

ADENOSINE DEAMINASE ACTIVITY LEVEL AS A TOOL FOR DIAGNOSING TUBERCULOUS PLEURAL EFFUSION

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Abstract. The yield for using a pleural fluid culture to diagnose tuberculous pleural effusion (TPE) is low. Adenosine deaminase activity (ADA) has been shown to have good diagnostic value for TPE. The ADA cutoff point for the diagnosis of TPE is unclear. We attempted to determine the ADA level cutoff point for diagnosing of TPE in Thailand, where tuberculosis is endemic. We reviewed the medical records of patients with newly diagnosed pleural effusion aged >15 years who had a pleural fluid ADA level and who underwent a pleural biopsy. The study period was from March 1, 2010 to January 31, 2011. The diagnoses of TPE and malignant pleural effusion (MPE) were based on pathological findings. The diagnostic cutoff level for using ADA to diagnose TPE was determined. Forty-eight patients met study criteria. Of those, 18 patients (37.5%) were diagnosed with TPE. The mean ADA level was significantly higher among patients in the TPE group than in the MPE group (38.2 vs 14.8 U/l, $p < 0.001$). The cutoff level of 17.5 U/l gave sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 88.9%, 73.3%, 3.33, and 0.15, respectively. An ADA level >17.5 U/l had good diagnostic values among TPE patients in our study.

Keywords: adenosine deaminase activity, tuberculous pleural effusion, diagnosis

INTRODUCTION

Tuberculous pleural effusion (TPE) is the second most common form of extrapulmonary tuberculosis (Golden and Vikram, 2005). The rates for TBE vary by

country: 4% in the US and 23% in Spain (Vidal *et al*, 1986; Reider *et al*, 1990). TBE occurs by rupture of a subpleural foci of pulmonary tuberculosis leading to impaired pleural vascular permeability and accumulation of fluid (Chakrabarti and Davies, 2006).

A problem with TPE is how to diagnose it. Pleural fluid analysis may show an exudative lymphocytic pleural effusion which could have several etiologies. A positive acid-fast stain or a positive cul-

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ture for tuberculosis from the pleural fluid gives a definitive diagnosis of TPE. TPE can also be diagnosed by finding granulomatous changes in the pleural tissue. The first two methods have a low sensitivity, similar to pleural biopsy (Light, 1999).

A better diagnostic tool for TPE is needed. Examining the pleural fluid for tuberculosis with polymerase chain reaction has a low sensitivity (range 42-81%) and is costly (de Lassence *et al*, 1992; Querol *et al*, 1995; Villena *et al*, 1998). Adenosine deaminase activity (ADA) is another diagnostic tool for TPE. The benefits of using ADA are that it is not expensive and easy and fast to do. Several studies have evaluated various ADA level cutoff points to diagnose TPE, but there is no general agreement. Here, we attempted to determine the ADA cutoff value for diagnosing TPE in Thailand where tuberculosis is endemic. Cutoff points may vary in different parts of the world; particularly when comparing developed with developing countries.

MATERIALS AND METHODS

We retrospectively reviewed the charts of patients with pleural effusion at Sappasittiprasong Hospital, Ubon Ratchathani, Thailand. The inclusion criteria were a newly diagnosed pleural effusion in a patient aged >15 years, in whom an ADA level was measured in the pleural fluid and who underwent pleural biopsy. We excluded patients clinically suspicious for or diagnosed with parapneumonic effusions. The diagnosis of TPE is made by the presence of granulomatous changes in the pleural tissue. Finding malignant cells in pleural tissue gave the diagnosis of a malignant pleural effusion.

ADA pleural fluid levels were measured by using an adenosine deaminase

assay kit (Diazyme Laboratories, Poway, CA). The ADA levels were reported in U/l using a single calibrator with 0.9% saline as a zero reference. ADA pleural fluid levels were compared between patients with TPE and patients with malignant pleural effusions. Cutoff levels were analyzed to give an appropriate sensitivity, specificity, positive likelihood ratio (LHR+), negative likelihood ratio (LHR-), and receiver operating characteristic (ROC) for TPE. Categorical variables were compared with the chi-square test whereas continuous variables were compared with a *t*-test or a Mann-Whitney *U* test where appropriate. A two-sided $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS, version 15.0.

The study protocol was approved by the ethics committee on human research of Sappasittiprasong Hospital.

RESULTS

From March 1, 2010 to January 31, 2011, there were 48 patients who met study criteria. The mean age (SD) of the patients was 60.93 (15.71) years with a range of 25-88 years. Of those, 23 (47.90%) were male. The mean (SD) pleural fluid ADA level was 23.58 (16.50) U/l with the range of 3-61 U/l.

The diagnosis of TPE was made in 18 patients (37.5%), while 30 patients (62.5%) were diagnosed as having a malignant pleural effusion. The mean age of patients in the TPE group was slightly lower than that of the malignant pleural effusion group (Table 1). Sixty-six point seven percent of patients in the TPE group were male. The mean pleural fluid ADA level was significantly higher in the TPE group (38.2 vs 14.8 U/l, $p < 0.001$).

The area under the ROC curve for TPE was 0.89 with a 95% CI of 0.79-0.99

Table 1
ADA levels in patients with tuberculous pleural effusion and malignant pleural effusion.

Characteristic	Tuberculous n=18	Malignant n= 30	p-value
Age (years)	58.33 ± 18.43	62.50 ± 14.05	0.430
Male	12 (83.33)	11 (36.67)	0.044
Median ADA, U/l (range)	38.17 (8-61)	14.83 (3-40)	<0.001

ADA, adenosine deaminase activity

Table 2
Cutoff points for adenosine deaminase activity for diagnosing tuberculous pleural effusion.

Cutoff level	Sensitivity	Specificity	LHR+	LHR-
7.0	100.0	13.3	1.14	0.00
17.5	88.9	73.3	3.33	0.15
24.0	77.8	80.0	3.89	0.28
40.5	50.0	100.0	Infinity	0.50

LHR, likelihood ratio

(Fig 1). A box-plot of the values categorized by pathological findings is shown in Fig 2. We suggest an ADA cutoff value of 17.5 U/l to give a sensitivity, specificity, LHR+, and LHR- of 88.9%, 73.3%, 3.33 and 0.15, respectively. Three other cutoff levels and their diagnostic values as shown in Table 2.

DISCUSSION

A cutoff level of 17.5 U/l gives fair sensitivity, specificity and likelihood ratios. Our chosen cutoff point has different diagnostic properties than other studies. A study of 462 patients chose a cutoff point of 50 U/l with higher sensitivity and specificity than our study (Burgess *et al*, 1995). Another study found using a cutoff ADA level of 45-160 U/l (mean 100 U/l) gave a sensitivity and specificity of 100% (Mathur *et al*, 2006). A meta-analysis of

9 studies and 1,674 patients from Brazil using cutoff levels of 30-60 U/l gave a mean sensitivity and specificity of 91.8% and 88.4%, respectively (Morrison and Neves, 2008).

Our cutoff level of 17.5 U/l gave similar sensitivity and specificity values to a meta-analysis from Brazil (Morrison and Neves, 2008). The diagnostic properties of the ADA level therefore were not different. Two other studies gave better diagnostic values with higher cutoff points (Burgess *et al*, 1995; Mathur *et al*, 2006). A cutoff point of 24.0 U/l gave a lower sensitivity and higher specificity than the cutoff point of 17.5 U/l in our study. The cutoff point may vary by country.

A previous study from northeastern Thailand (Reechaipichitkul *et al*, 2001) used a cutoff point of 48 U/l, giving a somewhat lower sensitivity (80% vs 88.9%)

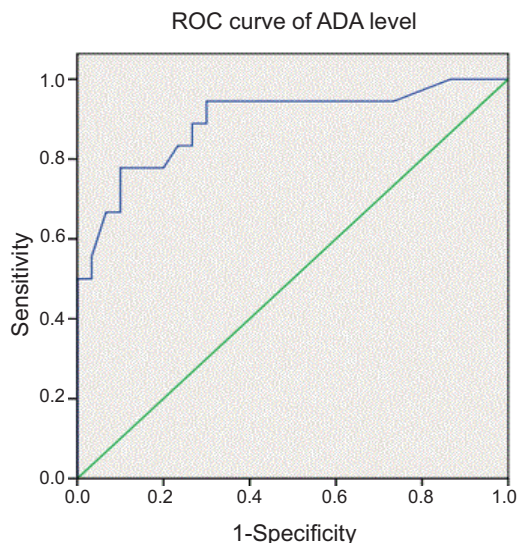


Fig 1—The receiver operating characteristic (ROC) of adenosine deaminase activity level for diagnosing tuberculous pleural effusion. The area under the ROC was 0.89.

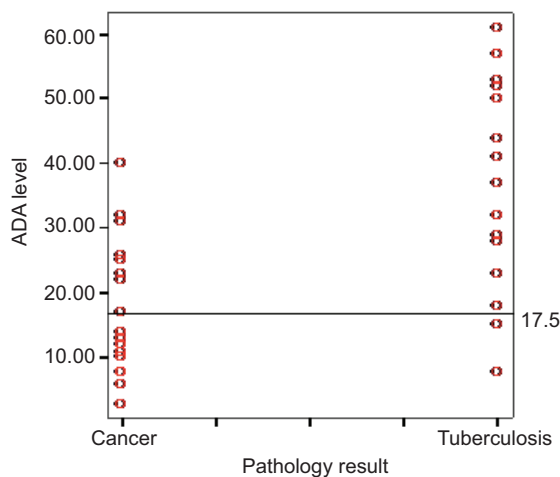


Fig 2—Adenosine deaminase levels in the pleural fluid of patients with tuberculous or malignant pleural effusion. The horizontal line shows the cutoff level.

and somewhat higher specificity (80.5% vs 73.3%). Their cutoff point was higher than the present study. The diagnosis of TPE in their study was made by meeting one

of three criteria: a culture positive for *M. tuberculosis*, finding a caseous granuloma on pleural biopsy or clinical response to antituberculous treatment. Only finding a caseous granuloma on pleural biopsy was used in the present study. Although both studies were done in the same region of Thailand, the diagnostic criteria for TPE were not the same.

Our chosen cutoff point of 17.5 U/l gave good sensitivity (88.9%) and fair specificity (73.3%). The likelihood ratio, was similar to the positive and negative predictive values, but not influenced by the prevalence rate. The chosen cutoff level gave a fair LHR+ and a very good LHR-. Regarding the diagnostic properties, 89% of TPE patients had an ADA level >17.5 U/l and 73.3% of non-TPE patients had an ADA level <17.5 U/l.

An ADA level of 40.5 U/l gave 100% specificity in our study; 100% of malignant pleural effusion patients in our study had an ADA level <40.5 U/l and none of the patients in the malignant pleural effusion group had an ADA level >40.5 U/l.

The strength of this study was the diagnosis of either TPE or malignant pleural effusion was made pathologically. The malignant pleural effusion group was a good control group for calculating diagnostic properties. The small sample size was a weakness of our study.

In conclusion, an ADA level of 17.5 U/l in TPE-suspected pleural effusion patients gave good diagnostic properties. An ADA level >40 U/l gave a high likelihood of being a TPE.

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