EKSÜDA TRANSÜDA AYIRIMI PLEVRAL SIVI STANDART BİYOKİMYASAL PARAMETRELERİN ÖLÇÜMÜ İLE MÜMKÜN MÜDÜR?

IS IT POSSIBLE TO DIFFERENTIATE BETWEEN EXUDATE AND TRANSUDATE ONLY BY STANDARD BIOCHEMICAL PARAMETERS IN PLEURAL FLUID?

Ülkü AKA AKTÜRK, Dilek ERNAM, Nagihan DURMUŞ KOÇAK, Makbule Özlem AKBAY

Süreyyaşa Göğüs Hastalıkları ve Göğüs Cerrahisi EAH, Göğüs Hastalıkları, İstanbul, Türkiye

Anahtar sözcükler: Eksuda, transüda, plevral sıvı

Keywords: Exudative, transudative,pleural fluid

Geliş tarihi: 09 / 08 / 2017 Kabul tarihi: 13 / 10 / 2017

ÖZ

Amaç: *Plevral sıvılar sık karşılaştığımız tanısal ve klinik bir problemdir. Tanı aşamasında ilk basamak eksuda transüda ayırımının yapılmasıdır.Bu çalışmada amacımız transüda eksüda ayırımında sadece plevral mayide bakılan biokimyasal parametrelerin kullanılabilirliğini değerlendirmektir.*

Yöntem ve Gereç: *Hastane kayıtlarından 1 Mayıs 2013-1 Mart 2015 tarihleri arasında plevral sıvı analizi yapılan hastaların verilerine ulaşıldı. İleri tetkik ve invaziv işlemler sonucu son tanısı konanlar çalışmaya dahil edildi. Son tanılar esas alınarak eksuda transüda ayırımında plevral LDH total protein ve ADA için cut-off değerler belirlendi, sensitivite ve spesifiteleri hesaplandı.Light kriterleri ile karşılaştırıldı.*

Bulgular: *Toplamda hastane kayıtlarından dahil edilme kriterlerine uyan 1433 hasta çalışmaya dahil edildi. Son tanıları esasa alındığında hastaların %75.1'i eksuda, %24.9'u ise transuda vasfında sıvıya sahipti. Plevral sıvı LDH için 171 IU/L ve protein için 3.2 g/L cut-off değer olarak ele alındığında eksuda vasfındaki sıvıları ayırt etmede sensitivite, spesifite, PPD ve NPD sırası ile 95.0%, 64.4%,88.9% and 81.0% olarak saptandı. Öte yandan Light kriterleri için eksuda tarnsüda*

ABSTRACT

Aim: *The pleural fluid often presents diagnostic and clinical problems.The first step in the examination of pleural effusion is to differentiate between transudate and exudate.The aim of this study was to evaluate the clinical utility of standard pleural fluid parameters in the differentiation of transudative and exudative pleural effusion in tuberculosis endemic country.*

Material and methods: *The records of patients who had pleural fluid analysis between 1 May 2013 and 1 March 2015 were electronically obtained.On the basis of the classification according to certain diagnosis after the careful evaluation of clinical data and diagnostic procedures, the cut-off values of pleural lactate dehydrogenease(LDH), total protein(TP) and adenosine deaminase(ADA) were determined. The sensitivity and spesifity of these parameters used in exudate-transudate differentiation were calculated and compared with Light's criteria.*

Results: *Totally 1433 precisely diagnosed patients with appropriate criteria were included in the study. On the basis of certain diagnosis 75.1% of them were exudate and 24.9% of them were transudate. When 171 IU/L was taken as the cut-off value of pleural LDH, the rates of sensitivity,*

ayırımında sensitivite, spesifite, PPD ve NPD sırası ile %96.0, %75.0, %92.0 and %85.9 olarak tespit edildi.

***Sonuç:** Bu çalışmada eksuda transuda ayırımında belirli cut-off değerlerinde plevral LDH ve protein kombinasyonunun sensitivite ve spesifite değerlerinin Light kriterleri ile karşılaştırılabilir olduğu görülmüştür. Klinik pratikte eksuda transüda ayırımında laboratuar imkanlarının kısıtlı olduğu durumlarda daha kolay ve ucuz olması nedeniyle sadece plevral sıvı parametrelerinin kullanımı akılda tutulabilir.*

specificity were 85% and over, while 3.2 g/L was taken as the cut-off value of the pleural total protein, the rates of sensitivity and spesifity were between 72 % - 85 %. The most appropriate combination parameters for clinical use were those of LDH at the level of 171 IU/L and total protein at the level of 3.2 g/L. In this combination; the sensitivity, specificity, PPV, NPV in determining the exudative fluids were determined as 95.0%, 64.4%, 88.9% and 81.0% respectively. On the basis of certain diagnosis, the sensitivity, specificity, PPV, NPV of Light's critera in determining the exudative fluids were determined as 96.0%, 75.0%, 92.0 %, and 85.9 % respectively.

***Conclusion:** In this study, the sensitivity and spesifity of pleural LDH and TP at certain cut-off values was found to be comparable with Light's criteria in the exudate-transudate differentiation.In clinical practice, to use only pleural fluid parameters may be considered as easier and simple approach for the differentiation of exudate and transudate when the laboratory facilities are limited.*

INTRODUCTION

The pleural fluid often presents diagnostic and clinical problems. Although cancer and tuberculosis (TB), congestive heart failure and parapneumonic effusion are the most frequent causes of pleural effusion, the incidence of TB pleurisy is higher than other countries in TB endemic areas similarly in our country (1).

The first step in the examination of pleural effusion obtained by thoracentesis is to differentiate between transudate and exudate. Differentiation between transdutae and exudate according to Light's criteria is still considered a pragmatic first step in the diagnostic work-up of pleural effusions. In 1972, Light et al. introduced the criteria for differentiation between pleural exudate and transudate. Accordingly, meeting at least one of the criteria stated in the following is interpreted in favor of exudate: a ratio of pleural fluid/serum protein greater than 0.5, a ratio of pleural fluid/serum lactate dehydrogenase (LDH) greater than 0.6, and a pleural fluid LDH value of greater than 2/3 of the serum LDH upper limit. The Light's criteria show high sensitivity, but inadequate specificity (2).

Differentiating transudates from exudates by the classical Light's criteria helps knowing the pathogenic mechanism resulting in pleural effusion, and it is also useful for differential diagnosis purposes. In addition to thoracosentesis, a diagnostic hypothesis based on medical history, physical examination, blood analysis and imaging tests, the diagnostic effectiveness will significantly increase in order to establish a definite or high probable diagnosis in a substantial number of patients (3).

There have been studies investigating the use of cholesterol, bilirubin, albumin, copeptin, and adenosine deaminase (ADA) as markers in the differentiation between exudate and transudate (4-10) and also studies investigating the role of ADA, an enzyme frequently assessed in countries where TB is highly prevalent, in the differentiation of exudate and transudate as well as in the diagnosis (9-11).

In Turkey, ADA is often measured in the pleural fluid specimens due to the high prevalence of pleural TB. Different from Light's criteria, in this study, we tried to differentiate

between exudate and transudate without blood analysis. The aim of this study was to evaluate the clinical utility of plevral fluid LDH, total protein (TP) and ADA in the differentiation of transudative and exudative pleural effusion and to compare with Light's criteria.

MATERIAL AND METHODS

Study design: Retrospective cohort

Study population: From the automation recording system of our hospital, the records of patients who had thoracentesis and pleural fluid analysis between 1 May 2013 and 1 March 2015 were electronically obtained and studied.

Among the studied cases, those who had undergone thoracentesis and were found to have pus/empyema and/or hemothorax and those whose pleural ADA, LDH and TP levels had not been determined, were excluded from the study. The patients who did not have certain diagnosis after investigation were also excluded from the study (Figure 1).

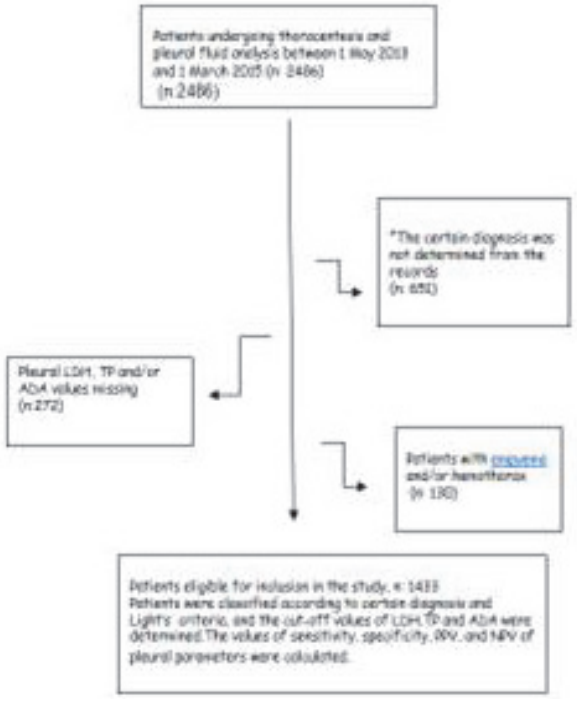

Figure 1 Flow chart

Definitions

Malignant pleural effusion was diagnosed when the pleural fluid cytology and/or pleural biopsy findings were positive for malignancy.

Para-malignant effusion was defined as effusion secondary to lung cancer without evidence of pleural invasion. It occurs due to indirect effects of tumor without invasion of pleura.

TB pleurisy was diagnosed according to positive mycobacterium TB culture findings in the pleural fluid and/or the presence of caseous granulomas in the pleural biopsy specimen, in the absence of other pleural granulomatous disease.

Para-pneumonic effusion was diagnosed according to the presence of cough, fever and a radiographic pulmonary infiltrate that disappeared with antibiotics.

Pulmonary embolism was confirmed when an abnormal contrast enhanced pulmonary computerized tomography angiography scanning showed a filling defect or sharp arterial cut-off ot when there was a high clinical suspicion together with a high probability ventilation-perfusion scan.

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.

Renal failure was identified according to increased urea and creatinine levels and clinical evidence of fluid overload and absence of purulent sputum, malignancy or pulmonary infiltrates.

Measurements

In our hospital biochemical parameters of pleural fluids were determined using a chemical analyzer (Beckman Coulter). TP concentrations (g/L) were estimated by the

photometric colour method. The LDH level was measured using the kinetic UV method. ADA activity was determined using the coclorimetric method described by Guisti.

Data

The demographic features, pleural fluid and blood serum values of those patients carrying the appropriate criteria were enlisted. Pleural effusion specimens of the patients were classified as transudate or exudate according to Light's criteria. The files of the patients were examined and the certain diagnosis after investigations were recorded. On the basis of the classification according to certain diagnosis, the cut-off values of pleural LDH, TP, and ADA were determined and specificity, sensitivity, negative predictive value (NPV), and positive predictive value (PPV) used in exudate-transudate differentiation were calculated. The sensitivity and spesifity of Light's criteria were also calculated on the basis of the certain diagnosis such as transudative and exudative.

This study was conducted in a tertiary chest and thoracic surgery teaching hospital with a high patient bed capacity. The study was approved by the local ethics committee of the hospital in consistence with the Declaration of Helsinki (the approvel date and number: 05.02.2015 and no: 4).

Statistical Evaluation

For statistical analyses, the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used. In the evaluation of the obtained data, descriptive statistical tests (mean, standard deviation, frequency, ratio, minimum, maximum) were used. For comparison of the continuous variables, parametric (independent-samples t-test) and non-parametric (Mann-Whitney U) tests were performed according to type of the distribution. The comparison of the categorical variables was made by chi-square test. Receiver operating characteristic (ROC) curves were used for determination of sensitivity, specificity, and cut-off values in differentiating between exudate and transudate. Diagnostic screening tests (sensitivity, specificity, PPV, NPV, accuracy) and ROC curve analysis were performed to determine the cut-off values of the parameters. The level of $p<0.05$ was accepted as significant.

RESULTS

From the automation recording system of our hospital, the records of 2486 patients who had thoracentesis and pleural fluid analysis between 1 May 2013 and 1 March 2015 were electronically obtained and studied. Totally 1433 patients with appropriate criteria were included in the study, and according to certain diagnosis, their pleural fluid specimens were differentiated as exudate or transudate (Figure 1).

The data of 1433 patients included in the study were analyzed. Of the patients, 55.3% were males, and the mean age was 63.4±18.3 years. When classified according certain diagnosis, 75.1% (n=1076) of the patients had exudate and 24.9% (n=357) transudate. Among patients with transudates, 79.0 % of them had congestive heart failure whereas 16.6% had chronic renal failure and 4.4 % had hypoproteinemia. Among patients with exudates 38.6 % had malignant pleural effusions whereas 23.6 % had tuberculosis, 19.6 % had parapneumonic pleural effusions and 8.4 % had paramalignant pleural effusions, and 5.6 % had pulmonary embolism, 4.2 % had connective tissue disease. As expected, the LDH, ADA, and TP values in exudates were found to be significantly higher than those in transudates ($p<0.001$, $p<0.001$, and $p<0.001$, respectively). In view of the significantly higher values of pleural ADA, LDH and TP in exudates, ROC analysis, determination of cut-off values, and sensitivity, specificity, PPV and NPV of these parameters were carried out. The ROC curves of each of the three pleural parameters were drawn, and areas under the curve (AUC) were calculated (Figure 2).

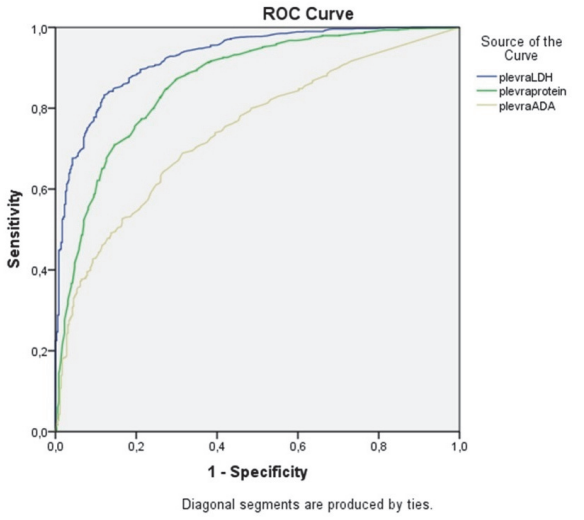

Figure 2. ROC curves for pleural lactate dehydrogenase (LDH), adenosine deaminase (ADA), and total protein (TP) values and areas under the curves

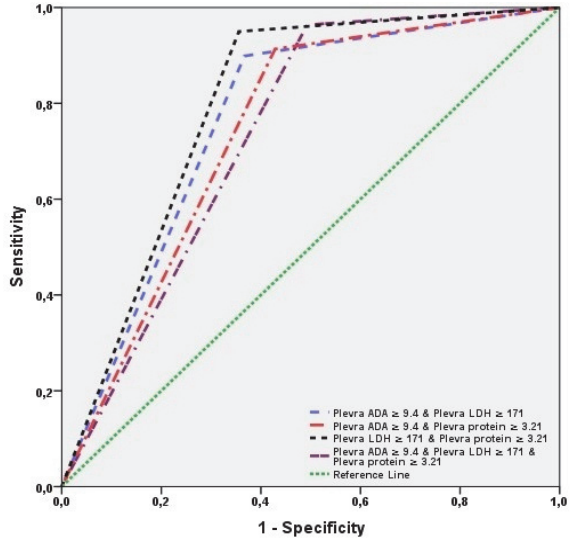

Figure 3. Screening test ROC curves of combinations of pleural fluid parameters and areas under the curves

The rates of sensitivity, specificity, PPV, NPV and accuracy of pleural parameters at different cut-off values were calculated. The most appropriate cut-off value to be used in clinical practice for pleural ADA was determined as 9.4 IU/L, for pleural LDH as 171 IU/L, and for TP as 3.2 g/L. Based on the cut-off values mentioned, the sensitivity, specificity, PPV, NPV, and accuracy rates of these three parameters in the differentiation between exudate and transudate have been presented in Table 1.

In order to enhance the diagnostic value of these three parameters, different combinations were carried out and sensitivity, spesifitiy, PPV and NPV were studied (Table 2). ROC curves of combinations of pleural fluid parameters and AUCs were calculated (Figure 3).The most appropriate combination parameters for clinical use were those of LDH at the level of 171 and higher, and total protein at the level of 3.2 and higher. In cases with pleural LDH at the level of 171 and higher, and pleural protein at the level of 3.2 and higher; the sensitivity, specificity, PPV, NPV in determining the exudative fluids were determined as 95.0%, 64.4%, 88.9%, and 81.0%, respectively (Table 2).

When the patients were classified according to Light's criteria, 72% of them had exudate, 28% of them had transudate. The sensitivity, spesifity, NPV, PPV of the Light's criteria were studied on the basis of certain diagnosis. On the basis of certain diagnosis, the sensitivity, specificity, PPV, NPV of Light's critera in determining the exudative fluids were determined as 96.0%, 75.0%, 92.0 %, and 85.9%, respectively.

Table 1. Results of diagnostic screening tests for pleural adenosine deaminase (ADA), lactatedehydrogenase (LDH), and total protein (TP) at different cut-off values

Parameters	Sensitivity	Specificity	NPV	PPV	Accuracy
Pleural ADA≥9.4 (IU/L)	64.5	73.1	87.8	40.6	66.6
Pleural LDH≥171 (IU/L)	84.9	85.4	94.6	65.3	85.1
Pleural TP>3.2 (g/L)	84.9	72.3	90.2	61.4	81.8

NPV: Negative prediction value, PPV: Positive prediction value

Table 2. Results of diagnostic screening test for combinations of pleuraladenosinedeaminase (ADA), lactatedehydrogenase (LDH), and total protein (TP)

	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Pleural ADA ≥9.4(IU/L)& Pleural LDH(IU/L) ≥ 171	90.1	61.9	87.7	67.4	83.0	0.8
Pleural ADA ≥9.4(IU/L)& Pleural TP ≥ 3.2 (g/L)	91.4	57.1	86.5	68.7	82.8	0.8
Pleural ADA ≥9.4(IU/L)& Pleural LDH ≥ 171(IU/L) & Pleural TP ≥ 3.2(g/L)	96.4	50.7	85.5	82.3	85.0	0.8
Pleural LDH ≥ 171(IU/L) & Pleural TP ≥3.2(g/L)	94.9	64.4	88.9	81.0	87.4	0.8
Light'scriteria	96.0	75.0	92.0	85.9	92.0	0.9

PPV: Positive prediction value, NPV: Negative prediction value AUC: Area under curve

DISCUSSION

In the present study, excluding the serum values, the use of only pleural LDH, TP, and ADA values for the differentiation between exudate and transudate was investigated. In the differentiation, pleural LDH and TP showed a high sensitivity and specificity of over 80%. On the other hand, the pleural ADA value showed sensitivity and specificity between 60-74%. When these parameters were combined to enhance the diagnostic value, an increase in specificity and sensitivity was observed. The pleural LDH and TP combination yielded increased specificity, sensitivity, PPV, and NPV values at certain cut-off values. The diagnostic value of pleural LDH and TP combination seems to be comparable with Light's criteria.

The Light's criteria have been used for about 40 years for the differentiation between exudate and transudate (2,12). Many biochemical markers have been investigated as possible alternatives to Light's criteria (11,13,14).

Mehta et al. have reported that the differentiation between exudate and transudate with only pleural LDH, ADA, and TP values has high sensitivity (98.8%) and specificity (93.7%), and that such an approach could be a new easy and cost-effective method comparable to Light's criteria (11).

Maranhao et al. have investigated the role of only pleural LDH and TP in exudate-transudate differentiation and found their sensitivity and specificity as 99.4% and 72.6% in exudates and as 98.5% and 83.4% in transudates, respectively (15).

A study by Atalay et al. on the role of pleural ADA in transudate-exudate differentiation has reported that pleural ADA has a sensitivity,

specificity and diagnostic accuracy at levels similar to those of albumin and protein gradients and that pleural ADA is an appropriate parameter to be used for differentiation (16). In contrast to the results of Atalay et al. we found pleural ADA to have low sensitivity and specificity in the differentiation between exudate and transudate.

Heffner et al. have studied the role of pleural LDH, TP, and cholesterol in the differentiation between exudate and transudate, and after having determined the cut-off values of these parameters, have calculated the sensitivity and specificity of their double- and triple combinations. They have found the sensitivity and specificity of pleural LDH-cholesterol combination as 97.5% and 71.9%, and those of pleural LDH-cholesterol-TP combination as 98.4% and 70.4%, respectively (17). In our study, it was not planned to add a different parameter such as cholesterol other than Light criteria because of our study design.

One of the limitation of current study is the exclusion of high number of patients because of missing data may have unintentionally decreased the objectivity in patient selection. Another limitation is due to its being a single-tertiary-care center study, our results may not be generalized.

CONCLUSION

Although, we found low efficacy of pleural ADA, high specificity and sensitivity was determined using only pleural LDH in the exudate-transudate differentiation. When pleural LDH was combined with pleural TP, the sensitivity, specificity, PPV and NPV were increased. Our diagnostic screening tests were showed relatively lower performance than Mehta's study but they were comparable with Light's criteria.

In clinical practice, to use only pleural fluid parameters may be considered as easier and simple approach for the differentiation of exudate and transudate when the laboratory facilities are limited.

REFERENCES

1 Ilgazli A, Boyaci H, Basyigit i, Yildiz F. Extrapulmonary tuberculosis: clinical and epidemiologic spectrum of 636 cases. Arch. Med. 2004; 35(5): 435–41

2 Light RW, Mac Gregor ML, Luchsinger PC, Ball WC. Pleural effusions; the diagnostic speration of transudates and exudates. Ann Intern Med 1972; 77(4): 507-13

3 Ferreiro L, Toubes ME, Valdes L. Contribution of pleural fluid analysis to the diagnois of pleural effusion. Med Clin(Barc) 2015 ; 145(4) : 171-77.

4 Hamm H, Brohan U, Bohmer R, Missmahl HP. Cholesterol in pleural effusions: a diagnostic aid. Chest 1987;92(2):296-302.

5 Metintas M, Alatas O, Alatas F, Colak O, Ozdemir N, Erginel S. Comparative analysis of biochemical parameters for differentiation of pleural exudates from transudates Light's criteria, cholesterol, bilirubin, albumin gradient, alkaline phosphatase, creatine kinase, and uric acid. Clin Chim Acta 1997;264(2):149-62.

6 Meisel S, Shamis A, Thaler M, Nussinovicht N, Rosenthal T. Pleural fluid to serum bilirubin concentration ratio for the separation of transudates from exudates. Chest 1990; 98(1):141-4.

7 Roth BJ, OÂ'Meara TF, Cragun YM. The serum effusion albumin gradient in the evaluation of pleural effusions. Chest 1990;98(3): 546-9.

8 Aziz Gümüş, Çınarka H, Karataş M, Kırbaş A, Kayhan S, Şahin Ü. Elevated pleural copeptin levels can distinguish to exudate from transudates. Tuberk Toraks 2014;62(4):267-72.

9 Atalay F, Ernam D, Hasanoglu HC, Karalezli A, Kaplan O. Pleural adenosine deaminase in the separation of transudative and exudative pleural effusions. Clin Biochem 2005;38(12):1066-70.

10 Oca-a I, Martinez-Vazquez JM, Segura RM, Fernandez-De-Sevilla T, Capdevila JA. Adenosine deaminase in pleural fluids. Test for diagnosis of tuberculous pleural effusion. Chest 1983;84(1):51-3.

11 Mehta M, Marwah S, Shah H, Trivedi A. A study of the utility of lactate dehydrogenase, total proteins and adenosine deaminase in the diagnosis of pleural exudates. A new statistical approach. Int J of Med.Sci.Public Health 2015; 4(2): 286-291.

12 Light RW. Diagnostic principle in pleural disease. Eur Respir J 1997; 10: 476-81.

13 Metintaş M, Alataş O, Alataş F, Colak O, Ozdemir N, Erginel S. Comparative analysis of biochemical parameters for differentiation of pleural exudates from transudates Light's criteria, cholesterol, bilirubin, albumin gradient, alkaline phosphatase, creatin ekinase, and uric acid. Clin Chim Acta 1997;264:149-62.

14 Gázquez I, Porcel JM, Vives M, Vicente de Vera MC, Rubio M, Rivas MC. Comparative analysis of Light's criteria and other biochemical parameters for distinguishing transudates from exudates. Respir Med 1998;92:762-5.

15 Maranhao BH, Silva Junior CT, Chibante AM,Cardoso GP. Determination of total proteins and lactate dehydrogenase for the diagnosis of pleural transudates and exudates: redefining the classical criterion with a new statistical approach. J Bras Pneumol 2010;36(4) :468-74.

16 Atalay F, Ernam D, Hasanoğlu HC, Karalezli A, Kaplan Ö. Pleural adenosine deaminase in the seperation of transudative and exudative pleural effusions. Clinical Biochemistry2005; 38(12): 1066-70.

17 Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Primary Study Investigators. Chest. 1997 Apr; 111(4):970-80.

Yazışma Adresi:

Dr. Ülkü Aka Aktürk
Süreyyaşa Göğüs Hastalıkları ve Göğüs Cerrahisi EAH, Göğüs Hastalıkları, İstanbul, Türkiye
drulkuakturk@yahoo.com