A New Approach in Distinguishing Exudative and Transudative Pleural Effusions

Plevral Sıvıların Transüda Eksüda Ayırımında Yeni Bir Yaklaşım

Tekin Yıldız[1], Abdurrahman Şenyiğit[1], Yusuf Çelik[2], Levent Akyıldız[1], Güngör Ateş[1], Sedat Çolakoğlu[1], Hasan Bayram[3], Sacide Rana Işık[1], Füsun Topçu[1]

[1]Dicle Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Diyarbakır, Turkey

[2]Dicle Üniversitesi Tıp Fakültesi, Biyoistatistik Anabilim Dalı, Diyarbakır, Turkey

[3]Gaziantep Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Gaziantep, Turkey

ABSTRACT

Objective: Light's criteria, which were accepted in 1972 for the differential diagnosis of pleural effusions as transudates or exudates, are widely used worldwide. It has been reported in various studies that Light's criteria have lower specificity, and new recommendations have emerged. The discriminative ability of Light's criteria and adapted formulas, which are our new proposal, were studied by Receiver Operating Characteristics (ROCs) analysis and Area Under the Curves (AUCs).

Material and Method: These criteria were evaluated in 451 patients in our study. Of these cases, 151 had transudates, while 300 patients presented with exudates.

Results: AUCs of Light's criteria (P/Sprot, P/SLDH, PLDH) were measured as 0.931 (95%CI: 0.899-0.963), 0.936(95%CI: 0.904-0967) and 0.957(95%CI: 0.934-0.981), respectively, and the differences between the measured values were found to be statistically significant (p<.001). AUCs of our new adapted formulas (F-1, F-2, F-3) were found to be slightly higher than those of Light's criteria, with the values of 0.987(95%CI: 0.976-0.998), 0.935(95%CI 0:.908-0.963) and 0.980(95%CI: 0.966-0.993), respectively, and the differences were also significant (p<.001).

Conclusion: In our opinion, further studies are needed with a wider study population to determine the value of the new formulas in differentiating exudative and transudative pleural effusions. Proving our proposal would be useful in clinical practices.

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Key words: Pleural fluid, transudates, exudates, Light's criteria

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ÖZET

Amaç: Light kriterleri plevral sıvıların transüda eksüda ayırımında ilk tanımlandıkları 1972 yılından beri tüm dünyada yaygın bir şekilde kullanılmaktadırlar. Ancak daha sonraki çeşitli çalışmalarda Light kriterlerinin spesifisitelerinin düşük oldukları bildirilmiş ve yeni öneriler gündeme gelmiştir. Light kriterleri ile bizim önerdiğimiz yeni formüllerin ayırt edici yetenekleri Receiver Operating Characteristics (ROCs) incelemeleri ve Area Under the Curves (AUCs) ile değerlendirildi.

Gereç ve Yöntem: Çalışmamızda toplam 451 hasta, Light kriterleri ve bizim önerdiğimiz formüllerle değerlendirildi. Bu hastaların plevral sıvılarının 151'i transüda, 300'ü eksüdaydı. Light kriterleri ve bizim formüllerimiz Receiver Operating Characteristics (ROCs) analizi ve Area Under the Curves (AUCs) ile karşılaştırıldı.

Bulgular: Light kriterlerinin AUC değerleri (P/Sprot, P/SLDH, PLDH) sırasıyla .931 (%95 CI: .899-.963), .936(%95 CI: .904-.967) ve .957(%95 CI: .934-.981) idi ve değişkenler istatistiksel olarak anlamlıydı (p<.001). Diğer taraftan, bizim formüllerimizin AUCs değerleri (F-1, F-2, F-3) sırasıyla .987(%95 CI:.976-.998), .935(%95 CI:.908-.963) ve .980(%95 CI:.966-.993) idi ve değişkenler anlamlıydı (p<.001).

Sonuç: Mevcut veriler, formüllerimizin transüda eksüda ayırımında daha geniş serili çalışmalarda değerlendirilmesi gerektiğini düşündürmüştür. Formüllerimizin klinik pratikte yararlı olabileceğini düşünmekteyiz.

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Anahtar sözcükler: Plevral sıvı, transuda, eksüda, Light kriterleri

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INTRODUCTION

The first question to ask in assessing a patient with a pleural effusion is whether that effusion is a transudate or an exudate by using Light's criteria [1]. These criteria are nearly 100 percent sensitive at identifying exudates, but approximately 20 percent of patients with pleural effusion caused by heart failure may fulfill the criteria for an exudative effusion after receiving diuretics [2-6]. Therefore, new biochemical parameters, such as pleural (P) cholesterol level, P/serum (S) cholesterol ratio, P bilirubin level, P/S bilirubin ratio, S–P albumin gradient, Kokturk's formulae and our formulae have better sensi-

Address for Correspondence / Yazışma Adresi: Tekin Yıldız, Dicle Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Diyarbakır, Turkey
Phone: +90 412 248 80 01 E-mail: tyildiz@dicle.edu.tr

tivity and specificity and are being presented in the latest literature [1,3,4,7-13].

In the current study, three new formulas adapted from Light, Roth and Meisel which separate the exudative and transudative pleural fluid samples were presented [1,10,11]. Pleural fluid samples were evaluated by Light's criteria and new formulas. Also, the discriminative ability of Light's criteria and new formulas were analyzed by using Receiver Operating Characteristics (ROCs) analysis and Area Under the Curves (AUCs).

MATERIAL and METHOD

Our department of Chest Diseases and Tuberculosis at the University Hospital in the city of Diyarbakir serves a defined population of around 7,000,000 people in the southeastern part of Turkey. Our University Hospital has the biggest department of Chest Diseases for the city of, Diyarbakir and receives cases from the city and surrounding area.

Study Design

This study was conducted in the Department of Chest Diseases and Tuberculosis (DCTD) of the university hospital in Diyarbakir, in the southeastern Anatolia Region of Turkey. We performed a retrospective study to evaluate the kind of pleural fluid samples (exudates and transudates) to diagnose the related diseases. The study was conducted from January 1998 to December 2007 over a period of 10 years in the DCTD of the hospital. The Light's criteria were used in order to obtain a diagnosis of exudative pleural effusion [1].

All patients were informed about the thoracentesis procedures, and their informed consent was received. A total of 451 consecutive patients with pleural effusions were studied: three hundred patients with exudative pleural effusions due to pneumonia, tuberculous pleurisy, malignant effusions from primary and metastatic lung cancers, malignant pleural mesothelioma, and 151 with transudative pleural effusions due to heart failure, hypoproteinemia, liver cirrhosis, chronic renal failure, nephrotic syndrome.

Diagnosis of the Diseases

Diagnosis of heart failure was based on history, physical examination, chest X-rays, electrocardiogram and/or transthoracic echocardiographic findings, and response to diuretic therapy. Transudative effusions due to hepatic cirrhosis were defined as an effusion secondary to cirrhosis in the presence of ascites.

Exudative effusions were determined as malignant effusions when a positive pleural fluid cytology and/or positive pleural biopsy were seen. Exudative effusions secondary to pneumonia were diagnosed as parapneumonic effusions. Tuberculous pleurisy was diagnosed if Ziehl–Neelsen stains or Löwenstein-Jensen cultures of pleural fluid, sputum or pleural biopsy tissue samples were positive, a pleural biopsy showed granuloma in the pleura, or an exudative lymphocytic effusion which had elevated levels (>40 U/L) of adenosine deaminase cleared in response to antituberculous therapy.

All biochemical measurements in pleural fluid and serum were performed on a selective discrete multichannel analyzer (Abbot Architect C1600 Autoanalyzer, USA) by using standard methodology.

Biochemical analysis

All pleural fluid and blood samples were taken within the first 24 hours of admission. Thoracocentesis was performed under sterile conditions. Biochemical analyses (measurement of protein, LDH, albumin, cholesterol and bilirubin levels), bacterial cultures and cytological examination of the first successful thoracentesis fluid were performed in exudative fluids.

Blood and pleural fluid were collected in tubes containing the ethylene tetra-acetic acid (EDTA) for cell counting. The tubes were centrifuged at 3,000 rpm for 10 min. Cell smears were prepared from the sediments after centrifugation of the pleural fluid for cytological investigation. Bacteriological cultures were performed in other samples taken under sterile conditions.

Light's Criteria and New Formulas

Light's Criteria (LC):

These criteria classify an effusion as exudate if one or more of the following are present:

- LC-1: The ratio of pleural fluid protein to serum protein is greater than 0.5,
- LC-2: The ratio of pleural fluid LDH to serum LDH is greater than 0.6, or
- LC -3: The pleural fluid LDH level is greater than two thirds of the upper limit of normal for serum LDH [1].

New adapted formulas (F):

These new adapted formulas classify an effusion as transudate if one or more of the following are present:

- F- 1: The ratio of albumin gradient (introduced by Roth 1990) to LC-1 is greater than 2.4,
- F- 2: The ratio of albumin gradient to bilirubin ratio (introduced by Meisel 1990) greater than 2,
- F- 3: F-1 plus F-2 greater than 4.4 [13].

Statistical Analysis

The mean and standard deviation ($\bar{\chi} \pm$ SD) and confidence interval (95%CI) of the means for continuous variables were calculated. The assumptions of statistical methods need to be satisfactory. The variables included in the analysis of Student's t test have to show a normal distribution. Because of the positive skewed of variables (LC-2, LC-3, F-1, F-2, F-3), the logarithmic transformation was performed [14]. Then, Student's t test was used to compare the means of LC-1, LC-2, LC-3, F-1, F-2, F-3 variables belonging to exudates and transudates. ROCs analysis and AUCs were carried out to determine the discriminative ability of Light's criteria and new adapted formulas of exudative and transudative pleural effusions. Standard Error of Light's criteria and new adapted formulas were calculated. Two-sided p-values were considered statistically significant at $p<0.05$. Statistical analyses were carried out by using the statistical packages for SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Table 1. The etiology of pleural effusions in the whole study population

FLUID CHARACTERISTICS	Female	Male	Total
TRANSUDATES			
Congestive hearth failure (CHF)	37	54	91
Hepatic hydrothorax	8	16	24
Nephrotic syndrome	6	14	20
Chronic renal failure (CRF)	6	6	12
Hypoalbuminemia	2	2	4
Total (n)	59	92	151
EXUDATES			
Malignant pleural mesothelioma (MPM)	33	42	75
Tuberculous pleurisy	32	55	87
Parapneumonic pleurisy	17	40	57
Non-small cell lung cancer (ca) metastasis	16	31	47
Small cell lung ca metastasis	2	4	6
Malignant pleurisy	3	6	9
Benign asbestos pleurisy	1	3	4
Pancreas ca metastasis		3	3
Colon ca metastasis	1	2	3
Lymphoma metastasis	3	4	7
Dressler's syndrome		2	2
Total (n)	**108**	**192**	**300**

Table 2. Comparison of the pleural fluid data classified as transudates and exudates using Light's criteria and the newly adapted formulas

	EXUDATES	TRANSUDATES	P
	$\bar{\chi}$± SD	$\bar{\chi}$± SD	
Light's Criteria (LC)			
LC-1	0.627±0.178	0.308±0.109	<0.001
LogLC-2	0.027±0.277	0.535±0.247	<0.001
LogLC-3	2.379±0.323	1.843±0.251	<0.001
Newly Adapted Formulas (F-1, F-2, F-3)			
LogF-1	0.083±0.046	0.831±0.292	<0.001
LogF-2	0.159±0.86	0.583±0.298	<0.001
LogF-3	0.300±0.162	1.052±0.329	<0.001

RESULTS

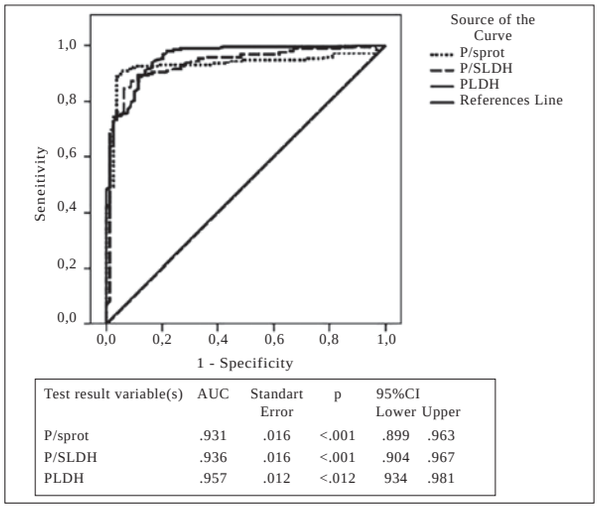
Four hundred fifty one consecutive patients were included in the study; 166 were female (%36.80) and 285 (63.20%) were male. Of the cases, 151 were found to have transudative effusions, whereas 300 had exudative effusions. Transudative group contained 59 (39.07%) female and 92 (60.93%) male patients. On the other hand, exudative group had 107 (35.66 %) female and 193 (64.34%) male patients. Average ages of the transudative and exudative groups were calculated as 58.35±18.05 (16 to 82 years of range), and 45.82±18.20 (15 to 78 years of range), respectively (p<0.05). This significance can be explained, on the basis of the fact that congestive heart failure (CHF), which causes transudative pleural fluid, is widespread among the elderly patients.

The distribution of gender and the clinical characteristics of 451 pleural fluid samples are presented in Table 1. The mean, standard deviation, confidence interval (95%) of exudates and transudates, as well as the comparison results of Light's criteria and three adapted formulas are shown in Table 2. The mean values calculated according to Light's criteria and the newly adapted formulas were found to be significantly different for exudative and transudative effusions (p<0.001).

The discriminative ability of Light's criteria and newly adapted formulas for exudates and transudates were calculated by using ROCs analysis and AUCs. The ROC curve and its AUC values, the standard error, significance level (p) and the 95%CI of AUC of Light's Criteria and Newly Adapted Formulas are presented in by Figure 1 and Figure 2, respectively.

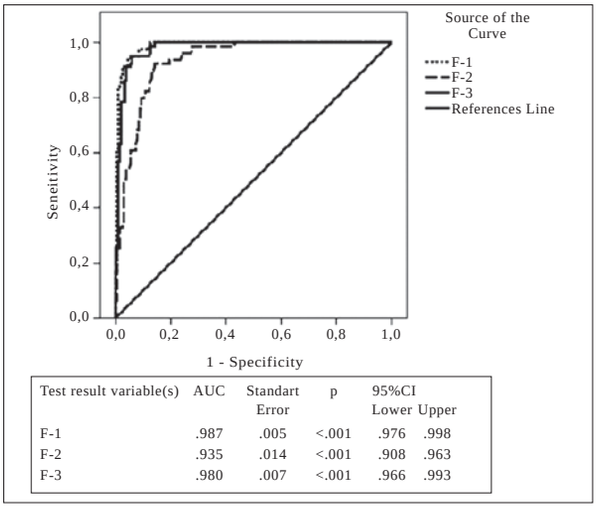
AUCs of Light's criteria (P/Sprot, P/SLDH, PLDH) were found to be significantly different and calculated as (p<.001), with the values .931(95%CI: .899-.963), .936(95%CI: .904-.967) and .957(95%CI: .934-.981), respectively.

AUCs of Newly Adapted Formulas (F-1, F-2, F-3) were found to be significantly higher (p<.001) than Light's criteria with the values of .987(95%CI: .976-.998), .935(95%CI: .908-.963) and .980(95%CI: .966-.993), respectively. The standard errors of AUCs of Newly



Test result variable(s)	AUC	Standart Error	p	95%CI Lower	Upper
P/sprot	.931	.016	<.001	.899	.963
P/SLDH	.936	.016	<.001	.904	.967
PLDH	.957	.012	<.012	934	.981

Figure 1. The ROC curve and AUC values of Light's Criteria



Test result variable(s)	AUC	Standart Error	p	95%CI Lower	Upper
F-1	.987	.005	<.001	.976	.998
F-2	.935	.014	<.001	.908	.963
F-3	.980	.007	<.001	.966	.993

Figure 2. ROC curve and AUC values of the newly adapted formulas

Adapted Formulas were also slightly lower than the standard errors of the AUCs of Light's criteria. According to these results, it could be stated that the Newly Adapted Formulas have better discriminative ability than Light's criteria.

DISCUSSION

It is widely accepted that differentiation of exudates and transudates is important for the diagnosis of pleural fluid samples. In the current study, the newly adapted formulas were developed, and the ability to distinguish transudates from exudates was analyzed. The AUCs of those formulas indicated that the success of discrimination of transudates from exudates in pleural fluids by them was significantly high than the Light's criteria.

Although studied for over 100 years, the physiology of pleural fluid formation and absorption is still controversial [10]. Light's criteria were introduced in 1972 for differentiation of pleural effusions as transudates and exudates. However, it has been reported that Light's criteria have adequate sensitivity but less specificity [1].

Romero's criteria defines as P/S (modified Light's criteria) P/S protein>0.6 or P/S LDH≥0.9 or P LDH >280 IU due to low specificity of Light's criteria [2]. Furthermore, Valdes et al. applied the values with P/S protein ≥0.45, P LDH ≥140IU, P/S LDH ≥0.5 and compared the results with Light's criteria [15]. On the other hand Vives et al. defined their own criteria (P/S protein>0.5, P/S LDH >0.9 or P LDH >380 IU) and compared the results with both Light's and Romero's criteria [16]. They found that the modifications over Light's criteria would be more deterministic while differentiating transudates from exudates [16]. Another research confirmed better results when P protein 2.9g/dl, P LDH >0.45 and P cholesterol >45mg/dl setting is used. This study was carried out by Heffner et al., he did not used P LDH level in Light's criteria and called it as abbreviated Light's criteria [17].

Porcel and Vives objected to Heffner's method, claiming that abbreviated Light's criteria or any other modification method over Light's criteria do not provide an acceptable performance [18].

In recent years, many tests have been proposed for the separation of transudates from exudates; according to the pleural fluid cholesterol levels, P/S cholesterol ratio, S-P albumin gradient, pleural fluid-to-serum bilirubin ratio, P alkaline phosphatase (ALP), P/S ALP ratio, P/S creatine kinase, LDH isoenzymes, pleural ADA level, pleural amiloid A and CRP level, pleural fluid eosinophil rate, pleural fluid viscosity, oxidative stress markers, soluble leukocyte selectin, cytokines, uric acid, pleural fluid-to-serum cholinesterase ratio, NT-brain natriuretic peptide level [7-11,19-30].

In the current study, the new formulas were adapted from Light (1972), Roth (1990) and Meisel (1990). The first Newly Adapted Formula (F- 1) was the ratio of albumin gradient, (firstly introduced by Roth 1990), to LC-1, which was greater than 2.4; the second Newly Adapted Formula (F- 2) was the ratio of albumin gradient to bilirubin ratio, (firstly introduced by Meisel 1990), which was greater than 2, and the third Newly Adapted Formula (F- 3) was the sum of F-1 and F-2, which was greater than 4.4.

ROC analysis is useful for organizing classifiers and visualizing their performance. Therefore, it is of utmost importance to use this method in medical decision making. To compare classifiers, we may want to reduce ROC performance to a single scalar value representing the expected performance. A common method is to calculate the area under the ROC curve, abbreviated as AUC. The AUC has an important statistical property. We determined the discriminative ability of these newly adapted formulas and also the Light's criteria with ROCs analysis and AUCs.

The discriminative ability found by AUC value of the first formula (S-Palb/(P/Sprot)) was adapted from Light and Roth was high with the value .987 (95%CI:.976-.998) [1,10]. This discrimination was higher than Light's first criteria (P/Sprot), which was found to be .931(95%CI: .899-.963).

The second formula (S-Palb/(P/Sbilirubin)) adapted from Light and Meisel was also found to have a discriminative ability with the value of .935 (95%CI: .908-.963) [1,11]. This value shows a better discriminative ability than Light's second criteria (P/S LDH), which was calculated as .936 (95%CI: .904-.967).

The third adapted formula was the sum of the first and the second adapted formulas. The discriminative ability of the third formula (.980(95%CI: .966-.993)) was also found to be higher than Light's corresponding third criteria (the level of pleural LDH), which was calculated as .957(95%CI: .934-.981).

Uslu et al. has compared Light's criteria, Kokturk's formulae (KF 1-3) and our formulae (F 1-3) in their study. In this study the sensitivity and specificity of Light's criteria were found as 100%, 74%, KF-1 98%, 91%, KF-2 95%, 94%, KF-3 96%, 94%and for our formulae were F-1%92, %91, F-2 and F-3 95%, 91%respectively. With results of this study they indicated that our formulae and Kokturk's formulae can be used as alternatives of Light's criteria [31].

When compared with the newly adapted formulas, the structure of Light's criteria is easier to remember and calculate for clinicians. However, the higher discriminative ability of newly adapted formulas is more advantageous, especially in cases where Light's criteria have been known to be of low specificity.

There are a few limitations of our study, one of which is that our formulas need to consider more parameters than Light's criteria. Therefore, it might be expensive and time consuming for clinicians. The second limitation is due to the mathematical complexity of the newly adapted formulas that might be undesirable for clinicians to apply.

We showed that the newly adapted formulas have better discriminative ability than Light's criteria. However, our results need to be studied on different patients with a variety of pleural diseases. Further studies would help gain more confidence in newly adapted formulas differentiating transudates from exudates. Finally, successful results could be achieved in the diagnosis of exudative and transudative fluids in the clinical practices.

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