AIMS Medical Science

AIMS Medical Science, 13(1): 57–66.
DOI: 10.3934/medsci.2026005
Received: 23 September 2025
Revised: 09 March 2026
Accepted: 18 March 2026
Published: 23 March 2026

http://www.aimspress.com/journal/medicalScience

Research article

The value of combining *Mycobacterium tuberculosis* immunoglobulin G with adenosine deaminase and D-dimer on the diagnostic accuracy of tuberculous pleurisy

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Abstract: This study aimed to investigate the association between adenosine deaminase (ADA), *Mycobacterium tuberculosis* immunoglobulin G (MTB-IgG), and d-dimer (D-D) levels in pleural fluid, as well as to assess the diagnostic value of their combined detection in tuberculous pleurisy. A total of 255 patients admitted between July 2022 and July 2024 were included in the study and categorized into two groups: tuberculous pleural (TBP) group (148 cases, 57.6%) and nontuberculous pleural (non-TBP) group (107 cases, 42.4%). Correlation analysis was conducted on adenosine deaminase (ADA), *Mycobacterium tuberculosis* immunoglobulin G (MTB-IgG), and D-dimer (D-D) in tuberculosis patients. The diagnostic outcomes of these three biological indicators alone as well as in combination were compared by setting the lowest threshold of different biomarkers. The levels of ADA (60.78 ± 27.58 U/L vs. 38 ± 4.96 U/L) and D-D (6.18 ± 5.38 mg/L vs. 1.29 ± 0.69 mg/L) in TBP patients were found to be significantly elevated compared to non-TBP patients ($P < 0.001$). When the MTB-IgG test was positive, the diagnostic accuracy was as high as 77.4% in TBP patients, while non-TBP patients showed a low immune characteristic, and the MTB-IgG negative rate was as high as 80.4%. When combined with ADA + MTB-IgG (−), D-D + MTB-IgG (−), and ADA + D-D + MTB-IgG (−), the diagnostic accuracy of non-TBP patients can be significantly improved. The combined detection of pleural effusion ADA, D-D, and MTB-IgG can enhance the diagnostic accuracy of tuberculous pleurisy.

Keywords: tuberculous pleural; adenosine deaminase; mycobacterium tuberculosis immunoglobulin G; D-dimer; diagnosis

1. Introduction

Tuberculous (TB) is an inflammation of the pleura caused by *Mycobacterium tuberculosis* and is a common form of extrapulmonary tuberculosis [1,2]. Globally, more than 10 million people are still infected with tuberculosis each year. In 2022, tuberculosis was the second leading cause of death from a single infectious disease in the world after coronavirus disease (COVID-19), causing almost twice as many deaths as HIV/AIDS [3].

The disease has an acute onset and a variety of clinical manifestations, and its diagnosis usually relies on clinical presentation, pleural biopsy, and laboratory tests [4,5]. However, early diagnosis is difficult due to the lack of a typical clinical presentation, an etiological basis for the disease, and the difficulty of detecting *Mycobacterium tuberculosis* (MTB) in pleural fluid [6]. Misdiagnosis is frequent because its clinical manifestations are similar to other types of pleurisy, often being confused with pneumonia and malignant tumors [7,8]. Therefore, quickly and accurately diagnosing TB pleurisy faces critical clinical challenges [9]. A large number of current clinical studies have shown that the establishment of an efficient and stable diagnostic method is of great significance to improve the early diagnosis rate of TB pleurisy.

In recent years, with the rapid development of enzymology and molecular biology, enzymes and cytokines have received increasing attention in the pathogenesis of various immune diseases [10,11]. Over the past decades, many biological parameters have provided simple and cost-effective methods for the diagnosis of tuberculous pleurisy. Among all, interleukin (IL), adenosine deaminase (ADA), D-dimer (D-D), interferon-gamma (INF-γ), antibodies, and antigens have been gradually applied to the diagnosis of tuberculous pleurisy and have achieved interesting results [11,12]. High levels of ADA in the pleura are considered the gold standard for diagnosing tuberculous pleurisy; however, diagnosing TB remains a major challenge for patients with low levels of ADA in pleural accumulation [13]. D-dimer is an objective biomarker for predicting tuberculous pleural effusion (TPE) patients, and studies have shown that the level of D-dimer in TPE patients is significantly higher than that in non-TPE patients [14]. The response of IgG to *Mycobacterium tuberculosis* antigenic proteins in patients with pulmonary tuberculosis was estimated during the management of tuberculosis (TB) by accurate point-of-care testing (POCT), suggesting that antibodies directed against the natural proteins of *Mycobacterium tuberculosis* can be detected in patients with tuberculous pleurisy [15]. Excitingly, a growing number of studies have shown that combined simultaneous testing of multiple biomarkers improves the diagnostic accuracy of TB pleurisy compared to testing the results of one biomarker alone [2,16].

The aim of this study was to investigate the significance of the combined application of three biomarkers, adenosine deaminase (ADA), *Mycobacterium tuberculosis* immunoglobulin G (MTB-IgG), and D-dimer (D-D), in the diagnosis of tuberculous pleurisy. We compared the diagnostic performance of MTB-IgG and D-D with that of the classical TBP marker ADA and investigated whether the combination of ADA, D-D, and IgG might improve diagnostic accuracy.

2. Materials and methods

2.1. Patients

A total of 225 patients with pleural effusion admitted to Red Cross Hospital of Yulin City in China from July 2022 to July 2024 were selected, and patients under 1 year old were excluded after being included in the group of *pleural effusion patients*. Medical histories were inquired in detail, and related examinations such as physique, chest X-ray, pleural effusion routine, chest ultrasound, lung CT, biochemistry, pathological examination of pleural effusion, and conjugate mycin test were performed. All patients provided written informed consent. The retrospective study only collected clinical information on the patients, did not affect their treatment plan, and did not pose any risk to their physiology. We endeavor to protect the information provided by our patients without compromising their privacy.

2.2. Data collection and biochemical determination

Based on medical records, data collected included patient characteristics such as age, gender, past medical history, and current symptoms. ADA, d-dimer, and IgG of the first blood test were collected and analyzed. Under sterile conditions, pleural puncture was performed, and 10 mL of pleural effusion was extracted and placed into an anticoagulant tube containing 0.2 mL of sodium citrate solution (concentration of 1.108%). After centrifugation at low temperature (3000 rpm, 20 min), the supernatant was taken and stored at −80 ℃ for future examination. The levels of MTB-IgG and D-D were determined by enzyme-linked immunosorbent assay using a DxC 700 AU automatic biochemistry analyzer, and the kit was purchased from Kangzhu Biotech Company and BioMérieux China Company. In addition, 2 mL of fresh pleural effusion was taken to measure the ADA level by the enzymatic chromogenic method; the kit was purchased from Beijing Lidman Biochemical Technology Company. Data were analyzed, and graphs were drawn using Origin software (version 8.0) and GraphPad Prism software (version 5.0). Significant differences were determined by the Mann–Whitney test, and statistical significance was defined at $P < 0.05$.

2.3. Ethics approval of research

The study protocol was approved by the Ethics Committee of Red Cross Hospital of Yulin City (C202109-3).

3. Results

3.1. General information of patients

In our study, a total of 255 patients were included. 75% were male, including 148 patients with TBP, and 107 patients with non-TBP (Table 1). All patients were HIV-free. In the TBP and non-TBP groups, there was a mean age of 55.24 ± 20.35 and 63.72 ± 13.51 years, respectively (Figure 1). In the TBP group, 80% (n = 117) were males and 20% (n = 31) were females, while in the non-TBP

group, 68% (n = 73) were males and 32% (n = 34) were females. These results indicate that age and gender may have an impact on the outcome and diagnostic accuracy of the development of TBP.

Table 1. Basic demographic and clinical characteristics of patients with tuberculous pleural (TBP).

		Total number	Percentage (%)
Gender	Male	190	74.5
	Female	65	25.5
Diagnosis	TBP	148	57.6
	Non-TBP	107	42.4

Note: TBP: tuberculous pleural.

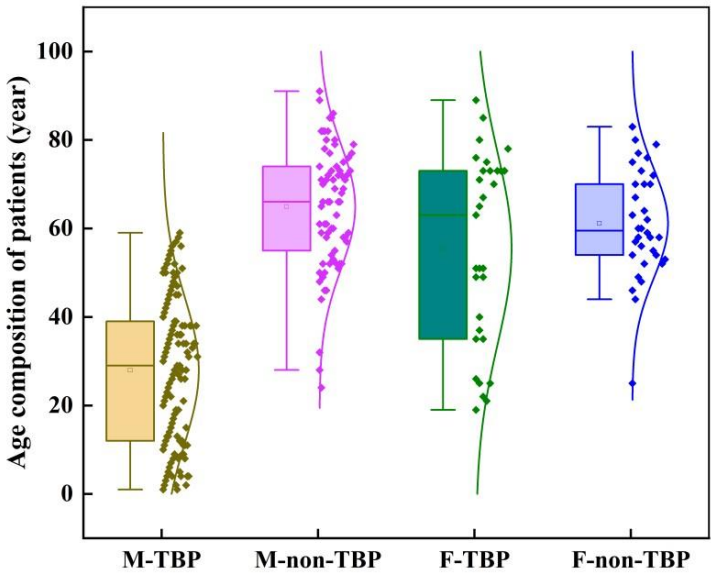

Figure 1. Comparison of age between groups. M-TBP, male tuberculous pleural; F-TBP, female tuberculous pleural.

3.2. Value of ADA, MTB-IgG, and D-D on the diagnosis of tuberculous pleurisy

The mean pleural ADA concentration was significantly higher in TBP patients (60.78 ± 27.58 U/L) than in non-TBP patients (8.38 ± 4.96 U/L; $P < 0.001$; Figure 2A). Similarly, the mean D-D level was significantly higher in TBP patients than in non-TBP patients (6.18 ± 5.38 mg/L vs. 1.29 ± 0.69 mg/L, $P < 0.001$; Figure 2C). The results of MTB-IgG antibodies showed no significant difference in the IgG-positive rate compared to the IgG-negative rate in TBP patients (28.21% vs. 29.79%; Figure 2B). However, the IgG-negative rate was significantly higher than the IgG-positive rate in non-TBP patients (33.77% vs. 8.23%; Figure 2B). The results showed that the amount of ADA and D-D was significantly higher in TBP patients than in non-TBP patients, while the MTB-IgG negative rate was significantly higher than the positive rate in non-TBP patients, suggesting that ADA, D-D, and MTB-IgG could be effective biological indicators in the accurate diagnosis of TBP.

This article raises the question of whether a combination of two or three parameters has the potential to improve the adequacy of the diagnosis in differentiating tuberculous pleural effusion

from malignancy. Therefore, we further investigated the potential combined diagnostic value of ADA, MTB-IgG, and D-D. When two or three parameters of ADA, MTB-IgG, and D-D were used for diagnostic purposes, the measured concentrations of ADA + MTB-IgG (+) were elevated in patients with TBP, and the measured levels of D-D + MTB-IgG (+) were similar to the former (Table 2).

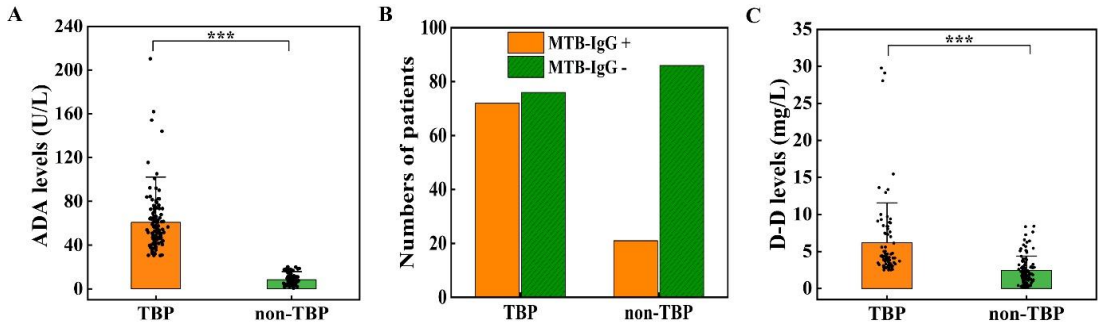

Figure 2. Comparison of levels of ADA, MTB-IgG, and D-D between TBP and non-TBP groups. (A) Pleural ADA concentration; (B) pleural MTB-IgG; (C) pleural D-D concentration. Statistical significance was defined as $P < 0.05$. ADA: adenosine deaminase; MTB-IgG: *Mycobacterium tuberculosis* immunoglobulin G; D-D: D-dimer; TBP: tuberculous pleural; (+), positive; (−), negative. Significant differences were determined by the Mann–Whitney test, $p < 0.05$; ***$p < 0.001$.

Table 2. Diagnostic performance of ADA, TBM-IgG, and D-D together.

Bio-parameter	TBP	Non-TBP	P-value
ADA + MTB-IgG (+)	69.44 ± 35.69 U/L	8.72 ± 4.02 U/L	<0.001
ADA + MTB-IgG (−)	53.19 ± 14.53 U/L	8.30 ± 5.17 mg/L	<0.001
D-D + MTB-IgG (+)	7.01 ± 6.31 mg/L	1.25 ± 0.72 mg/L	<0.001
D-D + MTB-IgG (−)	5.56 ± 4.54 mg/L	1.29 ± 0.69 mg/L	<0.001

Note: ADA, adenosine deaminase; MTB-IgG, *Mycobacterium tuberculosis* immunoglobulin G; D-D, D-dimer; TBP, tuberculous pleural; (+), positive; (−), negative. Significant differences were determined by Mann–Whitney test, and a P-value < 0.05 was considered statistically significant.

3.3. Diagnostic value of combined detection of MTB-IgG and D-D for tuberculous pleurisy

The subsequent analysis focused on evaluating the impact of multi-parametric coupling on the diagnostic outcome of TBP. The findings indicated that the combination of ADA + MTB-IgG (+), D-D + MTB-IgG (+), or ADA + D-D + MTB-IgG (+) did not significantly impact the rates of TBP-positive diagnosis (Figure 3A, B, D). Furthermore, the combination of ADA + D-D had no significant effect on diagnosing either TBP-positive or TBP-negative (Figure 3C). However, in the diagnosis of non-TBP patients, the combinations of ADA + MTB-IgG (−), D-D + MTB-IgG (−), or ADA + D-D + MTB-IgG (−) can significantly improve the diagnosis rate (Figure 3A, B, D). These findings indicate that the presence of MTB-IgG has a significant impact on the diagnostic outcome of non-TBP. This suggests that combining MTB-IgG with other parameters could become an important method for diagnosing TBP.

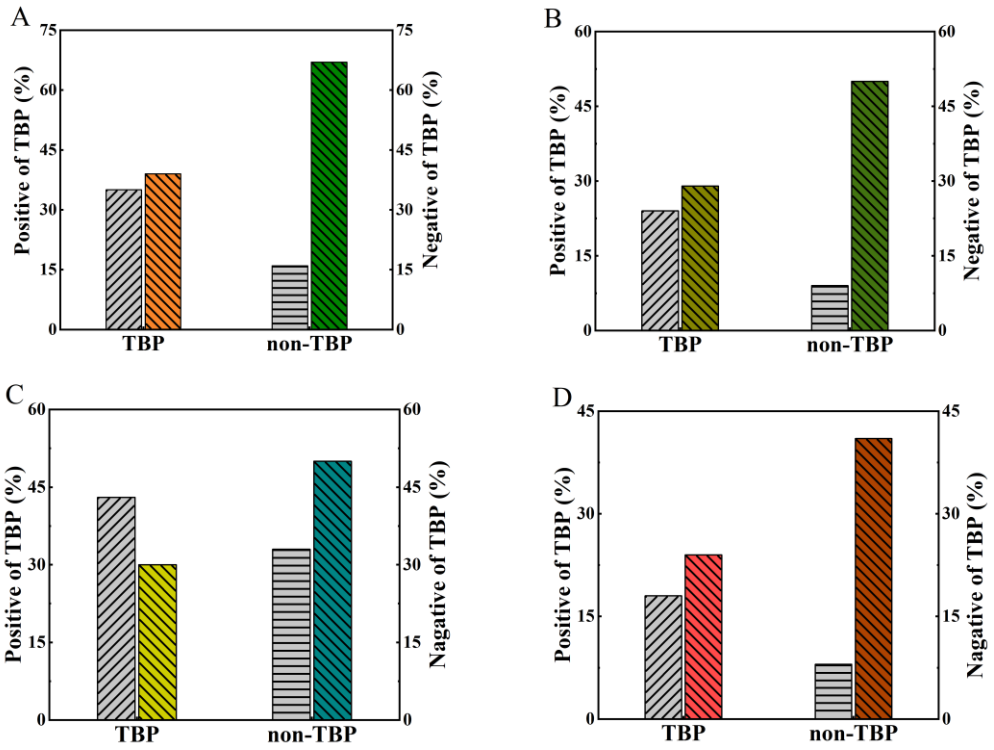

Figure 3. Impact of combinations of multiple parameters on the rate of confirmed TBP diagnosis. (A) Combination of ADA and MTB-IgG; (B) Combination of D-D and MTB-IgG; (C) Combination of ADA and D-D; (D) Combination of ADA, MTB-IgG, and D-D; ADA: adenosine deaminase; MTB-IgG: *Mycobacterium tuberculosis* immunoglobulin G; D-D: D-dimer; TBP: tuberculous pleural.

4. Discussion

Tuberculous pleurisy is the most common form of extrapulmonary lesions in adults, accounting for about 66.6% of inpatients with pleural effusion in China [17]. For patients with tuberculous pleural effusion, an early and efficient diagnostic test is necessary to minimize complications such as pyothorax and lung injury caused by pleural effusion [2,18]. This study presents evidence supporting the use of ADA, D-D, and IgG measurements in pleural effusion for diagnosing TBP.

In this study, we independently assessed ADA outcomes and found that ADA levels were significantly higher in TBP patients than in non-TBP patients (Figure 2A). ADA is frequently utilized as a research instrument for the diagnosis of tuberculous pleural effusion (TPE), demonstrating a sensitivity of 90% and specificity of 92%. The study determined that ADA was a dependable biomarker for distinguishing between cases of TPE and non-TPE in younger individuals [19]. These findings suggest that assessing ADA assay values independently could potentially lead to some TPE false-positive results.

Several studies have shown elevated serum levels in patients with pleural exudates compared to healthy individuals and other exudates [20]. In this study, we assessed the outcome of D-D independently and found that TBP patients had significantly higher D-D levels compared to non-TBP patients (Figure 2C). Serum D-D testing was performed in the screening diagnosis of children with *Mycoplasma pneumoniae pneumoniae* (MPP), suggesting that elevated serum D-D levels can be used

as an early predictor of MPP and the development of complications [21]. High levels of D-D have been observed in malignant pleural effusions [22].

Kaisermann et al. were the first to document the existence of IgA antibodies to MPT-64 and MT-10.3 in pleural tuberculosis effusions; their findings indicated that IgA antibodies exhibit a sensitivity comparable to histopathological examination, suggesting that IgA antibodies may serve as a reliable marker for pleural tuberculosis [23]. A comparative analysis of the levels of antibodies and lymphocytes in patients with and without tuberculosis revealed that TB-positive patients exhibited detectable levels of IgG and IgA, whereas only IgA was detected in TB-negative patients [24]. Although MTB-IgG antibody test results showed that IgG did not significantly improve the diagnostic accuracy in TBP patients, it did significantly improve the diagnostic accuracy in non-TB patients in our study (Figure 2B).

In our results, it was found that the combination of two/three of ADA, D-D, and MTB-IgG had no significant effect on the diagnostic rate of TBP patients; however, the combination of ADA, D-D, and MTB-IgG significantly improved the diagnostic accuracy of non-TB patients (Figure 3). The IgA and IgG antibodies were assessed against *Mycobacterium tuberculosis* in both pleural fluid and serum samples obtained from patients diagnosed with pleural tuberculosis. The findings revealed that the immunosensitivity of IgA was robust, measuring 86.2% in pleural fluid and 51.7% in serum. However, the sensitivities of IgG were determined to be 65.5% and 51.7% in pleural fluid and serum, respectively. Subsequently, a combination of both IgA and IgG demonstrated an enhanced sensitivity of 93.1%, accompanied by a specificity rate of 92.3%. Furthermore, when combining ADA with IgA, the maximum sensitivity achieved was found to be 96.6%, while maintaining a specificity rate of 92.3% [25].

5. Conclusions

The present study demonstrates that the combination of pleural fluid ADA, D-D, and MTB-IgG testing enhances the accuracy of diagnosing tuberculous pleurisy. This assay holds potential as a valuable tool for the detection of tuberculous pleura and has the capability to enhance the diagnostic accuracy of tuberculous pleura in challenging clinical scenarios, particularly in cases where conventional diagnostic tests with limited resources may yield inaccurate results.

Author' contributions

Chong Liang and Jie Chen: conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and tables, authored or reviewed drafts of the article, and approved the final draft. Chungang Wu: analyzed the data, prepared figures andor tables, authored or reviewed drafts of the article, and approved the final draft. Chunhong Qiu and Guangge Feng: reviewed drafts of the article, and approved the final draft.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Acknowledgments

This research was funded by Yulin Scientific Research and Technology Development Plan, grannumber 20220653.

Ethical approval of the research and informed consent

Written informed consent was obtained from all individuals prior to enrollment.

Conflict of interest

The authors declare no conflict of interest.

References

1. Tan Y, Tan Y, Li J, et al. (2021) Combined IFN-γ and IL-2 release assay for detect active pulmonary tuberculosis: a prospective multicentre diagnostic study in China. *J Transl Med* 19: 1–8. https://doi.org/10.1186/s12967-021-02970-8
2. Fenhua J, Daohui W, Hui L, et al. (2021) Diagnostic value of combined pleural interleukin-33, adenosine deaminase and peripheral blood tuberculosis T cell spot detection TB for tuberculous pleurisy. *Bmc Infect Dis* 21: 861. https://doi.org/10.1186/s12879-021-06575-w
3. WHO (2023) Global Tuberculosis Report 2023. Available from: https://www.hncdc.com.cn/sitesources/sjk/upload/202312/20231228163632873 76.pdf.
4. Zhang M, Xiong D, Li H, et al. (2018) Diagnostic value of T-Spot TB combined with INF-gamma and IL-27 in tuberculous pleurisy. *Exp Ther Med* 15: 1871–1874. https://doi.org/10.3892/etm.2017.5464
5. Bian Y, Deng M, Zhang Q, et al. (2022) Global trends of research on tuberculous pleurisy over the past 15 years: A bibliometric analysis. *Front Cell Infect Microbiol* 12: 9937811. https://doi.org/10.3389/fcimb.2022.937811
6. Ma Z, Ji X, Yang H, et al. (2020) Screening and evaluation of Mycobacterium tuberculosis diagnostic antigens. *Eur J Clin Microbiol* 39: 1959–1970. https://doi.org/10.1007/s10096-020-03951-3
7. Choe J, Shin SH, Jeon K, et al. (2024) Features which discriminate between tuberculosis and haematologic malignancy as the cause of pleural effusions with high adenosine deaminase. *Resp Res* 25: 17. https://doi.org/10.1186/s12931-023-02645-6
8. Zhang X, Meng Q, Miao R, et al. (2022) The diagnostic value of T cell spot test and adenosine deaminase in pleural effusion for tuberculous pleurisy: A systematic review and meta-analysis. *Tuberculosis (Edinb)* 135: 102223. https://doi.org/10.1016/j.tube.2022.102223
9. Antonangelo L, Faria CS, Sales RK (2019) Response to: Necessity of co-operation between pulmonologists and internists in tuberculous pleurisy diagnosis. *Expert Rev Respir Med* 13: 1039. https://doi.org/10.1080/17476348.2019.1667235

10. Shi H, Yang L, Zhang F, et al. (2023) Diagnostic Value of CD25, CD69, and CD134 on Tuberculosis-Specific Antigen-Stimulated CD4+ T Cells for Tuberculous Pleurisy. *J Immunol Res* 2023: 5309816. https://doi.org/10.1155/2023/5309816
11. Manbenmad V, So-ngern A, Chetchotisakd P, et al. (2023) Evaluating anti-GPL-core IgA as a diagnostic tool for non-tuberculous mycobacterial infections in Thai patients with high antibody background. *Sci Rep* 13: 1883. https://doi.org/10.1038/s41598-023-45893-8
12. Li J, Zhou K, Duan H, et al. (2022) Value of D-dimer in predicting various clinical outcomes following community-acquired pneumonia: A network meta-analysis. *Plos One* 17: e263215. https://doi.org/10.1371/journal.pone.0263215
13. Feng M, Sun F, Wang F, et al. (2019) The diagnostic effect of sequential detection of ADA screening and T-SPOT assay in pleural effusion patients. *Artif Cells Nanomed Biotechnol* 47: 3272–3277. https://doi.org/10.1080/21691401.2019.1647221
14. Li X, Qin Y, Ye W, et al. (2021) Diagnostic performance of D-dimer in predicting pulmonary embolism in tuberculous pleural effusion patients. *BMC Pulm Med* 21: 177. https://doi.org/10.1186/s12890-021-01546-y
15. Dewi DNSS, Mertaniasih NM, Soedarsono, et al. (2023) Antibodies against native proteins of Mycobacterium tuberculosis can detect pulmonary tuberculosis patients. *Sci Rep* 13: 12685. https://doi.org/10.1038/s41598-023-39436-4
16. Rabbi MF, Ahmed MN, Patowary MSA, et al. (2023) Pleural fluid adenosine deaminase to serum C-reactive protein ratio for diagnosing tuberculous pleural effusion. *BMC Pulm Med* 23: 349. https://doi.org/10.1186/s12890-023-02694-z
17. Kang W, Yu J, Du J, et al. (2020) The epidemiology of extrapulmonary tuberculosis in China: A large-scale multi-center observational study. *Plos One* 15: e0237753. https://doi.org/10.1371/journal.pone.0237753
18. Antonangelo L, Faria CS, Sales RK. (2019) Tuberculous pleural effusion: diagnosis & management. *Expert Rev Resp Med* 13: 747–759. https://doi.org/10.1080/17476348.2019.1637737
19. Jiang CG, Wang W, Zhou Q, et al. (2020) Influence of age on the diagnostic accuracy of soluble biomarkers for tuberculous pleural effusion: a post hoc analysis. *BMC Pulm Med* 20: 178. https://doi.org/10.1186/s12890-020-01219-2
20. El-Habashy MM, Elmahalawy II, Sonbol A (2014) Value of D-dimer and alkaline phosphatase in the diagnosis of pleural effusion. *Egypt J Chest Dis Tu* 63: 869–872. https://doi.org/10.1016/j.ejcdt.2014.07.008
21. Huang X, Li D, Liu F, et al. (2021) Clinical significance of D-dimer levels in refractory Mycoplasma pneumoniae pneumonia. *BMC Infect Dis* 21: 14. https://doi.org/10.1186/s12879-020-05700-5
22. Matveychuk A, Rashid G, Fridman Z, et al. (2012) Pleural ELFA D-dimer assay: A surrogate marker for malignant pleural effusion. *Thromb Res* 129: 648–651. https://doi.org/10.1016/j.thromres.2011.07.036
23. Kaisermann MC, Sardella IG, Trajman A, et al. (2005) IgA antibody responses to Mycobacterium tuberculosis recombinant MPT-64 and MT-10.3 (Rv3019c) antigens in pleural fluid of patients with tuberculous pleurisy. *Int J Tuberc Lung Dis* 9: 461–466.

24. Cázares-Sosa FR, Hernández-Solís A, Andrés-Dionicio AE, et al. (2019) Comparative analysis of antibodies and lymphocytes in pulmonary tuberculosis patients with negative and positive cultures. *J Infect Dev Ctries* 13: 28–34. https://doi.org/10.3855/jidc.10583
25. Da Silva RJ, Da Silva Corrêa R, Sardella IG, et al. (2019) IgA and IgG antibody detection of mycobacterial antigens in pleural fluid and serum from pleural tuberculous patients. *BMC Immunol* 20: 36. https://doi.org/10.1186/s12865-019-0315-y

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