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ORIGINAL ARTICLE

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Diagnostic utility of total adenosine deaminase as a biomarker in patients with transudates from pleural effusion syndrome

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ABSTRACT

Introduction: Accurately identifying pleural fluid as either transudate or exudate is critical. P-ADA, or the total pleural adenosine deaminase enzyme, is a reliable biomarker for distinguishing between transudates and exudates. **Objective:** This study aimed to identify P-ADA diagnostic parameters for pleural transudate diagnosis by establishing a cutoff value using the receiver operating characteristic curve. **Methods:** The P-ADA assay was performed using a kinetic technique. The performance of the model was evaluated using the area under the receiver operating characteristic curve (AUC-ROC) and diagnostic parameters. The ideal cutoff value for P-ADA in pleural transudates was determined using the Youden index in the ROC curve. **Results:** A total of 157 patients with exudative pleural effusion (n=124, 79%) and transudative pleural effusion (n=33, 21%) were included in this observational retrospective cohort study. The optimal cutoff value of P-ADA was ≤8.21 U/L. The diagnostic parameters as sensitivity, specificity, positive and negative predictive values, positive and negative likelihood values, odds ratio, and accuracy were 66.0 (95% CI, 0.48-0.82); 81.0 (95% CI, 0.73-0.87); 48.0 and 90.0 (95% CI, 0.33-0.64; 0.83-0.94); 4.9 and 0.56 (95%CI, 2.21-11.2; 0.39-0.82); 8.78 (95%CI, 0.78-18.34), and 78.0 (95%CI, 0.80-0.91), respectively (chi-square=29.51, p=0.00001). The AUC was 0.8203 (95% CI, 0.7270-0.8838); SE, 0.0393; Z-value to test, 8.157; p<0.0001. An AUC >0.75 was clinically useful. The Hosmer-Lemeshow test showed excellent discrimination. **Conclusion:** P-ADA levels can be used to obtain reliable diagnostic and predictive parameters for discriminating between transudative and exudative pleural effusions.

Keywords: pleural effusion; biomarkers; adenosine deaminase; extracellular fluid; cross-sectional studies; Indicators (Statistics).

INTRODUCTION

Identifying whether a pleural effusion syndrome (PES) is an exudate or a transudate is the first step in determining the etiology[1]. A transudative pleural effusion usually represents an outward sign of disease in another organ. So, the main causes are renal, hepatic, and cardiac disorders[2,3].

Adenosine deaminase (ADA) is an important enzyme in the purine salvage pathway. In humans, 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 intracellular adenosine levels. ADA2 has autocrine activity, induces monocyte proliferation, and aids in the differentiation of anti-inflammatory macrophages (M2)[4].

The total pleural adenosine deaminase (P-ADA, U/L; enzyme code, 3.5.4.4) is a reliable biomarker for distinguishing between exudates and transudates[5-7]. The "gold standard" for diagnosing exudates and transudates, because of their high sensitivity, is the criterion of Light et al.[2]. This distinction determines the differential diagnosis, therapeutic management, and pathophysiologic mechanisms that lead to the increase of fluid in the pleural cavity.

Pleural exudate occurs when the permeability of the mesothelial-microvascular/capillary barrier to macromolecules is elevated. In addition, other mechanisms are involved, such as impairment of lymphatic drainage. The pleural exudates have their origin from an obstruction in the lymphatic system, including the stomas, thoracic duct, or mediastinal lymph nodes, caused by fibrosis, malignancy, lymphatic dysfunction, as in yellow nail syndrome or lymphangioleiomyomatosis, and fibrin deposition in the later stages of a parapneumonic pleural effusion[8]. The presence of a transudate indicates that the systemic or pulmonary pressures are influencing the formation or reabsorption of pleural fluid. Therefore, the barrier permeability characteristics are maintained for transudates, and the transpleural

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transport of macromolecules is the same as that under physiological conditions[8,9]. However, to the best of our knowledge, no research has been published on a P-ADA-based cutoff criterion for transudative pleural effusion.

This study was conducted to determine the P-ADA classification threshold for pleural transudates using receiver operating characteristic (ROC) curve analysis with a nonparametric approach and Youden index criterion.

METHODS

Design

The STARD and STROBE recommendations were followed in the study design, findings, and reporting[10,11]. Our investigation was a traditional observational, retrospective cohort analysis performed at two hospitals in Rio de Janeiro, Brazil, between March 2015 and December 2019.

Ethics approval

Ethical approval for this study has been accepted by the Ethics Committee of the Faculty of Medicine, Federal Fluminense University under number 48946121.9.0000.5243.

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 a video-assisted thoracoscopic surgery (VATS) and a histopathological analysis if necessary[1]. Laboratory evaluations of pleural fluids, such as P-ADA paired with other disease biomarkers, were also performed. The diagnosis of transudate was confirmed using the Maranhão and Silva Junior

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criterion[3]. This criterion was validated according to Light's criterion but with dosages of total protein and total lactate dehydrogenase (LDH) only in pleural fluid[2,3].

The adequate collection, storage, and processing of the pleural fluids were observed for an accurate diagnosis[12]. The exclusion criteria were absolute contraindications or refusal to undergo thoracentesis or VATS; use of immunosuppressive medications; hemolysis in pleural liquids; jaundice; chronic renal failure because ADA is inhibited by urea; HIV infection; use of drugs such as allopurinol, diuretics, acyclovir, aspirin, or diclofenac; and pleural effusion of unknown cause[13-15].

P-ADA assay

A commercial kit was used to perform the P-ADA assay using a kinetic approach. Briefly, the P-ADA assay is based on the enzymatic deamination of adenosine to inosine, which is converted to hypoxanthine by purine nucleoside phosphorylase. Hypoxanthine is transformed to uric acid and hydrogen peroxide by xanthine oxidase. Hydrogen peroxide reacted with N-Ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline and 4-aminoantipyrine (4-AA) in the presence of peroxidase to generate quinone dye, which is measured in a kinetic manner. One unit of P-ADA was defined as the amount of ADA that generates one μmole of inosine from adenosine per minute at 37 °C. The assay was linear from 0-200 U/L (r2 >0.99).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[16].

Statistical approach

Descriptive and inferential statistics, including ROC curve analysis, were produced using the statistical tools NCSS version 2022, GraphPad version 5.0, and MedCalc version

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20.11. The Grubbs double-sided method, which examines the most extreme values on both sides of the data, was used to detect outliers. The normality and variance homogeneity of the data were evaluated using the Shapiro-Wilk test (W). The median and interquartile range were used to express non-normal distributions. When the sample was not normally distributed, the Wilcoxon-Mann-Whitney U test was used to compare data. The t-test, a parametric test of difference, was used when our data were independent and normally distributed. The chi-square test was used to compare the groups and proportions. The two-sided p-value was 0.05.

Sample size

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[17]. 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 (transudates) and 38 in the negative group (exudates or controls), giving a total of 57 cases. The sample size in this study consisted of 157 pleural fluid samples from 157 patients with proven transudative (n=33) and exudative pleural effusion (n=124).

Optimal P-ADA threshold

The nonparametric technique of DeLong et al.[18] was used to analyze the ROC curve of P-ADA for the diagnosis of transudates. The Youden index was used to determine the optimal P-ADA threshold (J). The J value is the highest sum of the sensitivity and specificity[19]. Pearson's chi-square test was also used to determine the relationship or association between the transudate and the P-ADA cutoff value[20].

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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, diagnostic parameters with 95% confidence intervals, and Cohen's kappa coefficient according to the Landis and Koch guidelines[10,21].

Discrimination refers to the ability of a biomarker to distinguish between individuals with or without a disease or condition. Discrimination was classically evaluated using AUC-ROC (C-statistic) with a 95% confidence interval (CI)[22-24]. Hosmer and Lemeshow proposed the following classifications as a general rule for the discrimination accuracy of a logistic regression model based on the AUC space: 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)[22].

Clinical usefulness refers to whether a biomarker has practical utility in a clinical setting, such as helping to diagnose a disease, predicting disease progression, or guiding treatment decisions. Potential clinical usefulness can be evaluated using the AUC or clinical utility index (CUI) for diagnostic biomarkers[25]. In general, an AUC >0.75 is clinically useful[26].

RESULTS

Demographic characteristics and causes of pleural exudates and transudates

The 157 cases of pleural exudates and transudates were represented by demographic information and laboratory analyses (Table 1). Exudates were more common than transudates [124 (79 %) vs. 33 (21 %) patients]. The transudate cases included twenty-six patients with congestive heart failure, three patients with cirrhosis of the liver and ascites, three with acute renal failure, and one patient with low total protein levels. This last patient was diagnosed as pure transudate because they had other pleural biomarkers, such as a total nucleated cell count of fewer than 1000 cells per mm^3 and extrathoracic ultrasonography compatible with

transudate[1,27]. The exudates included 44 cases of tuberculosis, 37 cases of adenocarcinoma, 15 cases of simple parapneumonic effusions, 8 cases of complicated parapneumonic effusions/empyema, 7 cases of lymphoma, 7 cases of squamous cell carcinoma, and 6 cases of other exudates, which included patients with confirmed diagnoses of pseudo-Meigs' syndrome (n=1), Dressler's syndrome (n=3), chylothorax (n=1), and leukemia (n=1).

Adenosine deaminase analysis in pleural exudates and transudates

The pattern of missing data was MAR, or missing at random. Only 3% of exudates and 6% of transudates had missing P-ADA values. For the exudate of a patient with lymphoma, the Grubbs test yielded an outlier value of 1121.1 U/L of P-ADA. There were no digitization errors, and this value was consistent with the causative diagnosis. However, a median of 18.4 U/L was used instead of this result.

The median values of P-ADA were significantly different (U=679.5; p<0.0001) between exudates (18.4 U/L, IQR, 9.85 – 41.4) and transudates (6.85 U/L, IQR, 2.67 – 11.26). Regarding male sex, there was no significant difference in the proportion, as calculated by the chi-square test, between exudates and transudates (p=0.9415). The same was observed for the female sex in both groups (p=0.9416). 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).

The values of total proteins and total LDH in the pleural fluid were in agreement with the Light et al.[2] and Maranhão-Silva Junior[3] criteria (Table 1). Figure 1 shows the ROC curve obtained using the method described by DeLong et al.[18]. For diagnostic purposes with transudates, according to the Youden index (J=0.4812; distance to the ROC curve corner =0.3815), the optimal cutoff value was ≤8.21 U/L of P-ADA. For discrimination of the model, there was an AUC of 0.8203, a 95% CI of 0.7270-0.8838, an SE of 0.0393, and a Z-value to

test of 8.157 with a two-sided p value <0.0001. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular cutoff point (Figure 1). The percentage agreement between a confirmed diagnosis of transudate using the inclusion criteria and the ideal cutoff point was 78%. Cohen's kappa coefficient had moderate agreement (k=0.4245) according to the Landis and Koch guidelines[21]. To check another performance of the model, Table 2 was created with the diagnostic parameters for P-ADA, with the best cutoff point selected for pleural transudates.

DISCUSSION

This study aimed to evaluate the diagnostic parameters of P-ADA as a biomarker for pleural transudates. AUC is currently used in medical research to evaluate the performance of diagnostic biomarkers[22-24].

In our results, P-ADA values were absent in only 3% of exudates and 6% of transudates. The diagnostic parameters did not change significantly when less than 10% of the data were missing[28].

The sex and median age were comparable to those reported in earlier studies[3,5]. P-ADA level was statistically significant in separating pleural transudates and exudates, according to Table 1 and other studies[5-7]. The median P-ADA levels were significantly lower in transudates (6.85 U/L) than in exudates (18.4 U/L). 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 a weight of 42 kDa. Therefore, transpleural transport from the sera occurs via diffusion[9].

Depending on the objectives of biomarker dosage, several methods for selecting an optimal cutoff value have been proposed by expert authors[19,29,30]. The repercussions of

receiving a false-positive result for a diagnostic test are serious. Therefore, it was crucial to choose an optimal cutoff value of P-ADA ≤8.21 U/L for pleural transudates with high specificity using the Youden index (Table 2).

The AUC only shows 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. However, the choice of an 'optimal' cutoff point for dichotomizing a continuous biomarker is not arbitrary. Youden's index is a better criterion because it selects biomarkers with larger values of both sensitivity and specificity[31]. The discrimination with an AUC of 0.820 was very good, according to the Hosmer–Lemeshow scale[22]. An AUC > 0.75 was clinically useful[26].

The kappa coefficient is another new method of assessing the performance of a diagnostic biomarker. It is used to evaluate the agreement between observers (two or more) for the quantification of categorical data. Cohen's kappa coefficient was 78% in our study. According to the Landis and Koch guidelines, the P-ADA had moderate (k=0.41-0.60) agreement (k=0.4245) for pleural transudate with the cutoff selected (≤8.21 U/L) in the ROC curve by the Youden index. A highest kappa coefficient (0.81-1.0) means stronger agreement with the response at a specific cutoff reference point[21,32].

There was some overlap between these evaluations of different aspects of biomarker performance. Therefore, it is important to evaluate a biomarker using multiple metrics and to consider the context in which it will be used[10,11].

To differentiate pleural exudate from transudate, Jadhav et al.[5] accepted an ideal cutoff value of 22.0 U/L of P-ADA. The ROC curve method and cutoff criterion were not mentioned by the authors. A study published by Mehta et al.[6] investigated the utility of P-ADA in pleural exudates. The optimal cutoff value published to distinguish pleural exudates from transudates was >35.0 U/L with an ROC curve. However, the criterion for selection was not explicitly

stated. In another study on exudates, the optimal cutoff point for P-ADA was >15.3 U/L with the Youden's index criterion[7].

The P-ADA activity is also an accurate biomarker for tuberculous pleural effusion with high diagnostic performance in countries with an elevated incidence and prevalence of tuberculosis. In Brazil, our research group did not execute a closed needle pleural biopsy for the diagnosis. In inconclusive cases after two thoracenteses, the patient is directly referred to a VATS procedure[33].

Despite its observational methodology and analysis, this study had limitations. Before adopting accurate models in clinical practice, more studies using data from many hospitals are required for external validation. In addition, a single diagnostic biomarker may be inadequate. A panel of biomarkers is ideal to improve performance, such as diagnostic parameters and AUC. However, adequate statistical approaches with nonparametric analysis were the main reason for the correct interpretation of the results and conclusions. A better test for a scientific study depends on the research objectives. The choice depends on several factors, such as sample size, dataset distribution, statistical power, assumptions, and central tendency. The main advantage of nonparametric tests is that they are more robust and flexible than parametric tests, meaning that they can handle data that is skewed, has outliers, or has different scales or units. They also do not require large sample sizes or random sampling to be valid. Nonparametric tests are more common in medical statistics because they are a robust alternative to traditional methods when the test assumptions about the data distribution are not met. A common error in medical journals is to apply parametric statistical techniques to nonparametric data because medical researchers have been trained mainly on parametric tests, and many statistics packages actively support parametric statistical techniques[34-36].

Future perspectives are positive because our diagnostic model is crucial for clinical practice and can be utilized to identify transudative pleural effusions with acceptable discrimination and predictive power (Figure 1, Table 2).

Conclusion

This study concluded that the P-ADA biomarker with a cutoff selected of ≤ 8.21 U/L using receiver operating characteristic curve analysis with the Youden index criterion had a high diagnostic performance for pleural transudates.

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Table 1: Demographic characteristics with laboratory analysis in transudates and exudates in 157 pleural fluids.

Parameter	Transudate	Exudate	Statistical test (2-sided p-value)
Sample size, n	33	124	-
Prevalence (%)	21.0	79.0	χ^2 =39.288 (p<0.0001)
Age, years, median IQR (25^{th} – 75^{th} %)	76.0 (63.0 – 86.0)	58.0 (41.0 – 73.0)	U=895 (p<0.0001)
Male, n (%)	16 (48.0)	58 (47.0)	χ^2 =0.005 (p=0.9438)
Female, n (%)	17 (52.0)	66 (53.0)	χ^2 =0.005 (p=0.9416)
Total pleural ADA, median IQR (25^{th} – 75^{th} %)	6.85 (2.67 – 11.26)	18.4 (9.25 – 41.4)	U=679.5 (p<0.0001)
Total pleural protein, mean ± standard deviation*	2.64 ±1.52	5.05±1.10	t=2.498 (P=0.0186)
Total pleural LDH, median, IQR (75^{th} – 25^{th} %)	190.5 (100.5 – 278.8)	568.5 (400.3 – 822.5)	U=306.0 (p<0.0001)

Abbreviations: ADA, adenosine deaminase; LDH, lactate dehydrogenase; IQR, interquartile range. Statnote: The Shapiro–Wilk test (W) rejected the normal data from pleural total ADA, age, and pleural total LDH in exudates (p<0.05), but not pleural total protein in transudates (p=0.0881). (*) After the logarithmic transformation of data.

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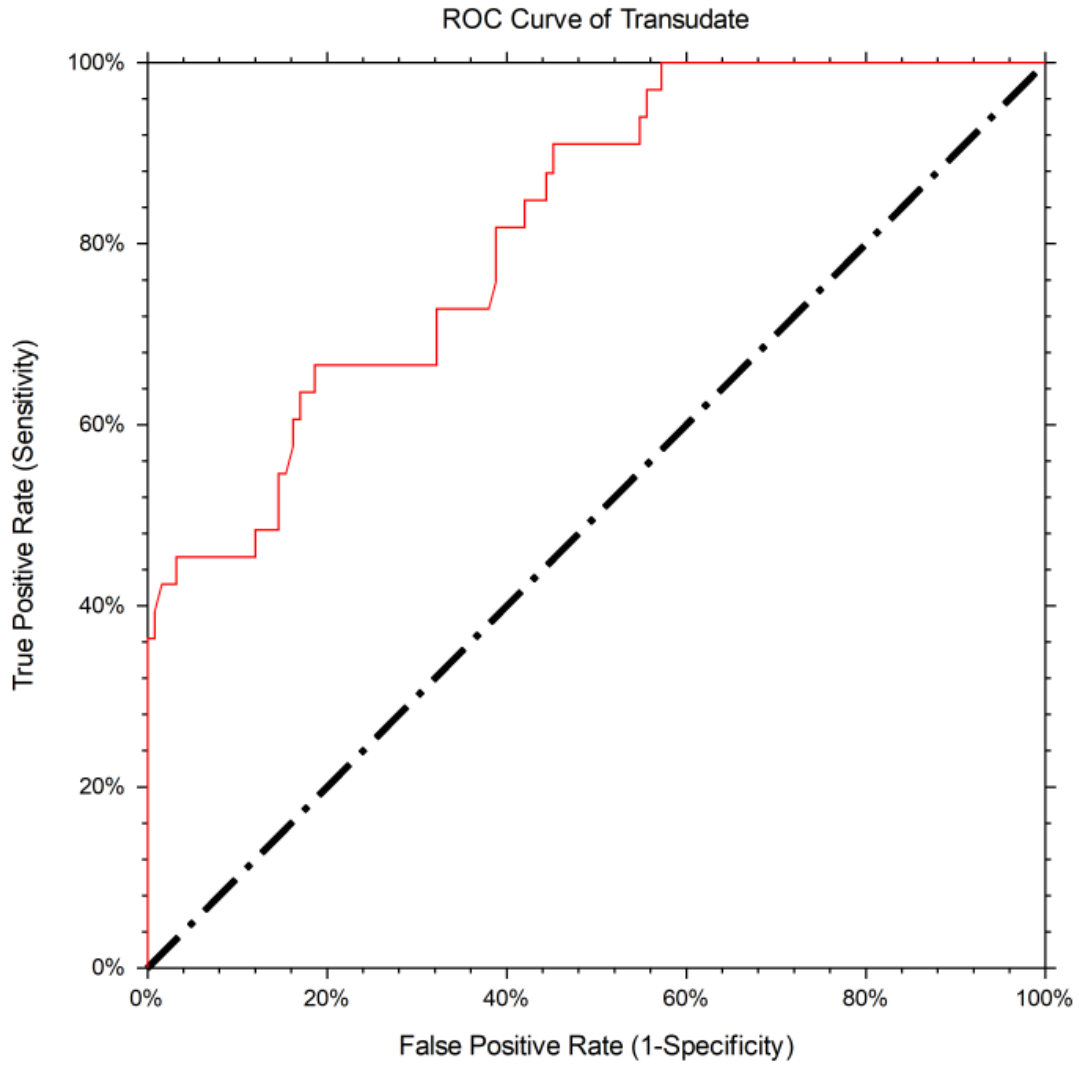

Figure 1: Nonparametric ROC curve of pleural adenosine deaminase for transudate diagnosis. The selection criterion was the Youden index (J=0.4812; distance to the ROC curve corner=0.3815). The optimal cutoff value for ROC curve concavity was ≤8.21 U/L of P-ADA. Evaluation metric for checking the model's performance: AUC, 0.8203; 95% CI, 0.7270-0.8838; SE, 0.0393; Z-value to test, 8.157; p value, <0.0001. Abbreviations: CI, confidence interval; AUC, area under the ROC curve; SE, standard error.

Table 2: Measures of diagnostic parameters of adenosine deaminase following selection of the best cutoff point for pleural transudates according to the Youden index in the ROC curve.

Diagnostic parameter	Result (%)**	95% Confidence interval
Best cutoff (U/L)	≤8.21	-
Sensitivity	66.67	48.17-82.04
Specificity	81.45	73.48-87.66
Positive predictive value*	48.89	33.70-64.23
Negative predictive value*	90.18	83.11-94.99
Positive likelihood ratio	4.97	2.21-11.2
Negative likelihood ratio	0.56	0.39-0.82
Diagnostic odds radio	8.78	0.78-18.34
Predictive accuracy*	78.34	80.28-91.53
Disease prevalence*	21.0	-

(*) These values are dependent on disease prevalence. (**) The chi-square statistic=29.5138 (p=0.00001). Statnote: The Youden index at the ROC curve is the optimal cutoff value that provides the best tradeoff between sensitivity and specificity.

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