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# Pleural adenosine deaminase in the separation of transudative and exudative pleural effusions

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**Abstract**

**Objective:** The purpose of this study was to evaluate the usefulness of a new parameter, pleural adenosine deaminase (PADA), for separating transudative pleural effusion from exudative pleural effusion, and to compare the results with other tests (albumin gradient and protein gradient).

**Methods:** From November 2001 to January 2003, 359 consecutive patients with pleural effusion who underwent a diagnostic thoracentesis were included in the study. Effusions were individually classified as transudates or exudates after the careful evaluation of all clinical data and biochemical parameters of pleural fluid and serum of patients on the basis of Light's criteria. The means and standard deviations of PADA, pleural/serum ADA (P/S ADA) ratio, albumin gradient and protein gradient were evaluated for transudative and exudative effusions. The best cut-off values for each test were identified by using the receiver operating characteristic (ROC) curve. The optimum cut-off level was determined by selecting points of test values that provided the greatest sum of sensitivity and specificity.

**Results:** There were 113 transudates and 246 exudates. For each test, differences in mean value between the transudate group and the exudate group were statistically significant (*t* test, $P < 0.001$). The optimum cut-off levels for PADA and P/S ADA were 15.3 U/L and 0.66 U/L, respectively. ROC analysis confirmed previous recommendations for albumin gradient (12 g/L) and protein gradient (31 g/L). For detecting exudates, the PADA test yielded a sensitivity and specificity of 85.8% and 82.3%, respectively. Sensitivity and specificity of the albumin gradient were found to be 88.5% and 79.3%, and of the protein gradient 85% and 83.2%, respectively. The areas under the curve (AUC) data and accuracy demonstrated similar discriminative properties in the examined tests.

**Conclusions:** The measurement of PADA is suggested as a reliable test in the separation of pleural exudates from transudates with accuracy similar to that of the albumin gradient and protein gradient.


*Keywords:* Pleural effusion; Adenosine deaminase (ADA); Transudates

## Introduction

Adenosine deaminase (ADA) is an enzyme involved in purine catabolism which catalyzes the deamination of adenosine to inosine and deoxyadenosine to deoxyinosine. ADA is found in most cells, particularly in lymphocytes [1]. ADA can aid in the diagnosis of tuberculous pleural effusions, but false-positive findings have been reported not only from lymphocytic effusions such as malignancy, lymphoma, collagen vascular diseases (i.e., rheumatoid arthritis and systemic lupus erythematosus) and post-coronary artery bypass grafting [2–5] but also from neutrophilic effusions like parapneumonic effusions, empyemas and pulmonary embolus [6–10].

All of these pleural effusions, which are of an exudative nature, showed high pleural ADA levels. We therefore hypothesized that determination of pleural ADA (PADA) may have great value for distinguishing pleural exudates from transudates. The purpose of this study, therefore, was to evaluate the usefulness of PADA in the separation of pleural transudates from exudates and to compare the results with the other tests (albumin gradient and protein gradient).

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## Materials and methods

From November 2001 to January 2003, 395 consecutive patients with pleural effusion who underwent a diagnostic thoracentesis in Atatürk Chest Disease Chest Surgery Center were included in the study. The diagnosis of the disease causing the effusion was considered to be confirmed when the following conditions were met:

*Congestive heart failure* (CHF) was determined by: (1) an enlarged heart and pulmonary venous congestion on the chest roentgenogram with clinical or echocardiographic evidence of cardiac dysfunction; (2) the following alterations: an elevated central venous pressure, peripheral edema, ventricular gallop, response to CHF treatment and (3) the absence of pulmonary infiltrates, purulent sputum, thrombophlebitis, pleuritic chest pain and malignancy.

*Tuberculosis pleurisy* was diagnosed by positive mycobacterium tuberculosis culture findings in pleural fluid or tissue and/or the presence of caseous granulomas in the pleural biopsy specimen, in the absence of other pleural granulomatous disease.

A pleural effusion was categorized as *malignant pleural effusion* if pleural fluid cytology and/or pleural biopsy findings were positive for malignancy.

*Paramalignant effusion* was considered as effusion secondary to lung cancer without evidence of pleural invasion. Increased negative pleural pressure (trapped lung) and vena cava superior syndrome (VCSS) were considered transudates after any other possible causes of transudative pleural effusion were eliminated.

*Parapneumonic effusions* were identified by the presence of cough, fever and a radiographic pulmonary infiltrate that disappeared with antibiotics.

*Empyema* was diagnosed when one or more of the following findings in the patients with pneumonia were seen: bacterial invasion of the pleural effusion, pus cells, bacteria in a Gram stain smear or culture and low pleural fluid glucose concentration (less than 40 mg/dL) with high lactate dehydrogenase (LDH) ($\geq$1000 U/L) [11].

*Diagnosis of pulmonary embolism* was confirmed when an abnormal contrast-enhanced spiral computerized tomography (CT) scanning showed a distinct filling defect or sharp arterial cut-off or when there was a high clinical suspicion together with a high probability ventilation-perfusion scan with demonstration of deep vein thrombosis by ultrasonography.

*Renal failure* was diagnosed when there were raised urea and creatinine levels in the presence of clinical evidence of fluid overload and an absence of purulent sputum, malignancy or pulmonary infiltrates.

*Other miscellaneous exudates* were effusions clearly caused by the Dressler syndrome and collagen vascular diseases.

Patients who met the diagnostic criteria of more than one of the previous groups or had pleural effusions of undetectable or obscure origin or had an obvious hemathorax secondary to trauma were excluded from this study. This left 359 patients for analysis. Effusions were individually classified as transudates or exudates after the careful evaluation of all clinical data and biochemical parameters of pleural fluid and serum of patients on the basis of Light's criteria [12].

The following studies were performed on pleural fluid samples: glucose, protein, albumin, lactate dehydrogenase (LDH), adenosine deaminase (ADA), bacterial culture, acid-fast bacilli smear and culture and cytology. Biochemical parameters were also studied in the serum of patients taken at the same time of thoracentesis. Only the results of the first thoracentesis were considered. Further studies, including pleural biopsy, were done for other exudative pleural effusions which could not be diagnosed by clinical and laboratory findings.

Biochemical parameters were determined using a chemistry analyzer (ILAB 1800). Total protein concentrations (g/dL) were estimated by the Biuret method. The LDH level was measured using the kinetic method. The upper normal limit (serum) was defined as 460 IU/L. Albumin concentration was determined by bromcresol green (BCG). ADA activity was determined using the colorimetric method described by Guisti [1]. The cut-off points were determined for PADA, pleural/serum (P/S) ADA, albumin gradient and protein gradient. According to these criteria, the nature of the effusions (transudate or exudate) was evaluated. Cut-off points recommended in the literature were used for Light's criteria [12].

### *Statistical analysis*

Differences in quantitative variables between groups were assessed by means of an unpaired *t* test. A Chi-square test was used to assess differences in categorical variables between groups. Receiver operating characteristic (ROC) curves and areas under the ROC curves (AUC) with 95% confidence intervals were calculated for each of the criteria for evaluating the optimum cut-off points. In addition to using the cut-off points derived from ROC curves, the utility of each criteria for identifying exudates was evaluated by calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), and the

Table 1
The mean and standard error of PADA, P/S ADA ratio, albumin gradient and protein gradient

| Criteria | Transudates mean ± SEM | Exudates mean ± SEM | *P* value |
|---|---|---|---|
| PADA | 10.38 ± 0.67 | 46.38 ± 2.66 | $P < 0.001$ |
| P/S ADA | 0.50 ± 0.05 | 2.04 ± 0.12 | $P < 0.001$ |
| Albumin gradient | 1.94 ± 0.06 | 0.74 ± 0.05 | $P < 0.001$ |
| Protein gradient | 3.98 ± 0.10 | 2.01 ± 0.07 | $P < 0.001$ |

PADA: pleural adenosine deaminase; P/S: pleural/serum.