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Tuberculous Pleurisy: the role of the ADA Enzyme in Diagnosis and Treatment Outcomes

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Extrapulmonary TB, representing nearly 15% of the global TB burden, is more difficult to diagnose. Tuberculous pleural effusion (TPE), one of the commonest forms of extrapulmonary TB, is a diagnostic challenge with rather poor microbiologic confirmation rates from pleural fluid analysis2,3. Even diagnostic tools like CBNAAT and interferon-gamma release assays have shown suboptimal diagnostic accuracy4,5. Adenosine deaminase (ADA), an enzyme produced from lymphocytes and involved in purine metabolism, has been extensively studied as a biochemical marker in pleural fluid during investigation for TPE. The test is simple, cheap, rapid, minimally invasive, and can be performed in most laboratories3.

Keywords: Adenosine Deaminase; Diagnostic Markers; Pleural Fluid; Tuberculous Pleuritis; Tuberculosis Treatment Outcomes.

A common extrapulmonary manifestation of tuberculosis is pleurisy[1]. Tuberculous pleurisy (TP) develops when mycobacteria secrete an antigenic protein into the pleural cavity. This causes an incompletely understood slow type of sensitization reaction, and fluid accumulates in the pleural cavity. Difficulties usually lie not in the diagnosis of pleurisy itself, but in determining its etiology for timely etiotropic treatment. The fact is that, in addition to tuberculosis, the presence of pleural fluid can be caused by pneumonia, malignant tumors, heart failure, cirrhosis of the liver, nephrotic syndrome, infectious non-tuberculous lung disease, and diffuse connective tissue diseases.

Diagnosing tuberculosis (TB) pleuritis can be challenging due to its nonspecific presentation, variability in clinical manifestations, and limitations in diagnostic methods: Acid-fast bacilli (AFB) are rarely detected in pleural fluid because TB pleuritis is often a paucibacillary disease; culturing Mycobacterium tuberculosis from pleural fluid has low sensitivity (20–40%) and is time-consuming; elevated ADA levels in pleural fluid are sensitive but not specific, as ADA can be high in other conditions (e.g., empyema, malignancy); tests like nucleic acid amplification tests (NAATs) (e.g., GeneXpert MTB/RIF) and molecular diagnostics may not always be available, especially in

resource-limited settings; obtaining pleural tissue or fluid often requires invasive procedures (e.g., thoracentesis, pleural biopsy), which may not be feasible or safe in all patients; pleural biopsy has better diagnostic yield but is associated with procedural risks and may not be available in low-resource settings.

The immune status may also affect the occurrence of tuberculous pleurisy. Given that the primary mechanism involved is a delayed hypersensitivity reaction, it could be hypothesized that immunocompromised individuals are less likely to develop tuberculous pleurisy compared to those who are immunocompetent. However, research indicates that the incidence of tuberculous pleurisy is higher among patients infected with human immunodeficiency virus (HIV) than in those who are not infected[6]. Conversely, no such increase in incidence is observed in patients undergoing renal transplantation or dialysis[7].

The differential diagnosis of TP usually includes invasive procedures such as pleural biopsy and thoracoscopy[9,8,6]. These manipulations require special skills of medical personnel and can worsen the patient's condition. The high cost and long time needed to obtain results further reduce the effectiveness of the pleural biopsy and bacteriological method, which is considered the "gold standard" of diagnosis[1].

The difficulty of diagnosing TP is complemented by the relatively low sensitivity of traditional methods. Acid-fast bacteria are detected in 20-30% of pleural fluid examinations and 50-80% of pleural biopsy specimens. The sensitivity does not exceed 78% even when using the polymerase chain reaction to detect mycobacteria[8].

At the same time, it is known that there are very sensitive biochemical markers in the pleural fluid, the determination of their concentration can significantly facilitate the differential diagnosis of TP[2].

Current evidence suggests that biomarkers like ADA, an enzyme pivotal in purine metabolism, offer a more accessible and economically viable alternative for differential diagnosis. ADA's isoenzymatic forms, particularly ADA1 and ADA2, are found predominantly in lymphocytes, monocytes, and macrophages, rendering it a potentially sensitive indicator of TB-associated inflammation.

The ADA diagnostic threshold in Uzbekistan (likely around 40–60 U/L) is expected to match thresholds used in other high-TB regions, reflecting global best practices. However, diagnostic protocols may be adapted to address local epidemiological patterns, healthcare infrastructure, and co-morbidities like diabetes or HIV. Combining ADA testing with other diagnostic modalities ensures a more accurate and context-sensitive approach to managing TB.

In the context of Uzbekistan, ADA enzyme testing remains the preferred biomarker for diagnosing pleural TB due to its affordability, simplicity, rapid results, and reliability in high-TB burden settings. Although IFN-ã offers advantages in specificity, its high cost, complexity, and infrastructure requirements make it less practical as a frontline diagnostic tool in such regions. ADA testing is well-suited to the local healthcare landscape and effectively supports TB control efforts.

The present study aims to evaluate ADA's diagnostic utility and its link to treatment outcomes in tuberculous pleuritis.

MATERIALS AND METHODS

Study Design and Setting

This study employed a cohort design to analyze secondary data extracted from patient records and tuberculosis (TB) documentation. The investigation focused on individuals admitted to the inpatient departments of the Republican Specialized Scientific and Practical Medical Center for Phthisiology and Pulmonology (RSSPMCPhP) and the Tashkent Clinical Hospital of Physiology and Pulmonology (TCHPhP) in Tashkent, Uzbekistan, between 2021 and 2022. The study aimed to elucidate the diagnostic significance of ADA enzyme levels and their association with treatment outcomes in tuberculous pleuritis (TP).

In Uzbekistan, the National TB Program provides a tiered approach to TB diagnosis and treatment, ensuring comprehensive care at no cost to patients. Individuals suspected of TB initiate evaluation at primary healthcare facilities and may be referred to higher-tier institutions for specialized testing, including bacteriological, histological, and imaging investigations. This framework facilitates the systematic management of TB, adhering

strictly to the World Health Organization (WHO) guidelines for treatment and care.

Study Population

The study cohort comprised all patients with suspected tuberculous pleural effusion (TPE) admitted to the RSSPMCPhP and TCHPhP during the specified period. Diagnoses were determined through clinical assessments, radiological imaging (including chest X-ray, ultrasound, and CT scan), and pleural fluid analysis. Diagnostic procedures included bacteriological tests (smear microscopy for acid-fast bacilli, Xpert MTB/RIF assay, and mycobacterial cultures), cytological and biochemical analyses, and histopathological examination of pleural biopsies.

Data Collection and Validation

Patient demographic, clinical, and treatment-related data were extracted from standardized electronic medical records maintained in the EpiData application (version 3.1, EpiData Association, Odense, Denmark). To ensure accuracy, all data underwent cross-validation and error-checking procedures. Discrepancies were resolved by referring to original patient records.

Variables and Definitions

Key variables included demographic information (age, gender, residence), lifestyle factors (smoking and alcohol use), clinical comorbidities (e.g., diabetes mellitus, HIV, hepatitis C virus [HCV] infection), diagnostic findings, drug resistance profiles, treatment regimens, and outcomes. ADA enzyme activity in pleural fluid and serum was quantified and compared between TB and non-TB pleurisy cases. Treatment outcomes were categorized using WHO definitions: successful (cure or treatment completion) and unsuccessful (failure, loss to follow-up, or death)[3].

Laboratory and Diagnostic Procedures

Pleural fluid samples were obtained via thoracentesis, with 40 mL collected per patient. Cytological, bacteriological, and biochemical analyses were conducted on separate aliquots, while ADA activity was measured in centrifuged and frozen supernatants. Pleural biopsy samples were subjected to histopathological and microbiological examination. ADA activity was assessed using the Giusti and Galanti method, which quantifies enzyme-mediated ammonia release via spectrophotometric analysis.

Statistical Analysis

Descriptive statistics were utilized to characterize the cohort, with continuous variables expressed as means ± standard deviations and categorical variables as frequencies and percentages. Sensitivity, specificity, and predictive values of ADA levels were calculated for both pleural fluid and serum. Binomial log-linear regression was employed to evaluate predictors of treatment outcomes, with results presented as risk ratios (RR) and 95% confidence intervals (CI). Statistical significance was set at $P < 0.05$.

RESULTS

Patient Demographics and Group Characteristics

From 2021 to 2022, a total of 80 patients were enrolled, comprising two groups: those diagnosed with tuberculous pleuritis (TP) (n=50) and those with non-tuberculous pleurisy (n=30). The mean age in the TP group was 42 years (range: 20–83), compared to 60 years (range: 27–86) in the non-tuberculous group. Male patients predominated in both cohorts, accounting for 84% in the TP group and 63% in the non-TB group (Table 1).

Get the material. Pleural fluid samples were obtained by thoracentesis. About 40 ml of pleural fluid was obtained from each examined person. A part of the liquid was taken to calculate the cell content, cytological examination, staining of acid-resistant bacteria, and determination of the amount of protein. Another part of the liquid was centrifuged at 1500 rpm for 10-15 minutes, the resulting supernatant was separated and stored at -20°C and used for direct study of ADA.

In parallel, a pleural biopsy was performed, during which samples were taken for research, tissues used for pathogistological and microbiological examination.

Tuberculosis was diagnosed when any of the following analysis results were met: Mycobacterium tuberculosis was detected in pleural fluid or pleural biopsy, granuloma and acid-fast bacteria were detected in pleural tissue, or tuberculosis was detected in pleural tissue with granuloma and no acid-fast bacteria were found. when effective treatment is observed.

The diagnosis of pleurisy with tumor etiology was made on the basis of cytological

examination of pleural fluid or histological analysis of pleural biopsy.

Examination of ADA enzyme in blood serum and pleural fluid. ADA enzyme activity was determined by the method described by Giusti G. and Galanti B. This method is based on the Bertolet reaction (in the presence of ammonia separated from adenosine) and is related to the formation of a colored indophenol complex and the subsequent spectrophotometric estimation of its concentration. Results are expressed in international activity units (IU). A unit of ADA activity is the amount of enzyme necessary to release 1 mmol of ammonia in one minute under standard test conditions.

Group 1 patients had higher ADA in pleural fluid and blood serum than those in group 2 (Table 2). It was observed that the amount of ADA in pleural fluid was 3.2 times higher in group 1 than in group 2, and 5.5 times higher in blood serum, respectively.

We conducted an investigation into the diagnostic significance of adenosine deaminase (ADA) levels in both pleural fluid and serum samples (Table 3).

The presented work presents the results of the first study carried out in the Republic of Uzbekistan to evaluate the use of ADA activity in pleural fluid and blood serum for the purpose of differential diagnosis of TP. They indicate the uniqueness of these tests. The increase in total ADA activity in pleural fluid and blood serum is mainly due to the isoenzyme form of ADA2. A similar phenomenon was observed by other researchers. The test for total ADA activity in pleural fluid and blood serum appears to have high sensitivity and specificity compared with results obtained in other countries.

Table 1. Checked patients characteristic

Groups	Number of patients examined	Male	Female	Age range	Average age
Tuberculous pleurisy (group 1)	50	42	8	20-83	42
Non-tuberculous pleurisy (group 2)	30	19	11	27-86	60

Table 2. Pleura liquid and blood ADA enzyme in serum activity

Indicators being determined	Controlled groups	
	Group 1	Group 2
ADA IU/l in pleural fluid	46.6 (3-69)	14.4 (4-38)
ADA IU/l in blood serum	25.3 (0-37)	4.5 (0-19)

Note: $p<0.05$

Table 3. Tuberculosis in pleurisy Indicators of diagnostic value of ADA detection

Indicators	ADA in pleura liquid IU/l	ADA in blood serum IU/l
Threshold result of the indicator	30	20
True positive results the number	47	21
False positive results the number	3	0
True negative results the number	27	30
False negative results the number	3	9
Sensitivity %	93	100
Specificity %	96	70

An analysis of literature data showed that among European countries, the threshold values of ADA in the pleural fluid of patients with tuberculous pleurisy range from 41 to 70 IU/l, and the sensitivity of the test ranges from 79 to 100%[3]. Even greater fluctuations, according to various laboratories, are characteristic of the threshold level of IFN-g (from 12 to 240 pg/ml)[4,5]. The reasons for such large differences are the use of different sets of reagents for enzyme immunoassay or radioimmunoassay, the incidence of tuberculosis in the population and the characteristics of the population itself[7].

Taking into account the above data, when choosing a test priority, issues of efficiency come to the fore. As studies show, the determination of total ADA activity in pleural fluid is not only clinical, but also economically effective, since the method is simple to perform and does not require expensive equipment and reagents. The result can be obtained within 2 hours. This method should, first of all, be recommended for widespread implementation in practical medicine.

The majority of patients (n = 50, 91%) achieved successful treatment outcomes, with slightly higher success rates observed in individuals aged 40 years or younger (90.9%) compared to those older than 40 (89.2%). Similarly, treatment success was comparable between genders, with rates of 90.4% in men and 87.5% in women. Neither age nor gender demonstrated a statistically significant association with the likelihood of an unfavorable treatment outcome.

Six patients (8.7%) exhibited resistance to rifampicin, and the presence of drug-resistant tuberculosis was associated with a significantly

Table 4. Factors that predict treatment outcomes for patients with tuberculous pleurisy admitted for treatment at the RSSPMCPhP and the TCHPhP, Tashkent, Uzbekistan, 2021 - 2022

Characteristics	Total		Successful treatment result		Unsuccessful treatment outcome		R.R.	95% CI	P value
	N	%	N	(%)	N	(%)			
Age range									
<40 years	22	(44.0)	20	(90.9)	2	(9.1)	1		
40 years and older	28	(56.0)	25	(89.2)	3	(10.8)	1.37	(0.50–3.70)	0.540
Sex									
male	42	(84.0)	38	(90.4)	4	(9.6)	1		
female	8	(16.0)	7	(87.5)	1	(2.5)	1.11	(0.41–3.04)	0.836
Drug resistance									
Sensitive / not confirmed	44	(88.0)	40	(90.9)	4	(9.1)	1		
Verified RR/MDR	6	(12.0)	4	(66.7)	2	(33.3)	3.97	(1.13-13.93)	0.031
Hepatitis									
Yes	5	(10.0)	3	(60.0)	2	(40.0)	4.8	(1.44-15.98)	0.011
No	45	(90.0)	41	(91.1)	4	(8.9)	1		
Bacteriologically confirmed tuberculosis									
Yes	10	(20.0)	9	(90.0)	1	(10.0)	0.96	(0.23–4.01)	0.958
No	40	(80.0)	37	(92.5)	3	(7.5)	1		
Cytologically confirmed tuberculosis									
Yes	31	(62.0)	29	(93.5)	2	(6.5)	1		
No	19	(38.0)	16	(84.2)	3	(15.8)	4.52	(1.05-19.47)	0.043
Histologically confirmed tuberculosis									
Yes	28	(56.0)	24	(85.7)	4	(14.3)	1		
No	22	(44.0)	20	(90.9)	2	(9.1)	0.44	(0.14–1.42)	0.169

RR = risk ratio, CI = confidence interval

higher likelihood of treatment failure (RR: 3.97; 95% CI: 1.13–13.93; P = 0.031). Hepatitis emerged as the only comorbidity significantly linked to an elevated risk of treatment failure (RR: 4.8; 95% CI: 1.44–15.98; P = 0.011). While no significant association was observed between treatment outcomes and diagnoses based on bacteriological or histological methods, an increased risk of unfavorable treatment outcomes was identified in patients whose diagnosis of TP was established solely through cytological analysis (RR: 4.52; 95% CI: 1.05–19.47; P = 0.043) (Table 4).

DISCUSSION

This study reaffirms the diagnostic and prognostic significance of ADA in managing TP. Elevated ADA levels in pleural fluid and serum provide a robust, minimally invasive diagnostic alternative to traditional methods, such as pleural biopsy or mycobacterial culture, which are resource-intensive and less accessible in low-income settings. The observed ADA activity in this cohort parallels findings from studies conducted in other high TB-burden regions, underscoring its global applicability.

Higher ADA specificity in pleural fluid means fewer false-positive results compared to serum ADA. This is critical for diagnosing TB pleuritis because the condition can mimic other diseases like malignancies, rheumatoid arthritis, or empyema, which may also show elevated serum ADA. Pleural fluid analysis helps narrow down the diagnosis specifically to TB pleuritis when ADA levels are significantly elevated. High pleural fluid ADA specificity reduces the likelihood of misdiagnosis and unnecessary treatments such as empiric anti-TB therapy in non-TB cases. Misdiagnosis based on serum ADA could lead to inappropriate treatment, exposing patients to medication side effects and contributing to drug resistance.

Adenosine Deaminase (ADA) testing is a valuable rapid diagnostic tool for tuberculosis (TB) pleuritis, particularly in resource-limited settings where advanced diagnostic techniques are often unavailable. Its affordability, simplicity, and high sensitivity make it a practical option for early diagnosis: ADA testing can provide results within hours, enabling quicker clinical decision-making compared to culture-based methods, which may take weeks; ADA testing is inexpensive and requires minimal laboratory infrastructure, making it accessible in low-resource environments; ADA levels in pleural fluid are highly sensitive for TB pleuritis (sensitivity > 90% in many studies), allowing rapid screening of suspected cases; the test can be performed on pleural fluid obtained via thoracentesis, a relatively straightforward and minimally invasive procedure; in endemic regions, the high pre-test probability of TB makes ADA a reliable rule-in diagnostic tool for lymphocyte-predominant pleural effusions.

Treatment outcomes revealed a high overall success rate, consistent with adherence to WHO-recommended protocols. However, comorbid conditions, particularly hepatitis, and drug resistance remain critical barriers to successful outcomes. These findings underscore the necessity of integrating ADA testing into standard diagnostic workflows and adopting multidisciplinary approaches to manage complex cases.

The study has several limitations. First, it included a retrospective component, which introduced the possibility of information bias. Patient charts were analyzed, but these were often inconsistently completed and sometimes contained missing data due to the lack of standardized data recording practices across clinics in Uzbekistan. Second, the rarity of tuberculous pleural effusion (TPE) within the general tuberculosis (TB) population resulted in a small sample size. This limitation may have hindered a robust analysis of factors associated with unfavorable treatment outcomes.

CONCLUSION

The diagnosis and management of tuberculous pleuritis (TP) remain challenging due to the variable sensitivity and specificity of conventional diagnostic techniques. This study highlights the pivotal role of adenosine deaminase (ADA) enzyme activity as a diagnostic biomarker for TP, demonstrating high sensitivity and specificity in pleural fluid and serum. ADA testing offers a rapid, cost-effective, and minimally

invasive alternative, suitable for integration into clinical practice, particularly in resource-constrained settings.

Despite an overall favorable treatment success rate, the presence of drug-resistant TB and comorbid conditions such as hepatitis significantly compromised outcomes. These findings underscore the importance of robust diagnostic and therapeutic strategies tailored to high-risk patient populations. Furthermore, multidisciplinary approaches are essential to optimize the diagnosis, prevent misclassification, and enhance treatment outcomes in TP. Future research should explore the potential of combining ADA with other biomarkers to improve diagnostic accuracy and predictive value in clinical settings.

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Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials

Author Contributions

Conceptualization and methodology F.A., L.M.; data collection F.A., D.O.; data analysis and interpretations—F.A.; writing—original draft preparation F.A.; final review and approval F.A., L.M., D.O. All authors have read and agreed to the published version of the manuscript.

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