ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

Thrice Monthly Volume 13 Number 19 July 6, 2025

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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Peer Reviewer of *World Journal of Clinical Cases*, Saurabh Jain, Associate Professor, MD, Department of Prosthetic Dental Sciences, College of Dentistry, Jazan University, Jazan 45142, Saudi Arabia. drsaurabhjain79@gmail.com

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Salim Surani

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
July 6, 2025

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World J Clin Cases 2025 July 6; 13(19): 101850

DOI: 10.12998/wjcc.v13.i19.101850

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Total adenosine deaminase cases as an inflammatory biomarker of pleural effusion syndrome

Bernardo Henrique Ferraz Maranhão, Cyro Teixeira da Silva Junior, Jorge Luiz Barillo, Joeber Bernardo Soares Souza, Patricia Siqueira Silva, Roberto Stirbulov

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D, Grade D

Novelty: Grade C, Grade C

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade C, Grade C

P-Reviewer: Mohsen Hammad DB; Ulasoglu C

Received: September 28, 2024

Revised: November 4, 2024

Accepted: March 4, 2025

Published online: July 6, 2025

Processing time: 171 Days and 16.7 Hours

Bernardo Henrique Ferraz Maranhão, Department of Specialized Medicine, Federal University of the State of Rio de Janeiro, Rio de Janeiro 20270004, State of Rio de Janeiro, Brazil

Cyro Teixeira da Silva Junior, Medical Clinics, Federal Fluminense University, Niteroi 24020080, Rio de Janeiro, Brazil

Jorge Luiz Barillo, Department of Thoracic Surgery, General Hospital Santa Teresa, Petropolis 25680-003, Rio de Janeiro, Brazil

Joeber Bernardo Soares Souza, Medical Clinics, Antonio Pedro University Hospital, Niteroi 24020-080, Rio de Janeiro, Brazil

Patricia Siqueira Silva, Professor Mazzini Bueno Tuberculosis Research and Assistance Center, Federal Fluminense University, Niteroi 24020-080, Rio de Janeiro, Brazil

Roberto Stirbulov, Department of Clinics, Rua Baronesa de Itu, São Paulo 1231001, São Paulo, Brazil

Corresponding author: Cyro Teixeira da Silva Junior, MD, PhD, Full Professor, Medical Clinics, Federal Fluminense University, 13 Conceição Avenue, State of Rio de Janeiro, Niteroi 24020080, Rio de Janeiro, Brazil. ctsilvajunior@predialnet.com.br

Abstract

BACKGROUND

Although inflammatory diseases commonly affect the pleura and pleural space, their mechanisms of action remain unclear. The presence of several mediators emphasizes the concept of pleural inflammation. Adenosine deaminase (ADA) is an inflammatory mediator detected at increased levels in the pleural fluid.

AIM

To determine the role of total pleural ADA (P-ADA) levels in the diagnosis of pleural inflammatory diseases.

METHODS

157 patients with inflammatory pleural effusion (exudates, n = 124, 79%) and non-inflammatory pleural effusion (transudates, n = 33, 21%) were included in this observational retrospective cohort study. The P-ADA assay was tested using a

kinetic technique. The performance of the model was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The ideal cutoff value for P-ADA in pleural inflammation was determined using the Youden index in the ROC curve.

RESULTS

The transudates included congestive heart failure (n = 26), cirrhosis of the liver with ascites (n = 3), chronic renal failure (n = 3), and low total protein levels (n = 1). The exudate cases included tuberculosis (n = 44), adenocarcinoma (n = 37), simple parapneumonic effusions (n = 15), complicated parapneumonic effusions/empyema (n = 8), lymphoma (n = 7), and other diseases (n = 13). The optimal cutoff value of P-ADA was ≥ 9.00 U/L. The diagnostic parameters as sensitivity, specificity, positive and negative predictive values, positive and negative likelihood values, odds ratio, and accuracy were 77.69 (95%CI: 69.22-84.75); 68.75 (95%CI: 49.99-83.88); 90.38 and 44.90 (95%CI: 83.03-95.29; 30.67-59.77); 2.48 and 0.32 (95%CI: 2.21-11.2; 0.27-0.51); 7.65 (95%CI: 0.78-18.34), and 75.82 (95%CI: 68.24-82.37), respectively (χ^2 = 29.51, P = 0.00001). An AUC value of 0.8107 (95%CI: 0.7174-0.8754; P = 0.0000) was clinically useful. The Hosmer-Lemeshow test showed excellent discrimination.

CONCLUSION

P-ADA biomarker has high diagnostic performance for pleural inflammatory exudates.

Key Words: Pleural effusion; Biomarker; Adenosine deaminase; Inflammation; transudate; Exudate

Core Tip: Non-specialists find it difficult to diagnose pleural effusions. Although diagnosing the syndrome through imaging is simple, determining the cause is more difficult. To treat pleural disease as soon as possible, it is crucial to determine whether it is inflammatory. To our knowledge, this study is the first in Brazil and the world to establish a reference value with strict statistical criteria to classify inflammatory pleural effusion syndrome.

Citation: Maranhão BHF, Junior CTDS, Barillo JL, Souza JBS, Silva PS, Stirbulov R. Total adenosine deaminase cases as an inflammatory biomarker of pleural effusion syndrome. *World J Clin Cases* 2025; 13(19): 101850
URL: https://www.wjgnet.com/2307-8960/full/v13/i19/101850.htm
DOI: https://dx.doi.org/10.12998/wjcc.v13.i19.101850

INTRODUCTION

Pleural effusion syndrome (PES) is an excess of pleural fluid (PF) between the layers of the pleura[1]. Patients with active pleural inflammation or pleurisy complain of acute pain, localized, increasing, or decreasing in intensity, with breathing or coughing. Pleuritic pain tends to subside when an effusion develops. However, the most important clinical effect of pleural effusion is shortness of breath, which can significantly reduce quality of life[1].

Identifying whether a PES is an exudate with inflammatory diseases or a transudate with noninflammatory diseases is the first step in determining its cause. This classification system has important diagnostic implications[1]. Transudative pleural effusion usually represents an outward sign of disease in another organ. Therefore, its main causes are renal, hepatic, and cardiac disorders[1]. Transudate occurs because of hydrostatic or oncotic pressure imbalance. Inflammation was not observed. Therefore, transudates have low cell counts and protein content. Usually, a surgical procedure for PF or tissue extraction is not necessary for causal diagnosis[1]. Exudates occur secondary to diseases that cause inflammation or infection in the pleural space and tissue with increased pleural vascular permeability. Vascular changes allow leukocyte diapedesis and transport of large molecules[2]. Usually, surgical procedures for the withdrawal of PF and/or tissue are necessary for diagnosis and treatment[1]. Inflammatory PF can lead to severe surgical complications, such as empyema and pleural thickening[1].

An inflammation arises from the interaction between immune cells and many mediators that protect an organism from damaging stimuli. Adenosine is an endogenous purine nucleoside that modulates several physiological processes. It is considered a key mediator of the immune response. Under physiological conditions, the extracellular concentrations of adenosine are maintained at low levels as a result of rapid metabolism. However, the highest levels were observed under conditions of increased metabolic demand, such as hypoxia, tissue injury, and inflammation. Under resting conditions, some adenosine triphosphate (ATP) is dephosphorylated to adenosine; however, dangerous stimuli can increase the intracellular conversion of ATP to adenosine. Once released into the extracellular space, adenosine can be deaminated to inosine by adenosine deaminase enzyme (ADA) or taken up directly by cells by specific nucleoside transporters and rephosphorylated to ATP[3-5].

ADA is an important biomarker in organic fluids of cellular and humoral immune responses and translates to monocyte and macrophage activation. It is also essential for the proliferation and differentiation of lymphoid cells, especially T cells, in inflammatory diseases[6]. ADA induces the production of inflammatory cytokines such as tumor

necrosis factor alpha, transforming growth factor beta, and interferon gamma. In humans, total ADA has two isoforms: ADA1 and ADA2. ADA1 is found in all human tissues. It is highly expressed by T and B cells and accounts for approximately 90% of total ADA activity. The primary role of ADA1 is to regulate the intracellular adenosine levels. ADA2 exhibits autocrine activity. It is involved in the maturation of monocytes in anti-inflammatory macrophages (M2), dendritic cells, B cells, neutrophils, and CD26-Tregs. There is indirect evidence of the possible role of ADA2 as an endothelial growth factor[5].

ATP, adenosine, and ADA modulate purinergic responses during inflammation. ADA levels increased in response to higher adenosine levels. As a result, the inflammatory response is amplified[7,8]. Specific studies have demonstrated a relationship between pleural ADA (P-ADA) levels and pleural inflammatory disease. Thus, P-ADA could be relevant in the management of PES. It can indicate the inflammatory nature of pleural effusions. Different studies in several countries conclude that higher levels of P-ADA indicate a greater likelihood of pleural tuberculosis[9,10]. However, elevated P-ADA levels are not exclusive to pleural tuberculosis. Very high levels (> 150 U/L) of P-ADA are unusual in pleural tuberculosis. Alternative diagnoses are bacterial empyema, lymphoma, leukemia, and multiple myeloma[10,11].

Although inflammatory and infectious diseases frequently involve the pleural space and pleura, the immunological and molecular mechanisms underlying pleural involvement remain unknown[7]. Some diseases are associated with the infiltration of different types of immune cells, such as neutrophils, eosinophils, and lymphocytes. In addition to infiltrating cells, mesothelial cells actively participate in pleural inflammation by releasing various mediators and proteins. Increased levels of several inflammatory mediators have been detected in PF, including lipid, cytokines, and proteins. The presence of these mediators emphasizes the concept of pleural inflammation. Moreover, certain inflammatory mediators appear to characterize a specific cause of PES[12]. This study aimed to determine the role of total pleural adenosine deaminase (P-ADA, U/L; adenosine amino hydrolase; enzyme code 3.5.4.4) level as a biomarker for the diagnosis of pleural inflammatory diseases.

MATERIALS AND METHODS

The STARD and STROBE recommendations were followed in the study design, findings, and reporting[13,14]. Our investigation was a traditional observational retrospective cohort analysis or chart review of a type series of cases performed at two hospitals in Rio de Janeiro, Brazil, between March 2015 and December 2019.

Inclusion and exclusion criteria

Clinical and imaging evaluations were performed to confirm the causative diagnosis of PES[1]. An initial thoracentesis procedure was performed, followed by video-assisted thoracoscopic surgery (VATS) and histopathological analysis if necessary[1]. The diagnosis of pleural transudate was confirmed using the Maranhão and Silva Junior criterion[15]. This was validated according to Light's criterion, but with dosages of total protein and total lactate dehydrogenase (LDH) only in the PF[16]. The exclusion criteria were absolute contraindications or refusal to undergo thoracentesis or VATS, hemolysis in PF, chronic renal failure, jaundice, PES of unknown cause, and use of immunosuppressive medications. This is because ADA levels may be modulated by antiretroviral therapy in HIV subjects[6].

ADA assay

Adequate collection, storage, and processing of PF were observed for accurate diagnosis. The PF used for the P-ADA test was non-hemolyzed[17]. The PF preserved at −20 °C were thawed, and several biomarkers in the samples were measured. The ADA was performed using a commercial kit with a kinetic approach. Briefly, the P-ADA assay is based on the enzymatic deamination of adenosine to inosine, which is then converted to hypoxanthine by purine nucleoside phosphorylase. Hypoxanthine is transformed to uric acid and hydrogen peroxide by xanthine oxidase. Hydrogen peroxide reacts with N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline and 4-aminoantipyrine in the presence of peroxidase to generate a quinone dye, which was measured in a kinetic manner. One unit of P-ADA was defined as the amount of ADA that generates one μmol of inosine from adenosine per minute at 37 °C. The assay was linear from 0-200 U/L ($r^2 > 0.99$). Ultracentrifugation did not affect the results. ADA was stable for one week at 4 °C. The reagents were stable for one year if stored at 2–8 °C in amber flasks. ADA activity in the serum of healthy humans has a reference value range of 0–15 U/L[18]. This ADA assay with automated kinetic methods was also validated for various organic fluids, and there were no differences in the diagnostic accuracy for pleural tuberculosis between the classic manual method of Giusti and this Diazyme ADA assay method[19,20].

Statistical approach

Descriptive and inferential statistics, with receiver operating characteristic (ROC) curve analysis, were analyzed using a combination of the statistical software including NCSS version 2022, GraphPad version 5.0, and MedCalc version 20.11. The Grubbs double-sided method, which examines the most extreme values on both sides of the data, was used to detect the outliers. The normality and variance homogeneity of the data were evaluated using the Shapiro-Wilk test (W). An unpaired *t*-test with standard deviation was used to compare the means of the two groups with a Gaussian distribution. The median and interquartile range were used to express non-normal distributions (IQR). When the sample was not normally distributed, the Wilcoxon-Mann-Whitney *U* test was used to compare data. The non-parametric Kruskal-Wallis (K-W) test (*H*-test) was used to check the hypothesis that several unpaired samples originated from the same population. A *post-hoc* test, according to Dunn's test, was performed when the K-W test had a *P* value less than the selected significance level. The χ^2 test was used to compare groups and proportions. The *P*-value for both sides was 0.05.

Sample size and sampling technique

The sample size calculation was based on the expected area under the ROC curve (AUC > 0.50), null value of the AUC (AUC = 0.50), and ratio of sample sizes between positive and negative cases (n = 2) according to the MedCalc software [21]. For an α-level of 0.05 and a β-level of 0.20 (statistical power = 80%), a sample of 19 cases was required in the positive group (exudates) and 38 in the negative group (transudates), giving a total of 57 cases. The sample size in this study consisted of 157 PF samples from 157 patients with proven transudative or non-inflammatory diseases used as controls (n = 33) and exudative pleural effusions with inflammatory diseases of several causes (n = 124). Bias was avoided because the data was recorded in a series of patients only with PES (cases and controls) with the purpose of management after a standard diagnostic protocol. In case series, information bias can occur but may be reduced by selecting an appropriate control group[14].

Optimal P-ADA threshold

The nonparametric technique of DeLong *et al*[22] was used to obtain the ROC curve to study the diagnostic parameters of P-ADA as an inflammatory biomarker. Youden index was used to determine the optimal P-ADA threshold (J). The J value is the highest sum of sensitivity and specificity[22,23].

Model performance, discrimination, and potential clinical usefulness

Model performance refers to how well a statistical model fits the data used to build it. It was evaluated using metrics such as AUC-ROC and diagnostic parameters with 95%CI[13,14]. Discrimination refers to the ability of a biomarker to distinguish between individuals with and without a disease or condition. Discrimination was classically evaluated using AUC-ROC (C-statistic) with 95%CI[24,25]. Hosmer and Lemeshow proposed the following classifications as general rules for the discrimination accuracy of a logistic regression model based on the AUC space[24]: Excellent discrimination (0.90-1.0), very good discrimination (0.80-0.90), good discrimination (0.70-0.80), sufficient discrimination (0.60-0.70), poor discrimination (0.50-0.60), and biomarker not useful (0.00–0.50). Clinical usefulness refers to whether a biomarker has practical utility in a clinical setting, such as in helping to diagnose a disease, predicting disease progression, or guiding treatment decisions. The potential clinical usefulness of P-ADA was evaluated using the AUC for diagnostic biomarkers in general, an AUC > 0.75 is clinically useful[26].

RESULTS

The 157 cases and causes of pleural exudates and transudates are represented with demographic information in Table 1. Exudates were more common than transudates [124 (79%) *vs* 33 (21%) patients, respectively]. Regarding the male sex, there was no significant difference in the proportion, as calculated by the χ^2 test, between exudates and transudates (P = 0.9415). The same was observed for the female sex in both groups (P = 0.9416). In the χ^2 test, only adenocarcinoma and lymphomas were significant (P = 0.0021 and P = 0.0003, respectively) for male sex.

Many quantitative studies on clinical biomarkers have demonstrated age-related changes in reference values. Early life, adolescence, old age, and after the menopause are important periods of life[27]. Regarding age, there was a significant difference in the medians (U = 895, P < 0.0001) between exudates (58.0; IQR: 41.5–73.5) and transudates (76.0; IQR: 63.0–86.25). However, it was not an objective of this study to evaluate a cutoff for P-ADA in relation to the range of ages for inflammatory diseases in PES.

The pattern of missing data was MAR or missing randomly. Only 3% of exudates (cases) and 6% of transudates (controls) had missing P-ADA values. For inflammatory diseases (exudates) in a patient with lymphoma, the Grubbs test yielded an outside value of 1121.1 U/L of P-ADA. There were no digitation errors, and this value was consistent with causal diagnosis. However, a median of 18.4 U/L was used (Table 2).

Table 3 shows that the median values of P-ADA were significantly different (U = 679.5; P < 0.0001) between inflammatory (18.4 U/L, IQR: 9.85–41.4) and non-inflammatory diseases (6.85 U/L, IQR: 2.67–11.26). The values of total protein and total LDH in the PF were in agreement with the Light and Maranhão and Silva Junior criteria[15,16].

Figure 1 shows the ROC curve obtained using the method described by DeLong *et al*[22]. For diagnostic purposes with inflammatory pleural effusions, according to the Youden index, the optimal cutoff value was ≥ 9.00 U/L of P-ADA. For discrimination of the model, there was an AUC of 0.8107, a 95%CI of 0.7174-0.8754. The standard error of the mean (SE) was 0.039. The Z-value to test was 7.837, with a two-sided P-value of 0.0000. The diagnostic parameters for P-ADA, with the best cutoff point selected for pleural inflammatory diseases, are listed in Table 4.

DISCUSSION

Retrospective studies sometimes reflect routine clinical practice better than prospective studies, although they may fail to identify all eligible patients and often result in lower quality data with more missing data. In this study, the author took care of the inclusion and exclusion criteria and the statistical treatment of missing data[13].

ADA modulates the immune system and plays an important role in several diseases, including rheumatoid arthritis with ADA modulating metabolic remodeling and joint destruction; chronic pulmonary diseases with ADA participating in modulating purinergic responses; inflammatory bowel diseases with ADA involved in modulating purinergic responses; sepsis with ADA playing a key role in modulating purinergic responses; and pleural tuberculosis with ADA

Table 1 Demographic characteristics and causes of inflammatory and noninflammatory diseases in 157 patients with pleural effusion syndrome in the State of Rio de Janeiro, Brazil, from March 2015 to December 2019, *n* (%)/median (25th-75th percentiles)

Cause	Patient (*n*)	Prevalence (%)	Age	Female	Male
Non-inflammatory[1]	33	21.0	76.0 (63.0-86.25)	17.0 (52.0)	16.0 (48.0)
Inflammatory	124	79.0	58.0 (41.5-73.5)	66.0 (53.0)	58.0 (47.0)
Tuberculosis	44	28.0	39.0 (29.7-58.2)	22.0 (50.0)	22.0 (50.0)
Adenoc.	37	24.0	61.0 (45.0-77.0)	25 (68.0)	12 (32.0)
Simple PPE	15	10.0	67.0 (56.0-85.0)	6 (40.0)	9 (60.0)
CPPE/Empiema	8	5.0	52.5 (33.5-78.75)	2 (25.0)	6 (75.0)
Lymphoma	7	4.0	53.0 (47.0-63.0)	0 (0.0)	7 (100.0).
Squamous cell	7	4.0	66.0 (55.0-66.0)	4 (57.0)	3 (43.0)
Other[2]	6	4.0	73.0 (53.0-79.0)	4 (67.0)	2 (33.0)
Total	157	100.0	58.0 (41.75-73.25)	80 (51.0)	77 (49.0)

[1]Transudates: Congestive heart failure (n = 26), chronic renal failure (n = 3), cirrhosis of liver with ascites (n = 3), and serum low total protein levels (n = 1).
[2]Other exudates: Pseudo-Meigs syndrome (n = 1), Dressler's syndrome (n = 3), chylothorax (n = 1), leukemia (n = 1).
CPPE: Complicated parapneumonic effusions.

Table 2 Levels of pleural adenosine deaminase evaluated in 157 cases of pleural effusion syndrome confirmed with reference standard diagnostic tests[1]

Cause	Pleural fluids–sample size (*n*)	P-ADA (medians) (U/L)	25th-75th percentile
Non-Inflammatory disease (control)			
Transudate	33	6.85	2.67-11.26
Inflammatory disease (case)	124	18.4	9.25-41.4
Tuberculosis	44	42.0	32.9-61.9
Adenocarcinoma	37	9.75	6.7-14.9
Simple parapneumonic effusion	15	9.38	5.68-9.97
CPPE and empyema	8	32.9	16.0-61.7
Lymphoma	7	401.2	11.2-990.5
Squamous cell carcinoma	7	13.11	11.0-28.2
Other	6	15.2	7.4-49.0

[1]Shapiro-Wilk test for pleural adenosine deaminase (W = 0.347, P < 0.0001). K-W test for pleural adenosine deaminase (H = 81.34, P < 0.0001) and Dunn's test with P < 0.05: Tuberculosis *vs* transudates, *vs* simple PPE, and *vs* adenocarcinoma, and P > 0.05: CPPE and empyemas, lymphomas, squamous cell carcinoma, and other exudates.
CPPE: Complicated parapneumonic effusions; P-ADA: Pleural adenosine deaminase.

deeply inducing the production of inflammatory cytokines in PF[4].

The pleura and the pleural space have fascinating pathophysiologies. Many pleural diseases are associated with local and systemic inflammations[7]. However, the underlying inflammatory mechanisms have not yet been elucidated. This study described the causes of various pleural inflammatory diseases. The role of adenosine deaminase as a diagnostic biomarker was evaluated using rigorous statistical methods.

As shown in Table 1, the sex proportion and median age were comparable to those reported in earlier studies[9-11]. The prevalence of tuberculosis and malignancy was similar to those reported in other studies[9-11]. Other authors have studied P-ADA in pleural inflammatory diseases from medical thoracoscopy, but tuberculosis was not in the group analyzed[28].

The P-ADA level was statistically significant in separating pleural transudates and inflammatory diseases, mainly tuberculosis, as shown in Table 2. In Brazil and other countries with an elevated incidence and prevalence of tuberculosis and other inflammatory diseases, P-ADA activity is also an accurate biomarker for tuberculous pleural effusion with false-positive results for complicated parapneumonic effusions, empyema, and lymphoma[10,29-31]. As shown in

Table 3 Laboratory analysis of adenosine deaminase, proteins, and lactate dehydrogenase in 157 cases of pleural fluids from inflammatory and non-inflammatory pleural effusion syndrome, median (25th-75th percentiles)/ mean ± SD[1]

Non-inflammatory pleural effusion (control)	Result
Total pleural ADA[a]	6.85 (2.67–11.26)
Total pleural protein[b]	2.64 ± 1.52
Total pleural LDH, median[c]	190.5 (100.5–278.8)
Inflammatory pleural effusion (case)	
Total pleural ADA[a]	18.4 (9.25–41.4)
Total pleural protein[b]	5.05 (4.47–5.60)
Total pleural LDH[c]	568.5 (400.3–822.5)

[1]The Shapiro–Wilk test (W) rejected the normal data from pleural total adenosine deaminase, and pleural total LDH in exudate cases ($P < 0.05$), but not pleural total protein in controls ($P = 0.0881$).
[a]$P < 0.0001$.
[b]$P < 0.0001$, after logarithmic transformation of data.
[c]$P < 0.0001$.
ADA: Adenosine deaminase; LDH: Lactate dehydrogenase; IQR: Interquartile range.

Table 4 Measures of diagnostic parameters of adenosine deaminase following selection of the best cutoff point for pleural inflammatory diseases according to the Youden index in the receiver operating characteristic curve

Diagnostic parameter	Result (%)[2]	95%CI
Best cutoff (U/L)	≥ 9.00	-
Sensitivity	77.69	69.22-84.75
Specificity	68.75	49.99-83.88
Positive predictive value or precision	90.38	83.03-95.29
Negative predictive value	44.90	30.67-59.77
Positive likelihood ratio[1]	2.48	2.21-11.2
Negative likelihood ratio[1]	0.32	0.27-0.51
Diagnostic odds radio	7.65	0.78-18.34
Diagnostic or predictive accuracy[1]	75.82	68.24-82.37
Disease prevalence[1]	50.48	44.78-56.17

[1]These values are dependent on disease prevalence.
[2]$\chi^2 = 29.5138$ (2-Sided P-value= 0.00001). Statnote: The Youden index at the receiver operating characteristic curve is the optimal cutoff value that provides the best tradeoff between sensitivity and specificity.

Table 2, the Kolmogorov-Smirnov test was significant for the P-ADA classification of inflammatory and non-inflammatory diseases (H = 81.34, $P < 0.0001$). Dunn's test was significant ($P < 0.05$) for pleural tuberculosis *vs* transudates, simple PPE, and adenocarcinoma. However, the difference was not significant ($P > 0.05$) for pleural tuberculosis vs. CPPE, empyemas, lymphomas, squamous cell carcinoma, and other exudates.

In adenocarcinoma, tumor cells induce immune suppression through the accumulation of regulatory T cells (Tregs) and many other mechanisms[32]. The increase in total P-ADA levels in pleural tuberculosis is largely caused by the ADA-2 isoenzyme present in monocytes and macrophages in response to pleural infection or inflammation caused by *Mycobacterium tuberculosis*[29]. Inflammatory processes in pneumonia occur in the peripheral alveolar spaces. Increased vascular permeability of local capillaries may lead to increased fluid accumulation in the lungs and pleural cavities. In addition, locally released inflammatory mediators may diffuse into the subpleural or pleural tissue, resulting in the local activation of constitutive cells such as mesothelial cells. Moreover, circulating inflammatory cells migrate into the pleural cavity. The predominance of an inflammatory white cell count within PF is of limited diagnostic value[1,30]. However, immunocytochemical analysis should be used to differentiate malignant cell types[1].

ADA-1 Levels play an important role in the differentiation of lymphoid cells, and ADA-2 in the maturation of monocytes into macrophages[4,29]. P-ADA activity in T-cell lymphomas is similar to that in B-cell lymphoma[31]. The median P-ADA level for the lymphoma patients was 401.2 U/L (Table 2). When total P-ADA levels are greater than 150

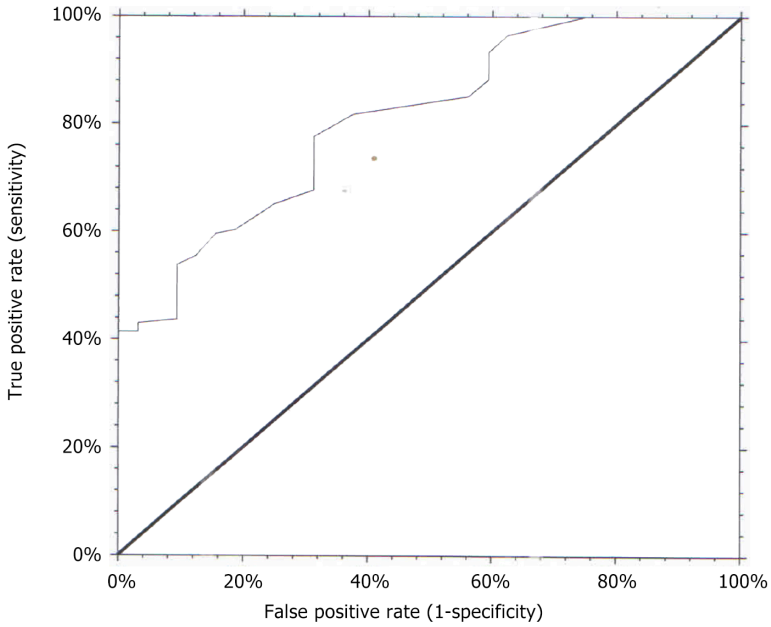

Figure 1 Nonparametric receiver operating characteristic curve of pleural adenosine deaminase for pleural inflammatory diseases. The selection criterion was the Youden index [J = 0.4644; distance to the receiver operating characteristic (ROC) curve corner = 0.3840]. The optimal cutoff value for ROC curve concavity was ≥ 9.00 U/L of pleural adenosine deaminase. Evaluation metric for checking the model's performance: Area under the curve (AUC), 0.8107; 95%CI: 0.7174-0.8754; SE: 0.039; *Z*-value to test (AUC ≠ 0.5), 7.837; 2-Sided *P*-value, 0.0000.

U/L, the differential diagnosis is CPPE, empyema, and lymphoid malignancies instead of tuberculous pleural effusion [31]. Therefore, in patients with cancer risk, high P-ADA levels should be interpreted with caution[33].

The median P-ADA levels were significantly lower in non-inflammatory diseases or transudates (6.85 U/L) than in inflammatory diseases or exudates (18.4 U/L) as shown in Table 3. The explanation for these findings is that a transudate, as opposed to an exudate, indicates that the pleural mesothelium is affected by systemic and/or pulmonary pressures. The barrier permeability characteristics were maintained. ADA has a low molecular radius of 29.10 angstroms and weight of 42 kDa. Therefore, transpleural transport from sera occurs *via* diffusion[2].

Depending on the objectives of biomarker dosage, several methods for selecting an optimal cutoff value have been proposed by expert authors[23,34]. The repercussions of receiving a false-positive diagnostic test result are serious. Therefore, it was crucial to choose an optimal cutoff value of P-ADA greater than or equal to 9.00 U/L for inflammatory diseases with high precision (90%) using the Youden index (Table 4). It is important to explain that there is no disagreement between the cutoff value greater than or equal to 9.0 U/L of P-ADA calculated by the ROC curve using the Youden criterion for pleural inflammatory diseases and the cut-off value found in the literature greater than or equal to 30.0 U/L. This last cutoff value of P-ADA was calculated using several criteria for the diagnosis of pleural tuberculosis [10]. Huan *et al*[35] established a P-ADA cutoff value of 29.6 U/L for tuberculosis pleural effusion (TPE). The authors concluded that optimizing the utility of P-ADA helps clinicians diagnose TPE when other initial laboratory workups are inconclusive. Masood *et al*[36] found a cutoff level for P-ADA of 30 U/L for tuberculosis PF with high sensitivity (71%) and specificity (82%).

The AUC indicates the potential of a biomarker. For clinical and practical purposes, we need to dichotomize the test results to classify the subjects as diseased or nondiseased. Therefore, the choice of an 'optimal' cutoff point for dichotomizing a continuous biomarker cannot be arbitrary. Youden's index is a better criterion because it selects biomarkers with larger values of both sensitivity and specificity[37]. The discrimination with an AUC of 0.8107 was very good according to the Hosmer–Lemeshow scale[24]. An AUC greater than 0.75 was clinically useful[26]. Another metric for evaluating the clinical usefulness of a biomarker is the clinical utility index, established by Åsberg *et al*[38]. There is some overlap between the evaluations of different aspects of the biomarker performance. Therefore, it is important to evaluate biomarkers using multiple metrics and consider the context in which they will be used[13,14]. In addition to the AUC, other values derived from the ROC curve are useful to define diagnostic characteristics of a biomarker. In contrast to diagnostic accuracy, predictive values provide more specific information of a biomarker. A high positive predictive value (PPV ≥ 80%) would be adequate to perform a diagnostic and initiate a treatment[39,40]. The PPV value found in this work for inflammatory PF was > 90%, as shown in Table 4. Yavuz *et al*[41] found a high sensitivity (91%) with a cutoff level de P-ADA greater or equal to 20.0 U/L for TPE. However, they observed a PPV of 67% and a specificity of 75%.

Despite its observational methodology, this study had limitations. Before adopting accurate models in clinical practice, additional studies using data from many hospitals are required for external validation[13,14]. Thus, a multicenter, worldwide study with accurately diagnosed cases with the highest number of subjects is necessary.

The future perspectives are positive. First, our diagnostic model is crucial in clinical practice and can be used to identify inflammatory pleural effusions with acceptable discrimination and predictive power. In addition, P-ADA levels also had high diagnostic performance for pleural tuberculosis worldwide (VPP > 80%) and rendered closed-needle

pleural biopsy unnecessary[9,10,20,33,35,42]. Second, purinergic signaling plays an important role in lung inflammation. The expression of adenosine receptors is altered in patients with airway inflammation. Adenosine receptor antagonists such as theophylline have therapeutic benefits in several inflammatory pulmonary diseases. Adenosine signaling has also been implicated in regulating the function of inflammatory cells such as macrophages and neutrophils[43]. Third, physiologically and acutely increased adenosine levels are associated with beneficial effects such as vasodilatation and a decrease in inflammation. In contrast, chronic overproduction of adenosine occurs under pathological conditions and is responsible for the adverse effects of adenosine associated with chronic lung and pleural inflammation, fibrosis, and tissue injury[44].

CONCLUSION

This study concluded that the P-ADA biomarker with the cutoff selected (≥ 9.0 U/L) using ROC curve analysis with the Youden index criterion had a high diagnostic performance for pleural inflammatory exudates.

ACKNOWLEDGEMENTS

The author, Cyro Teixeira da Silva Junior, is grateful to Professor Charles E. Metz (in memoriam) from the University of Chicago Medical Center for suggestions with ROC curve analysis that helped improve several papers in your academic career.

FOOTNOTES

Author contributions: Maranhão BHF and Stirbulov R executed the idea and planned, organized, and supervised the study; Souza JBS, Barillo JL, and Silva PS were responsible for data collection; da Silva Junior CT wrote the earlier and final drafts of the manuscript and was responsible for statistical analysis and interpretation of the results. All authors have read and approved the manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of the Faculty of Medicine, Federal Fluminense University (number 48946121.9.0000.5243).

Informed consent statement: Written informed consent was obtained from all participants before the study.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest regarding the content of this article. Funding The authors received no financial support for the research, authorship, or publication of this article.

Data sharing statement: sharing statement: The corresponding author can provide datasets that support the conclusions of this study upon request. The original datasets are not accessible to the general public because they contain data that may jeopardize the privacy of research participants.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement- checklist of items.

Country of origin: Brazil

ORCID number: Bernardo Henrique Ferraz Maranhão 0000-0002-4793-552X; Cyro Teixeira da Silva Junior 0000-0003-0067-1341; Jorge Luiz Barillo 0000-0002-6654-4997; Joeber Bernardo Soares Souza 0000-0002-1494-1050; Patricia Siqueira Silva 0000-0002-7397-8152; Roberto Stirbulov 0000-0003-0841-8105.

Corresponding Author's Membership in Professional Societies: Sociedade Brasileira de Pneumologia.

S-Editor: Liu H
L-Editor: A
P-Editor: Zhang XD

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