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Relation of ADA (Adenosin Deaminase) Test with Pleural Fluid Analysis and Cytology in Non-Tuberculosis Exudative Pleural Effusion

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KEYWORDS

Adenosine deaminase; pleural effusion; cytology; pleural fluid analysis; malignancy; exudative effusion

ABSTRACT:

Background and Objectives: Non-tuberculous exudative pleural effusion poses a diagnostic challenge due to overlapping clinical and biochemical features. Although Adenosine Deaminase (ADA) is widely used for diagnosing tuberculous pleuritis, its relevance in non-tuberculous effusions, particularly in relation to pleural fluid analysis and cytology, remains insufficiently explored. This study aimed to determine the association between ADA levels, pleural fluid characteristics, and cytological findings in patients with non-tuberculous exudative pleural effusion.

Materials and Methods: An analytical cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital, including 63 consecutive patients meeting inclusion criteria. Pleural fluid samples underwent biochemical analysis, cytology, and ADA testing. Data were analyzed using chi-square and correlation tests, with significance set at $p < 0.05$. ROC analysis assessed ADA's diagnostic performance.

Results: The mean ADA level was 20.27 IU/L. Malignant effusions demonstrated significantly higher ADA values (22.7 IU/L) than non-malignant cases (18.0 IU/L). ADA showed strong correlations with pleural pH, leukocyte count, LDH, and mononuclear predominance. ADA also differed significantly between infectious and non-infectious etiologies. ROC analysis revealed excellent diagnostic accuracy (AUC = 0.93), with an optimal cut-off of 21 IU/L yielding 80% sensitivity and 94% specificity for identifying malignant effusions.

Conclusions: ADA levels exhibit significant associations with cytology and key pleural fluid parameters, demonstrating strong diagnostic value in distinguishing malignant from non-malignant non-tuberculous exudative pleural effusions. ADA may serve as a useful complementary biomarker within a multiparametric diagnostic framework.

1. Introduction

Pleural effusion is a common clinical condition that arises from various localized pulmonary diseases or systemic disorders associated with organ dysfunction [1]. Under normal physiological conditions, pleural fluid is maintained through a dynamic balance of secretion and reabsorption. This fluid plays a crucial role in maintaining negative intrathoracic pressure and supporting optimal lung expansion during inspiration. Pleural effusion occurs when excessive fluid accumulates within the pleural cavity [2]. Globally, the condition affects approximately 3,000 cases per one million population, while in Indonesia, the Basic Health Research Survey (*Riskesdas*) 2018 recorded a prevalence of 2.7%, equivalent to an estimated 1.39 million cases [3, 4].

The development of pleural effusion is generally attributed to increased pleural fluid formation or impaired drainage, primarily involving the parietal pleura. Several mechanisms contribute to its pathogenesis, including increased pleural membrane permeability, reduced oncotic pressure, elevated hydrostatic pressure in pleural capillaries, increased oncotic pressure within the pleural space, tumor invasion, lymphatic obstruction, pulmonary

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inflammation, and increased interstitial lung fluid [5]. Clinically, diagnosing pleural effusion remains challenging because its manifestations often overlap with other thoracic conditions such as pneumonia, pulmonary embolism, acute coronary syndrome, pneumothorax, chronic obstructive pulmonary disease, heart failure, and pulmonary edema. Imaging modalities, including chest radiography, ultrasonography, computed tomography, and magnetic resonance imaging, are widely used to assist diagnosis [6, 7]. However, these tools still present limitations such as subjective interpretation, the need for specialized expertise, high operational costs, and radiation exposure [8].

In addition to imaging studies, pleural fluid cytology and biomarker analysis are commonly used to support diagnostic evaluation [9]. The sensitivity of cytology in detecting malignant cells ranges from 40% to 87%, with a minimum recommended volume of 25 mL required for optimal cytological assessment [9, 10]. Biomarkers such as lactate dehydrogenase, albumin, total protein, procalcitonin, and C-reactive protein are also widely used due to their accessibility, rapid processing time, objectivity, and relatively low cost [11]. However, despite their clinical utility, these biomarkers demonstrate variable sensitivity and specificity across different etiologies of pleural effusion, and none have consistently achieved high diagnostic accuracy [12]. Among the available biomarkers, Adenosine Deaminase (ADA) is well established, particularly in diagnosing tuberculous pleural effusion.

Adenosine Deaminase is an enzyme involved in purine metabolism and the maturation of mononuclear leukocytes, predominantly present in T lymphocytes and macrophages [13]. Although ADA is widely recognized as a reliable biomarker for tuberculous pleuritis, previous studies have also examined its levels in non-tuberculous effusions. Elevated ADA levels have been reported in parapneumonic effusions and empyema, sometimes exceeding 40 U/L, while malignant effusions generally exhibit low to moderate concentrations (10–40 U/L). Lower ADA values are also observed in rheumatoid effusion (<30 U/L), pericardial effusion (<40 U/L), systemic lupus erythematosus-related effusion (<30 U/L), and other exudative non-tuberculous effusions (<40 U/L) [14]. The ADA test is inexpensive, simple to perform, and offers rapid analytical turnaround [15]. Despite these advantages, the diagnostic utility of ADA varies depending on the etiology and characteristics of the effusion. While ADA demonstrates potential in identifying non-tuberculous pleural effusions, its diagnostic performance specifically in nonspecific exudative pleural effusion has not been adequately investigated.

This gap highlights the need to evaluate whether ADA can serve as a reliable biomarker for distinguishing nonspecific exudative pleural effusions. Accurate identification of such cases is essential for early and precise diagnosis, enabling timely therapeutic decision-making. Therefore, the present study aims to determine the association between ADA levels and pleural fluid analysis, including cytological findings, in patients with non-tuberculous exudative pleural effusion at Dr. Wahidin Sudirohusodo Hospital.

2. Materials and Methods

Study Design

This study employed an analytical cross-sectional design to evaluate the association between ADA levels and pleural fluid analysis, including cytology, in patients with non-tuberculous exudative pleural effusion treated at Dr. Wahidin Sudirohusodo Hospital.

Study Setting and Period

The study was conducted at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. Data collection began after receiving institutional approval and continued until the required sample size was achieved between April and June 2025.

Study Population

The study population consisted of patients diagnosed with non-tuberculous exudative pleural effusion at Dr. Wahidin Sudirohusodo Hospital. The target population included all individuals who underwent pleural fluid biochemical analysis, cytological examination, and ADA testing. The accessible population comprised all eligible patients presenting during the study period. A consecutive sampling technique was applied, whereby every patient who met the inclusion criteria was recruited sequentially. Although the minimum estimated sample size was 34 participants, the study successfully enrolled 63 patients, all of whom met the eligibility criteria and were included in the final analysis.

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Eligibility Criteria

Eligibility criteria were applied to ensure the inclusion of appropriate study participants. Individuals were eligible for enrollment if they were adults aged 18 years or older, had been diagnosed with non-tuberculous exudative pleural effusion, demonstrated negative Acid-Fast Bacilli (AFB) findings in pleural fluid, and provided written informed consent to participate. Patients were excluded if their pleural effusion was attributable to tuberculosis, if they had underlying autoimmune or immunosuppressive disorders, or if they declined participation in the study.

Data Collection

Data collection in this study involved both questionnaire-based and laboratory-based procedures. A sociodemographic questionnaire was used to obtain baseline characteristics such as age, sex, and other relevant patient information. Within the first 24 hours of hospital admission, laboratory assessments were performed to record clinical and pleural fluid parameters, including ADA levels, glucose concentration, total protein, and lactate dehydrogenase (LDH), as well as total leukocyte count and differential cell composition. Cytological examination of pleural fluid was also conducted to determine the presence or absence of malignant cells. The data collection process began with the identification of patients diagnosed with non-tuberculous exudative pleural effusion, followed by eligibility screening based on predefined inclusion and exclusion criteria. Patients who met these criteria were informed about the study objectives, procedures, risks, and potential benefits, and written informed consent was subsequently obtained. Thoracentesis was then performed to obtain pleural fluid samples, which were subjected to biochemical analysis, cytology, and ADA measurement. All clinical and laboratory information was systematically entered into the study database and later processed for statistical analysis in accordance with the research objectives.

Statistical Analysis

Statistical processing of the data was conducted using the SPSS software package. Descriptive or univariate analyses were first performed to summarize and characterize the distribution of each study variable. Subsequently, bivariate analyses were employed to evaluate the relationship between categorical variables, utilizing the Chi-square test as the primary analytical method. A significance level of $p < 0.05$ was applied to determine statistical significance throughout the analysis.

Ethical Approval

Ethical clearance for this study was granted by the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, on 20 June 2025 (Approval No. 421A/UN4.6.4.5.31/PP36/2025). Authorization to access medical records was provided by Dr. Wahidin Sudirohusodo Hospital. All participants gave written informed consent prior to inclusion in the study.

3. Results

Study Characteristics

A total of 63 patients with non-tuberculous exudative pleural effusion were enrolled in this study at Dr. Wahidin Sudirohusodo Hospital during April–June 2025. All participants met the inclusion criteria and completed pleural fluid analysis, cytology, and ADA testing. The general characteristics of the study population are summarized in Table 1.

Table 1. Study Characteristics

Variables	Mean ± SD / Median	Percentage
Age (years)	55.40 ± 8.89	
Sex		
- Male	31	48.39%
- Female	32	51.61%
Pleural Fluid pH	7.29 ± 0.15	-
Pleural Fluid LDH (U/L)	765.16	-
Pleural Fluid Protein (g/dL)	3.72 ± 0.45	-
Pleural Fluid Glucose (mg/dL)	170.47	-
Leukocyte Count (/µL)	2021.77	-
Leukocyte Type		
- PMN	63	38.39%
- MN	63	61.61%
Pleural Fluid Cytology		
- Malignancy	30	48.39%
- Non-Malignancy	33	51.61%
Disease Category		
- Infectious	33	50.00%
- Non-Infectious	30	50.00%
ADA (IU/L)	20.27	-

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The patients' ages ranged from 32 to 70 years, with a mean of 55.40 ± 8.89 years, and showed a statistically significant association with other variables (p = 0.001). The sex distribution was relatively balanced, with 48.39% males and 51.61% females. The mean pleural fluid pH was 7.29 ± 0.15, while the mean LDH level reached 765.16 U/L, reflecting elevated enzymatic activity consistent with inflammatory or malignant processes.

Pleural fluid protein levels averaged 3.72 ± 0.45 g/dL, supporting the exudative nature of the effusions. The mean glucose concentration was 170.47 mg/dL, and the leukocyte count averaged 2021.77 cells/μL, indicating a substantial inflammatory response. Differential cell count showed 38.39% PMN and 61.61% MN, suggesting a mixed inflammatory pattern.

Cytological examination revealed malignancy in 48.39% of samples, while 51.61% were non-malignant. Disease categories were evenly distributed between infectious and non-infectious etiologies (50% each). The mean ADA level in pleural fluid was 20.27 IU/L, serving as a key parameter examined in relation to diagnostic patterns. Overall, these data provide a comprehensive overview of the demographic and clinical profiles of the 63 patients included in the study, highlighting relevant laboratory and cytological characteristics associated with non-tuberculous exudative pleural effusion.

Cytological Characteristics of Pleural Fluid in Non-Tuberculous Exudative Effusion

This study evaluated the relationship between pleural fluid cytology results and ADA levels in patients with non-tuberculous exudative pleural effusion. Table 2 summarizes these findings and demonstrates a significant difference in ADA values between malignant and non-malignant effusions.

Table 2. Association Between Pleural Fluid Cytology and Adenosine Deaminase Levels in Non-Tuberculous Exudative Pleural Effusion

Pleural Fluid Cytology	n	ADA Value (Mean ± SD)	r	p-Value
Malignancy	30	22.7 ± 2.64	8.35	<0.001
Non-Malignancy	33	18.0 ± 1.72		

***Spearman Correlation **Chi-square test**

In the malignant group (30 patients), the mean ADA level was 22.7 ± 2.64 IU/L, which was higher than that observed in the non-malignant group. A strong and statistically significant correlation was identified between cytology and ADA levels in malignant effusions (r = 8.35; p < 0.001), indicating a robust association between elevated ADA and malignant cytological findings. In contrast, the non-malignant group showed a lower mean ADA value of 18.0 ± 1.72 IU/L, although correlation analysis for this group was not available, warranting further investigation. Overall, these results suggest that ADA levels are markedly associated with malignant pleural effusions, supporting their potential role in distinguishing between malignant and non-malignant causes of exudative pleural effusion.

Characteristics of Pleural Fluid Analysis in Non-Tuberculous Exudative Pleural Effusion

Table 3 presents the relationship between pleural fluid parameters and ADA levels in patients with non-tuberculous exudative pleural effusion. ADA is frequently used to help identify infectious or malignant processes, and several pleural fluid variables demonstrated significant correlations with ADA values.

Pleural fluid pH showed a very strong positive correlation with ADA (r = 0.99, p = 0.001), indicating that higher pleural pH values were associated with higher ADA levels. In contrast, pleural fluid glucose had no significant association with ADA (r = 0.005, p = 0.96). Total leukocyte count demonstrated a strong negative correlation (r = –0.81, p < 0.001), suggesting that higher leukocyte counts were linked to lower ADA levels. Mononuclear cells (MN) were positively correlated with ADA (r = 0.68, p < 0.001), while polymorphonuclear cells (PMN) showed a significant negative correlation (r = –0.68, p = 0.01), reflecting differences in inflammatory patterns.

Pleural fluid protein levels showed no meaningful correlation with ADA (r = 0.027, p = 0.83). Meanwhile,

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LDH demonstrated a strong negative correlation ($r = -0.76$, $p < 0.001$), indicating that higher LDH levels were associated with lower ADA values. Specific gravity also showed a significant negative correlation ($r = -0.40$, $p = 0.001$), with increasing fluid density linked to lower ADA. Overall, these findings indicate that several pleural fluid characteristics, particularly pH, leukocyte count, MN percentage, and LDH, have significant associations with ADA levels and may contribute to the diagnostic assessment of non-tuberculous exudative pleural effusion, while glucose and protein levels do not appear to influence ADA in this population.

Table 3. Association Between Pleural Fluid Analysis and Adenosine Deaminase Levels in Non-Tuberculous Exudative Pleural Effusion

Pleural Fluid Analysis	Mean ± SD	r	p-Value
Pleural Fluid pH	7.29 ± 0.03	0.99	0.001
Glucose (mg/L)	170.47 ± 48.5	0.005	0.96
Leukocytes (cells/mm³)	2021.7 ± 533.6	-0.81	<0.001
MN	39.39 ± 5.70	0.68	<0.001
PMN	60.61 ± 5.70	-0.68	0.01
Protein (g/dL)	3.72 ± 0.45	0.027	0.83
LDH (U/L)	765.1 ± 86.2	-0.76	<0.001
Specific Gravity	1030.26 ± 1.51	-0.40	0.001

***Spearman Correlation **Chi-square test**

Association Between Disease Category and Adenosine Deaminase Levels

Table 4 presents the association between disease category, Infectious versus Non-Infectious, and ADA levels in patients with non-tuberculous exudative pleural effusion. ADA measurement is often used to help differentiate effusions caused by infectious processes from those related to non-infectious conditions such as malignancy.

Table 4. Association Between Disease Category and Adenosine Deaminase Levels

Variables	n	ADA Test (Mean ± SD)	r	p-Value
Infectious	33	17.59 ± 1.59	-0.765	<0.001
Non-Infectious	30	22.6 ± 2.63		

***Spearman Correlation **Chi-square test**

In the infectious group (32 patients), the mean ADA level was 17.59 ± 1.59 IU/L, and a strong negative correlation was observed between disease category and ADA values ($r = -0.765$; $p < 0.001$). This indicates a highly significant association, suggesting that higher ADA levels are less likely to be associated with infectious effusions.

In the non-infectious group (30 patients), the mean ADA level was 22.6 ± 2.63 IU/L, higher than that of the infectious group. However, a correlation coefficient and p-value were not provided for this group, so further analysis would be required to determine the statistical relationship between ADA levels and non-infectious etiologies. Overall, these findings highlight that ADA levels differ substantially between infectious and non-infectious pleural effusions, with significantly lower values observed in infectious cases.

Adenosine Deaminase Levels in Non-Tuberculous Exudative Pleural Effusion

This section evaluates the diagnostic performance of pleural fluid ADA, including its AUC value, optimal cut-off, sensitivity, and specificity. A Receiver Operating Characteristic (ROC) analysis was conducted to assess the ability of pleural ADA levels to distinguish malignant from non-malignant causes of non-tuberculous exudative pleural effusion. The ROC curve is shown in Figure 1.

The diagnostic performance of ADA is summarized in Table 5. The analysis demonstrated that ADA has excellent discriminative ability, with an AUC of 0.93,

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indicating strong diagnostic accuracy in differentiating malignant and non-malignant effusions. The optimal cut-off value was 21 IU/L, which provided a sensitivity of 80% for correctly identifying malignant effusions and a specificity of 94% for accurately ruling out non-malignant cases. The associated p-value of 0.012 confirms that these findings are statistically significant.

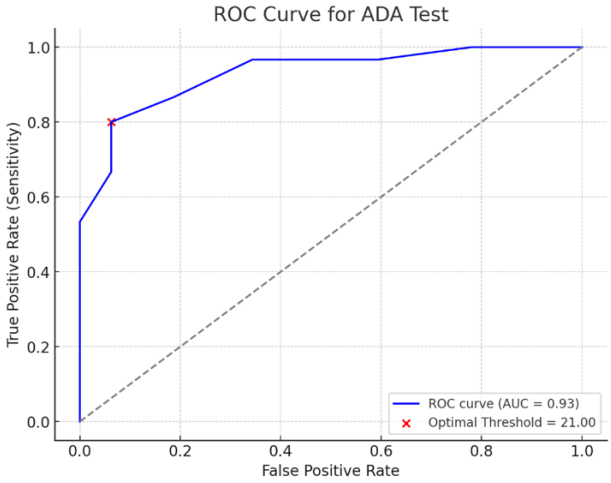

Figure 1. ROC Curve of Pleural Fluid ADA Levels in Non-Tuberculous Exudative Pleural Effusion

Table 5. Area Under the Curve (AUC) of Pleural Fluid Adenosine Deaminase in Non-Tuberculous Exudative Pleural Effusion

Parameter	Value
AUC	**0.93**
Cut-off optimal	21
Sensitivity	80%
Specificity	94%
p-value	0.012*
95% CI	0.871-0.993

Note: A significance level of $p < 0.05$ indicates that the AUC value is statistically significant.

Overall, the ROC analysis shows that pleural ADA has high diagnostic accuracy (AUC = 0.93), with an optimal cut-off of 21 IU/L yielding strong sensitivity and specificity. These results support the usefulness of ADA as a diagnostic marker in distinguishing malignant from non-malignant causes of non-tuberculous exudative pleural effusion.

4. Discussion

This study describes the demographic, biochemical, and cytological characteristics of non-tuberculous exudative pleural effusion and evaluates the diagnostic relevance of ADA across different etiological categories. The mean age of the patients (55 years) reflects the typical predominance of pleural diseases among middle-aged adults, consistent with findings by Ferreiro et al. and supported by age-related immunosenescence described by Weyand and Goronzy [1, 16]. The balanced sex distribution contrasts with earlier studies reporting male predominance, likely due to variations in local epidemiology and underlying diseases.

The biochemical profile aligns with classical exudative features. Elevated LDH (approximately 765 U/L) and protein levels support the presence of inflammatory or neoplastic processes, in agreement with Mercer et al. and Lin et al [3, 17]. Meanwhile, pleural glucose remained relatively high, suggesting that most cases represented non-complicated effusions. The predominance of mononuclear cells (61%) indicates a lymphocytic pattern commonly associated with malignancy or chronic inflammation, as also highlighted by Aggarwal et al. and Li et al [18, 19]. Cytology identified malignancy in 48% of samples, similar to reports by Psallidas et al. showing that 40, 60% of malignant effusions are of pulmonary or metastatic origin [20].

A key observation is the significantly higher ADA level in malignant effusions (22.7 IU/L) compared to non-malignant cases (18.0 IU/L), with a strong correlation between ADA and cytology. Although ADA is classically considered a biomarker for tuberculous pleuritis, previous studies, such as those by Jiménez Castro et al., Blakiston et al., and Choe et al., have shown that ADA may also rise in lymphocyte-predominant non-TB effusions, including malignancy [13, 14, 21]. These findings suggest that ADA elevation likely reflects enhanced T-cell activity within the pleural space rather than TB-specific immune activation.

Correlation analysis further clarifies ADA behavior. Strong positive correlation with pH and mononuclear cell percentage, along with negative correlations with leukocyte count, PMN proportion, LDH, and specific gravity, indicates that ADA increases in non-suppurative, lymphocyte-dominant environments, and

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decreases in necrotic or PMN-rich states. This pattern supports the mechanistic framework presented by Martinez-Navio et al. and Porcel et al., emphasizing the immunologic rather than purely biochemical nature of ADA [22, 23].

The relationship between ADA and disease category strengthens this interpretation. In infectious non-TB effusions, ADA values were significantly lower, aligning with the neutrophil-dominant inflammatory response described in parapneumonic effusions by Ferreiro et al. and Roy et al [1, 24]. Conversely, higher ADA values in non-infectious etiologies, particularly malignancy, reflect chronic T-cell activation and tumor-associated immune response. These findings reinforce the necessity to interpret ADA in context, especially in high-TB-burden regions, as emphasized by Blakiston et al. and Nicholson et al [13, 25].

From a diagnostic standpoint, ADA demonstrated excellent discrimination between malignant and non-malignant effusions (AUC = 0.93), with an optimal cut-off of 21 IU/L, sensitivity of 80%, and specificity of 94%. These values are comparable to reports by Lee et al. and da Silva et al., who found similar thresholds for differentiating exudative etiologies [26, 27]. The diagnostic yield is particularly valuable when cytology is inconclusive, as up to 40% of malignant effusions may produce negative cytological results.

Overall, these findings reaffirm ADA as a practical, cost-effective adjunct biomarker for evaluating non-tuberculous exudative pleural effusions. Its diagnostic value is maximized when interpreted alongside cytology, LDH, cell differential count, and clinical context. While ADA should not be used in isolation, its strong performance in this study supports its integration into multiparametric diagnostic models to guide initial clinical decision-making and reduce unnecessary invasive procedures.

5. Limitations

This study has several limitations. Its cross-sectional design allows only associative interpretation and cannot establish causal relationships between ADA levels and pleural fluid biochemical or cytological findings. The relatively small sample size and single-center setting may introduce selection bias and limit the generalizability of the results. The sensitivity of pleural fluid cytology also varies depending on sample volume and quality, creating the possibility of false-negative findings. Additionally, potential confounders, such as immunological status, medication use, or other systemic infections, were not fully evaluated. Despite these limitations, the study provides valuable preliminary insights into the role of ADA as a complementary marker in non-tuberculous exudative pleural effusion.

6. Conclusion

This study demonstrates that non-tuberculous exudative pleural effusions are characterized by relatively high pleural fluid pH, variable glucose and protein levels, and elevated LDH in several cases. Cytological evaluation revealed that malignant effusions constituted the largest proportion of samples. ADA levels were significantly higher in malignant compared to non-malignant effusions and showed a strong correlation with cytological findings. The diagnostic performance of ADA was excellent, with an AUC of 0.93, an optimal cut-off of 21 IU/L, a sensitivity of 80%, and a specificity of 94%, indicating high accuracy in differentiating malignant from non-malignant effusions. ADA levels also showed meaningful correlations with key pleural fluid parameters, including pH, total leukocyte count, mononuclear predominance, and LDH. Collectively, these findings highlight the potential role of ADA as a valuable complementary biomarker in the diagnostic evaluation of non-tuberculous exudative pleural effusion.

7. Declarations

Conflict of Interest

The authors declare that they have no competing interests related to the publication of this research.

Author's Contributions

A, ID, and SN participated in designing the study, developing the concept, managing the data, conducting formal analyses, and carrying out the investigation. JM, MI, and HI were responsible for drafting the initial manuscript, managing data processes, and performing manuscript preparation, review, and editing. All authors have reviewed and approved the final manuscript and accept full responsibility for every aspect of the work.

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Abbreviations

ADA: Adenosine Deaminase; AFB: Acid-Fast Bacilli; AUC: Area Under the Curve; LDH: Lactate Dehydrogenase; MN: Mononuclear cells; PMN: Polymorphonuclear cells; ROC: Receiver Operating Characteristic; TB: Tuberculosis

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