DIAGNOSTIC VALUE OF PLEURAL LIGHT'S CRITERIA, THE PROTEIN GRADIENT, AND THE ALBUMIN GRADIENT ALONE OR IN COMBINATION IN DIFFERENTIATION OF EXUDATES AND TRANSUDATES

PLEVRAL SIVILARDA TRANSÜDA- EKSÜDA AYRIMINDA LİGHT KRİTERLERİ, PROTEİN GRADİYENTİ, ALBUMİN GRADİYENTİNİN VE KOMBİNASYONLARININ TANISAL DEĞERİ

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SUMMARY

To determine the diagnostic efficacy of Light's criteria, the albumin gradient, and the protein gradient, alone or in combination, in the differentiation of pleural transudates and exudates.

Eighty-seven patients with pleural effusions, 51 (59%) of which were exudative and 36 (41%) of which were transudative, were assessed between January 2006 and February 2007. Of these patients, 71 (81.6%) were males and 16 (18.4%) were females. Total protein, albumin, and lactate dehydrogenase (LDH) levels were measured in the serum and pleural effusion samples were concurrently obtained. Calculations for Light's criteria, the albumin gradient, the protein gradient, Light's criteria and the albumin gradient, and Light's criteria and the protein gradient were performed.

Light's criteria classified all of the exudates correctly; however, the sensitivity in determining transudates was low. The sensitivities of Light's criteria, the albumin gradient, and the protein gradient in the differentiation of transudates and

ÖZET

Çalışmanın amacı; plevral efüzyonların transuda-eksuda ayırımında Light kriterleri, albumin gradienti ve protein gradientinin ayrı ayrı ve kombine kullanıldığında tanısal verimliliklerini araştırmaktır.

Bu amaçla, 87 plevral sıvılı olgu değerlendirildi. Eş zamanlı olarak alınan serum ve plevral sıvıda total protein, albumin, laktik dehidrogenaz (LDH) düzeyleri ölçüldü. Light kriterleri, albumin gradienti, protein gradienti, Light kriterleri + albumin gradienti ve Light kriterleri + protein gradienti hesaplamaları yapıldı.

Light kriterleri, eksuda olgularının tamamını doğru sınıflandırdı ancak, transuda olgularını saptamada duyarlılığı düşük bulundu. Transuda-eksuda ayırımında Light kriterleri, albumin gradienti ve protein gradientinin sırasıyla duyarlılıkları: %100, %82.3, %90.1, özgüllükleri: %58.3, %97.2, %83.3 ve doğruluk oranları: %82.7, %88.5, %87.3

exudates were 100%, 82.3%, and 90.1%, respectively; the corresponding specificities were 58.3%, 97.2%, and 83.3%, respectively; and the corresponding accuracies were 82.7%, 88.5%, and 87.3%, respectively. Fifteen cases of transudates were incorrectly classified as exudates by Light's criteria and were treated with diuretics. An increase in specificity and accuracy occurred by the additional assessment of the protein or albumin gradient when inconsistent results were obtained by Light's criteria in cases with pleural effusion clinically suspected to be a transudate and treated with diuretics. The specificity and accuracy were significantly higher with the combined use of Light's criteria and the albumin gradient compared to the combined use of Light's criteria and the protein gradient.

The combined use of the Light's criteria and albumin gradient may contribute to differentiation of transudates and exudates in patients particularly those treated with diuretics.

olarak saptandı. Transuda vasfında sıvısı olan 15 olgu, Light kriterlerine göre yanlış eksuda olarak nitelendirildi ve bu hastalar diüretik tedavisi almaktaydı. Klinik olarak transuda düşünülen ve diüretik tedavisi görmüş plevral sıvılı olgularda, Light kriterleri ile uyumsuz sonuç alındığında, ek olarak protein gradienti ya da albumin gradienti ile değerlendirmeyle özgüllük ve doğruluk oranlarında artış izlendi. Özgüllük ve doğruluk oranı, Light kriterleri-albumin gradienti kombine kullanımında, Light kriterleri-protein gradienti kombine kullanımına göre anlamlı olarak yüksek bulundu.

Sonuç olarak, özellikle diüretik kullanan plevral sıvılı olgularda transuda-eksuda ayrımında Light kriterleriyle birlikte albumin gradientinin kullanılmasının tanıya katkıda bulunabileceği kanısına vardık.

INTRODUCTION

The first step in the diagnosis of pleural effusions is the transudate-exudate differentiation. The primary importance for this differentiation is that transudative effusions do not require advanced diagnostic work-up and are managed by treating the underlying disease. Transudative pleural effusions result from diseases of the organs other than lungs, such as heart, liver, and kidneys in most cases. On the other hand, advanced and invasive diagnostic interventions are required to determine the etiology in exudative pleural effusions. Light's criteria have been widely used for this purpose since its first description in 1972 (1). In their original article the use of these criteria led to the correct classification of the pleural effusions tested in 99 percent of the cases. Subsequently, however, Light's criteria have been reported to have adequate sensitivity, but low specificity for exudates, which leads to the incorrect classification of 20-30% of transudates as exudates. Therefore, numerous new differentiation criteria, including the pleura-to-serum cholesterol ratio, the albumin gradient, the protein gradient, the pleura-to-serum bilirubin ratio, pH, pCO_2 and HCO_3, and cholinesterase, nitrite, nitrate, acute phase reactants, and inflammation markers levels have been investigated (2).

While pleural effusions due to heart failure are expected to be transudates, it is known that they may be classified as exudates according to biochemical criteria, especially when diuretic treatment is initiated. Diuretics lead to alterations in the levels of several substances, such as protein, albumin, lactate dehydrogenase (LDH), cholesterol, and cholinesterase in pleural effusions. It has been demonstrated in some studies that, among these parameters, protein and albumin gradients are the markers showing the least changes (3).

The aim of the present study was to determine the diagnostic efficacy of Light's criteria, the albumin gradient, and the

protein gradient, alone and in c ombination, in the differentiation of pleural transudates and exudates, and to determine the method or combination of methods with the highest sensitivity and specificity.

MATERIALS AND METHODS

Consecutive patients admitted with pleural effusions to the chest diseases in-or outpatients clinic of our hospital were prospectively included in the study from January 2006 through February 2007. (Approval no. of Scientific Council:). Patients with bleeding diathesis or on anticoagulation treatment, who had been treated for the current pleural effusion, who were uncooperative, who had less than 1 cm fluid on lateral decubitus position, who had respiratory failure, who did not accept thoracentesis and pleural biopsy, or who were in the terminal stage were excluded from the study.

All patients included in the study were assessed by history, physical examination, postero-anterior and lateral chest x-rays and routine blood tests. Thoracentesis was performed in all after clinical and radiological assessment. Pleural fluid samples were sent to microbiology laboratory for acid-fast bacterial and nonspecific bacterial smears and cultures, to biochemistry laboratory for total protein, albumin, lactate dehydrogenase and glucose measurements and to pathology laboratory for cytological examination. Biochemical parameters were determined using Olympus AU 2700 chemistry analyzer. Total protein concentration was measured by biuret method (4), albumin concentration by spectrophotometric method using bromcresol green (5), and lactate dehydrogenase concentration by enzymatic UV method (6).

For differentiation of transudates and exudates Light's criteria, albumin gradient and protein gradient were evaluated by using simultaneously obtained venous blood and pleural fluid samples. Light's criteria were described as follows: pleural fluid/serum total protein ratio greater than 0.5, pleural fluid/serum LDH ratio greater than 0.6 and pleural fluid LDH level equal to 200 U/L or greater than the 2/3 of upper level of serum LDH. If none of these criteria was present, it was considered as transudate. Albumin gradient was described as follows: if (serum albumin-pleural fluid albumin) was greater or equal to 1.2, fluid was considered as transudate; if it was less than 1.2, fluid was considered as exudate. Protein gradient was described as follows: if (serum protein-pleural fluid protein) was equal to or greater than 3.1, fluid was considered as transudate; if it was less than 3.1, fluid was considered as exudate.

Effusions were considered malignant if one of the following criteria was met: (1) demonstration of malignant cells at cytologic examination or in a biopsy specimen; or (2) histologically proven primary malignancy with exclusion of any other cause known to be associated with pleural effusions. Tuberculous pleurisy was diagnosed with positive culture for Mycobacterium tuberculosis or pleural biopsy specimen showing typical epithelioid cell granuloma. A pleural effusion was considered to be parapneumonic when there was an acute febrile illness with purulent sputum and pulmonary infiltrate in the absence of malignancy or diseases causing transudates. Congestive heart failure (CHF) was determined by an enlarged heart, pulmonary venous congestion on radiograph, peripheral edema, response to CHF treatment, and absence of malignancy or pulmonary infiltrates associated with an inflammatory process. The nephrotic syndrome was diagnosed when the patient had proteinuria, edema, and hypoalbuminemia.

Statistical analysis

Statistical analyses of the data were done by using SPSS and NCSS 2007 package program. Sensitivity, specificity and accuracy values were determined by using Bayes theorem and Receiver Operating Characteristics (ROC) curves. Agreement between the albumin and protein gradients in the differentiation of exudates was tested by kappa statistics. Distribution of the data was assessed by the Kolmogorov-Smirnov test. Student's t-test was used for comparison of normally distributed data, and the Mann-Whitney U test was used for comparison of non-normally distributed data. Diagnostic values were calculated and p values <0.05 were considered statistically significant.

RESULTS

Eighty-seven patients with pleural effusions, 71 (81.6%) of which were males and 16 (18.4%) of which were females, were assessed in the present study. The mean age of the study population was 58.2±18.1 years (range, 16-90 years). The exudate group consisted of 51 patients (59%) and the transudate group consisted of 36 patients (41%).

The etiology of the transudates was congestive heart failure (CHF) in 32 (88%) patients, and nephritic syndrome 4 (11.1%) patients. The most frequent cause of exudative effusions was malignant diseases (41.2%), followed by tuberculosis (39.21%). The distributions of the patients according to the diagnosis are presented in Table 1.

All 51 patients with exudates and 21 (58.4%) of 36 patients with transudates were correctly classified when Light's criteria were used alone. Of the incorrectly classified patients with transudates, 13 were due to cardiac-related pleurisy and 2 were due to nephritic syndrome. All of the incorrectly classified patients were under diuretic treatment.

Differentiation of transudates and exudates according to the albumin gradient (cut-off point, 1.2 g/dL) was correctly classified in 42 (82.4%) of 51 patients with exudates and 35 (97.3%) of 36 patients with transudates. Out of 15 incorrectly classified patients with transudates according to Light's criteria, 14 were correctly classified by the albumin gradient; whereas 9 correctly classified patients with exudates according to Light's criteria were incorrectly classified by the albumin gradient.

Differentiation of transudates and exudates in pleural effusions according to the protein gradient (cut-off point, 3.1 g/dL) was correctly classified in 46 (90.1%) of 51 patients with exudates and 30 (83.4%) of 36 patients with transudates. Among the patients with exudates correctly classified by Light' s criteria, 5 were

Table 1. Distribution of patients according to their diagnosis.

Disease	N (%)
Transudate	
Cardiac-related pleurisies	32 (88.9)
Nephritic syndrome-related pleurisies	4 (11.1)
Exudate	
Malignant pleurisies	21 (41.2)
Tuberculosis pleurisies	20 (39.2)
Parapneumonic pleurisies	8 (15.7)
Empyema	2 (3.9)

Table 2. Sensitivity, specificity, PPV, NPV, and accuracy percentage values for exudates.

Method	SEN (%)	SPE (%)	PPV (%)	NPV (%)	ACC (%)
Light's criteria	100	58.3	77	100	82.7
Albumin gradient	82.3	97.2	97	79	88.5
Protein gradient	90.1	83.3	88	85	87.3

SEN: Sensitivity, SPE: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, ACC: Accuracy, PF: Pleural effusion, S: Serum

Table 3. Number of cases with true- and false-positive and true- and false-negative results for exudates.

Method	TP	TN	FP	FN
Light's criteria	51	21	15	0
Albumin gradient	42	35	1	9
Protein gradient	46	30	6	5

TP: True positive, TN: True negative, FP: False positive, FN: False negative

incorrectly classified by the protein gradient. Among 15 patients incorrectly classified with transudates by Light's criteria, 11 were correctly classified by the protein gradient. While 1 patient with a transudate incorrectly classified by the albumin gradient was correctly classified by the protein gradient, 6 of 9 patients with exudates incorrectly classified by the albumin gradient were correctly classified by the protein gradient. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy values, as well as true and false positive/negative results of each test for exudates are presented in Tables 2 and 3.

When Light's criteria were used in combination with the albumin gradient, all 51 (100%) patients with exudates, and 35 (97.3%) of 36 patients with transudates were correctly classified. According to these results, it was found that the combined use of Light's criteria and the albumin gradient for exudates had a sensitivity, specificity, PPV, NPV, and accuracy of 100%, 97.2%, 98%, 100%, and 98.8%, respectively.

When Light's criteria were used in combination with the protein gradient, all 51 (100%) patients with exudates and 32 (88.9%) of 36 patients with transudates were correctly classified. The combined use of Light's criteria and the protein gradient for exudates had a sensitivity, specificity, PPV, NPV, and accuracy of 100%, 88.8%, 92.7%, 100%, and 95.4%, respectively. The sensitivity, specificity, PPV, NPV, and accuracy results for the combined use of Light's criteria and the albumin or protein gradients for exudates are demonstrated in Table 4. The true- and false-positive and true- and false-negative results calculated for the combined use of Light's criteria and the albumin or protein gradients for exudates are presented in Table 5.

While no significant difference was found between Light's criteria and the protein gradient in terms of sensitivity, the protein gradient was significantly superior to Light's criteria in terms of specificity ($p=0.003$). While Light's criteria was significantly superior to the albumin gradient in terms of sensitivity ($p=0.04$), the albumin gradient was significantly superior to Light's criteria in terms of specificity ($p=0.037$). No significant difference existed between the albumin and protein gradients in terms of

Table 4. Sensitivity, specificity, PPV, NPV, and accuracy in combined use of Light's criteria and albumin or protein gradient for exudates.

Method	SEN (%)	SPE (%)	PPV (%)	NPV (%)	ACC (%)
Light and albumin gradient	100	97.2	98	100	98.8
Light and protein gradient	100	88.8	92.7	100	95.4

SEN: Sensitivity, SPE: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, ACC: Accuracy

Table 5. Number of true- and false-positive and true- and false-negative cases in combined use of Light's Criteria and albumin or protein gradient for exudates.

Method	TP	TN	FP	FN
Light and albumin gradient	51	35	1	0
Light and protein gradient	51	32	4	0

TP: True positive, TN: True negative, FP: False positive, FN: False negative

sensitivity, while the albumin gradient was significantly superior to the protein gradient in terms of specificity (p=0.03). The differentiation power of these three criteria was also evaluated by the ROC curve method (Figure 1).

The area under the curve (AUC) was 0.791 (95% confidence interval (CI), 0.684-0.898) for Light's criteria, 0.897 (95% CI, 0.827-0.968) for the albumin gradient, and 0.867 (95% CI, 0.782-0.953) for the protein gradient. No statistically significant differences existed between the AUCs for Light's criteria and the protein gradient and between the AUCs for the protein g radient and the albumin gradient. However, a statistically significant difference existed between the AUCs for Light's criteria and the albumin gradient.

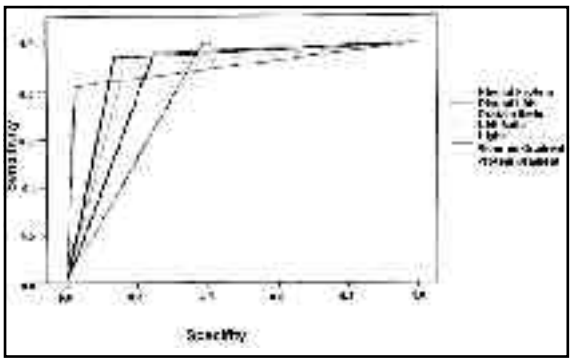

Figure 1. Receiver operating characteristics (ROC) curve.

Among these three criteria, Light's criteria had the highest sensitivity (100%), and the albumin gradient had the highest specificity (97.2%). The performance of the protein gradient in differentiation of exudates and transudates was between Light's criteria and the albumin gradient. The albumin gradient had the highest correct classification rate (88.5%).

In all pleural effusions, particularly those suspected of being transudates, the specificity increased to 88.8% and the accuracy incre ased to 95.4% when Light's criteria and the protein gradient were used in combination, and the specificity increased to 97.2% and the accuracy increased to 98.8% when Light's criteria and the albumin gradient were used in combination.

DISCUSSION

An accurate and rapid analysis of pleural effusions is mandatory for the appropriate management of patients with pl eurisy. Thus, it

is essential to first differentiate between transudates and exudates accurately. The main rationale behind this differentiation is that advanced diagnostic interventions are not required in patients with transudates, which should be managed by treating the underlying disease. Incorrect classification of these pleural effusions as exudates will lead to unnecessary diagnostic procedures and increased costs (7).

Until recently, several parameters have been introduced and developed to be used in the differentiation of transudates and exudates. While the pleural effusion density was initially used, Carr and Power (8) later defined a cut-off protein level of 3 g/dL in pleural effusions as the exudate criterion in 1958 and classified 6% of exudates and 16% of transudates incorrectly. In 1972, Light et al. (1) showed that transudate and exudate differentiation could be defined more accurately using the total protein ratio, the LDH ratio, and the absolute LDH value, and named these three parameters as Light's criteria. The use of Light's criteria has been confirmed by subsequent studies (9-11). In the original study, Light et al. (1) reported that these criteria, which are still currently in use, have a 99% sensitivity and a 98% specificity. However, sensitivities ranging from 76-100% and specificities from 48-98% have been reported for Light's criteria in studies conducted in the ensuing years (1,7,12). It has been suggested that these criteria are particularly insufficient in differentiating transudates from exudates, and therefore may lead to execution of unnecessary invasive procedures in some cases of transudates. A low specificity in these group of patients has been attributed to concomitant diuretic treatment. Chakko et al. (12) have reported in patients with CHF undergoing diuretic treatment that the pleural effusion protein and LDH concentrations and pleural effusion-to-serum protein and LDH ratios were significantly increased and transudative effusions may transform into pseudoexudates. In the current study, all of exudative effusions were correctly classified by Light's criteria with 100% sensitivity, 58.3% specificity, and 82.7% accuracy. Fifteen of 36 transudate cases were incorrectly classified. Low specificity was attributed to the use of diuretic treatment in patients with CHF. Our findings are in agreement with other studies suggesting the potential effect of diuresis on transformation of transudates into exudates (10,13,14).

Although the microvascular endothelium is intact in cases with transudative effusions, the pleural or pulmonary microvascular network is considered to be involved in the disease process in cases with exudative effusions. Based on the consequent increase in protein extravasation, it has been hypothesized that the albumin difference between serum and pleural effusions would be decreased in exudative effusions. This has led to the emergence of the albumin gradient concept. Roth et al. (4) were the first to use a serum-to-pleural effusion albumin gradient cut-off value of 1.2 in 1990 and reported 95% sensitivity and 100% specificity when used in combination with Light's criteria. They have also concluded that this parameter helps to differentiate transudates with a high rate of specificity, especially in CHF patients, even if they are on diuretic treatment (4).

Banter et al. (15) have reported in a review in 1996 that effusion characteristics may be altered in CHF patients due to diuretic treatment and the albumin gradient may aid in the differentiation of transudative effusions in these patients. It has been suggested in another study conducted in

50 patients with pleural effusions that the serum-to-pleural effusion albumin gradient could be used in exudate and transudate differentiation; however it was not superior to Light's criteria (16). In another study, the serum-to-pleural effusion albumin gradient (using a cut-off value of 1.2 g/dl) had a sensitivity of 89%, a specificity of 92%, and an accuracy of 89%, and 13 of 19 patients with transudates incorrectly classified by Light's criteria were classified correctly (15). Metintas et al. (17) have reported that the serum-to-pleural effusion albumin gradient had a sensitivity of 63% and a specificity of 81%, and emphasized that this method was not superior to Light's criteria. In the present study, the albumin gradient had a sensitivity of 82.3%, a specificity of 97.2%, and an accuracy of 88.5%; and the highest specificity and accuracy rates were obtained by the albumin gradient. Thus, it was considered that the albumin gradient may be a helpful parameter for transudate and exudate differentiation, especially in transudative pleural effusions of patients with CHF on diuretic treatment.

Although it is argued that the total protein level in the pleura is higher than albumin due to the excessive synthesis of non-albumin proteins as a result of the effects of diuretics, no significant difference has been noted between albumin and protein concentrations in pleural effusions. Among these parameters, while the serum-to-pleural effusion gradient is less affected by diuresis, pleural effusion concentrations or the pleural effusion-to-serum ratios are affected more. Therefore, gradients have a higher level of accuracy in differentiating transudates from exudates in patients under diuretic treatment. Although it is theoretically assumed that the albumin gradient reflects the changes in oncotic pressure more accurately than the total protein gradient, no significant difference was noted between the two methods in a recent comparative analysis. Owing to its similar differentiation power with the albumin gradient and lower cost, some authors have recommend the use of the protein gradient in transudate and exudate differentiation in patients receiving diuretic treatment (17). In the present study, it was found that the serum-to-pleural effusion protein gradient had a sensitivity of 90.1%, a specificity of 83.3%, and an accuracy of 87.3%. This parameter has also been suggested as a helpful parameter in transudate and exudate differentiation due to its close results to the albumin gradient,

Romero-Canderia et al. (18) have performed recurrent thoracenteses in CHF patients using diuretics and found that both the albumin and protein gradients demonstrated fewer changes compared to the albumin and total protein concentrations alone and the pleural effusion-to-serum ratios. In another study comparing Light's criteria with the albumin and protein gradients in patients under diuretic treatment, the accuracy rate was 83% for Light's criteria, 88% for the albumin gradient, and 86% for the protein gradient. The accuracy rate (93%) was found to be increased when Light's criteria were used in combination with the albumin or protein gradients in patients undergoing diuretic treatment (19). In agreement with previous studies, it was also found that the albumin gradient has the highest accuracy in differentiating exudates in the present study. No significant difference was found between the albumin gradient and the protein gradient in terms of sensitivity, while the albumin gradient was significantly superior to the protein gradient in terms of specificity. It should be noted; however,

that the protein gradient is a less expensive test compared to the albumin gradient since pleural effusions and serum protein levels are already measured in the context of Light's criteria. Moreover, no statistically significant difference was noted between the albumin and protein gradients in terms of AUC and specificity. Our findings of increased specificity and accuracy with the combined use of Light's criteria and the protein or albumin gradient in the differentiation of transudates and exudates in pleural effusions are in agreement with previous studies in which protein and albumin gradients were compared.

In conclusion, it was suggested that in patients with clinically suspected or equivocal pleural effusions according to Light's criteria or in patients undergoing diuretic treatment, use of the albumin or protein gradient may provide a more accurate and reliable approach for differentiating transudates and exudates.

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