 g/dL, while 18 had levels <4.31 g/dL. Among patients with MTB-negative results, 6 had protein levels >4.31 g/dL, whereas 10 had levels <4.31 g/dL. Meanwhile, among those with MTB Rifampicin-Sensitive/Resistant results, 11 had protein levels >4.31 g/dL, while 8 had levels <4.31 g/dL. These findings suggest variations in pleural fluid protein levels based on molecular test results.

Table 13. Respondent Characteristics and Pleural Fluid Protein Levels

	Paired T-Test (Pleural Fluid Protein)		
	t	*df*	*Sig.*
Pleural Fluid Cytology	*-9.437*	*34*	*.000**
Comorbid Disease	*-2.113*	*34*	*.042**
Nutritional Status	*-8.205*	*34*	*.000**
Molecular Rapid Test Result	*-11.060*	*34*	*.000**

The paired t-test results indicate a statistically significant difference in pleural fluid protein levels based on pleural fluid cytology, comorbidities, nutritional status, and Molecular Rapid Test results. Both pleural cytology and Molecular Rapid Test showed highly significant differences, suggesting pathophysiological variations affecting pleural protein levels. Comorbid conditions also played a role, likely through inflammatory mechanisms or metabolic disturbances. Additionally, nutritional status influenced protein metabolism and pleural membrane permeability. Overall, these findings highlight the importance of clinical and diagnostic factors in evaluating pleural effusion for optimal diagnosis and management.

Table 14. Correlation Between ADA and Protein Levels with Tuberculosis Diagnosis

	Pearson Correlation	
	Pearson Correlation	**Sig**
ADA Levels	.617	.000*
Pleural Fluid Protein Levels		

The Pearson correlation analysis demonstrated a significant positive correlation between Adenosine Deaminase (ADA) levels and the diagnosis of tuberculosis-related pleural effusion, with a correlation coefficient of 0.617 and a p-value of 0.000 ($p < 0.05$). This finding

suggests a strong association between pleural fluid ADA levels and tuberculosis diagnosis, reinforcing its role as a valuable diagnostic biomarker for tuberculous pleuritis.

Discussion

The results of this study indicate that Adenosine Deaminase (ADA) levels in pleural fluid have a significant association with the diagnosis of tuberculosis (Kim et al., 2020). This finding aligns with previous studies suggesting that elevated ADA levels in pleural fluid can serve as an indicator of tuberculosis-related pleural effusion (McNally et al., 2023). Increased ADA levels are associated with the activation of T lymphocytes in the immune response to Mycobacterium tuberculosis, leading to increased production of this enzyme (Udwadia & Sen, 2010).

Additionally, ADA levels were found to be higher in patients without comorbidities compared to those with underlying conditions such as HIV, congestive heart failure, type 2 diabetes mellitus, COPD, electrolyte imbalances, and chronic kidney disease (Shaw et al., 2019). This finding suggests that comorbid conditions may influence ADA levels in pleural fluid, possibly due to altered immune responses or more complex inflammatory processes (Vorster et al., 2015).

ADA levels also varied based on the patient's nutritional status. Patients with mild to moderate malnutrition tended to have higher ADA levels than those with good nutritional status or severe malnutrition (Kementerian Kesehatan Republik Indonesia, 2020). Malnutrition can affect immune function, and individuals with severe malnutrition may have a weaker immune response, leading to lower ADA levels (World Health Organization, 2022).

Analysis of pleural fluid protein levels also revealed a correlation with tuberculosis diagnosis. Higher pleural protein levels were observed in tuberculosis patients compared to other groups (World Health Organization, 2023). This finding can be explained by increased capillary permeability due to inflammation in tuberculosis infection, resulting in higher protein concentrations in pleural fluid (Porcel et al., 2014). These findings are consistent with previous studies stating that tuberculosis-related pleural effusion is typically exudative, with higher protein levels compared to transudative effusions caused by non-infectious etiologies (Valdés et al., 2018).

Furthermore, pleural protein levels varied in patients with comorbid conditions. Patients with HIV, COPD, and type 2 diabetes mellitus tended to have lower pleural protein levels (Wang et al., 2021). This may be attributed to immune system dysfunction and chronic inflammation, which can influence protein production and exudation into pleural fluid (Liu et al., 2020). These findings suggest that, in addition to ADA, pleural protein levels can serve as an additional parameter in evaluating tuberculosis-related pleural effusion, particularly in patients with comorbid conditions (Bhatnagar et al., 2015).

Statistical analysis demonstrated that ADA and pleural fluid protein levels were significantly associated with various clinical factors, including pleural fluid cytology, comorbid conditions, nutritional status, and GeneXpert results (Sharma & Mohan, 2020). This reinforces the potential of these parameters as diagnostic tools for tuberculosis-related pleural effusion (Lee et al., 2017).

Compared to previous studies, these findings support the notion that elevated ADA levels are a strong indicator of tuberculous pleural effusion (Luo et al., 2019). However, differences in ADA and protein level distribution based on comorbidities and nutritional status highlight the need to consider these factors when interpreting results (Seiscento et al., 2019). Therefore, combining ADA levels, pleural protein levels, and other clinical factors can enhance the diagnostic accuracy of tuberculous pleural effusion (Costa et al., 2022). Furthermore, recent advancements suggest that incorporating molecular diagnostic tools alongside conventional markers like ADA and protein can further improve diagnostic precision for tuberculous pleural effusion (Sehgal et al., 2016).

CONCLUSION

This study found a significant positive correlation between Adenosine Deaminase (ADA) and pleural fluid protein levels in patients with tuberculous pleural effusion, suggesting both biomarkers are valuable diagnostic indicators. The variations in these levels were influenced by clinical factors such as nutritional status, comorbidities, and bacteriological findings, underscoring the complexity of diagnosis. Future research should incorporate pleural biopsy as the diagnostic gold standard to improve accuracy and compare ADA levels with other diagnostic tools like the Ultra Molecular Rapid Test and BAL Molecular Rapid Test. Additionally, systematic malnutrition screening at admission and larger sample sizes are recommended to better understand the relationship between clinical factors and biomarker variation and to ensure findings are generalizable. These results can guide healthcare facilities, including H. Adam Malik Hospital, in optimizing ADA testing for diagnosing tuberculosis-related pleural effusion.

REFERENCES

Aggarwal, A. N., Agarwal, R., Gupta, D., Dhooria, S., & Behera, D. (2019). Adenosine deaminase for diagnosis of tuberculous pleural effusion: A systematic review and meta-analysis. *PLoS One*, *14*(3), e0213728.

Alsayed, S. S., & Gunosewoyo, H. (2023). Tuberculosis: pathogenesis, current treatment regimens and new drug targets. *International Journal of Molecular Sciences*, *24*(6), 5202.

Antonangelo, L., Faria, C. S., & Sales, R. K. (2019). Tuberculous pleural effusion: diagnosis & management. *Expert Review of Respiratory Medicine*, *13*(8), 747–759.

Arega, B., Woldeamanuel, Y., Tadesse, M., Sheleme, T., Visser, A., Mihret, A., Bekele, A., van Soolingen, D., Aseffa, A., & Berg, S. (2020). Epidemiology and the diagnostic challenge of extra-pulmonary tuberculosis in a teaching hospital in Ethiopia. *PLoS One*, *15*(12), e0243945.

Bhatnagar, R., Maskell, N. A., Zahan-Evans, N., Corcoran, J. P., Psallidas, I., Davies, H. E., Wrightson, J. M., Arnold, D. T., Hallifax, R. J., Mercer, R. M., Hassan, M., McCracken, D. J., Bedawi, E. O., Dobson, M., Nunn, A. J., Miller, R. F., John, L., Crosthwaite, N., Hooper, C. E., ... Rahman, N. M. (2015). The role of biomarkers in the diagnosis of tuberculous pleural effusion. *Current Opinion in Pulmonary Medicine*, *21*(4), 409-417.

Chakaya, J., Khan, M., Ntoumi, F., Aklillu, E., Fatima, R., Mwaba, P., Kapata, N., Mfinanga, S., Hasnain, S. E., & Katoto, P. D. M. C. (2021). Global Tuberculosis Report 2020–

Reflections on the Global TB burden, treatment and prevention efforts. *International Journal of Infectious Diseases*, *113*, S7–S12.

Chiner, E., Arriero, J. M., Signes-Costa, J., Marco, J., & Llombart, M. (2021). Clinical and Epidemiological Features of Tuberculous Pleural Effusion in Alicante, Spain. *Journal of Clinical Medicine*, *10*(19), 4392.

Costa, C., Rufino, R., Silva, J. R. L., & Lapa e Silva, J. R. (2022). Biomarkers for pleural effusion: Current advances and future directions. *Expert Review of Respiratory Medicine*, *16*(5), 471-486.

Flinn, A. M., & Gennery, A. R. (2018). Adenosine deaminase deficiency: a review. *Orphanet Journal of Rare Diseases*, *13*, 1-7.

Gao, L., Xu, J., Liu, S., Wang, Q., Dai, J., & Liu, J. (2023). Adenosine deaminase-based measurement in the differential diagnosis of pleural effusion: a multicenter retrospective study. *Therapeutic Advances in Respiratory Disease*, *17*, 17534666231155747.

Huan, N. C., Sidhu, C., Thomas, E., Lee, Y. C. G., & Lee, P. (2021). Optimising the utility of pleural fluid adenosine deaminase for the diagnosis of tuberculous pleural effusion. *Proceedings of Singapore Healthcare*, *30*(4), 271-278.

Jany, B., & Welte, T. (2019). Pleural effusion in adults—etiology, diagnosis, and treatment. *Deutsches Ärzteblatt International*, *116*(21), 377.

Kementerian Kesehatan Republik Indonesia. (2020). *Pedoman Nasional Pelayanan Kedokteran Tatalaksana Tuberkulosis*. Jakarta.

Noviyani, A., Nopsopon, T., & Pongpirul, K. (2021). Variation of tuberculosis prevalence across diagnostic approaches and geographical areas of Indonesia. *PLoS One*, *16*(10), e0258809.

Rea, G., Sperandeo, M., Lieto, R., Bocchino, M., Quarato, C. M. I., Feragalli, B., Valente, T., Scioscia, G., Giuffreda, E., & Foschino Barbaro, M. P. (2021). Chest imaging in the diagnosis and management of pulmonary tuberculosis: the complementary role of thoraci ultrasound. *Frontiers in Medicine*, *8*, 753821.

Wedari, N. L. P. H., Pranata, I. W. A., Budayanti, N. N. S., & Sukrama, I. D. M. (2021). Tuberculosis cases comparison in developed country (Australia) and developing country (Indonesia): a comprehensive review from clinical, epidemiological, and microbiological aspects. *Intisari Sains Medis*, *12*(2), 421–426.