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Research Article / Araştırma Makalesi

The Usefulness of Pleural Lactate Measurement for Differentiating Transudate and Exudate

Transuda ve Eksüdayı Ayırt Etmek İçin Plevral Laktat Ölçümünün Kullanılabilirliği

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Abstract

Our study aimed to evaluate pleural lactate levels, to identify the reliability and validity of determining pleural fluid quality in patients with pleural effusion.This is a prospective, observational study conducted on patients who were admitted to a university hospital between July 1, 2017, and January 31, 2018, and diagnosed with pleural effusion. Pleural fluid classification into transudates and exudates was made according to Light's criteria. The study group consisted of a total of 169 patients with pleural effusion, [99 (58.6%) male and aging 18-93 years (mean ± SD, 64.6 ± 16.1 years)]. Forty-four (26%) of the patients were evaluated as exudate and 125 (74%) as transudate. The median value of lactate was 3.20 mmol/L (min-max: 0.90-14.3) in exudate patients and 1.85 mmol/L (min-max: 0.90-4.70) in transudate patients, and a significant difference was detected in the comparison of both (z: 5.894; p<0.001). There was a positive correlation between pleural lactate levels and pleural LDH, pleural LDH/serum LDH and pleural protein/serum protein ratios. The cut-off value of the pleural fluid lactate level was determined to be 2.0 for the highest sensitivity and specificity (sensitivity: 85%, specificity: 64%; AUC: 0.799). Measurement of lactate levels in pleural fluid can be useful for the differentiation of transudate and exudate fluid. Moreover, detection of lactate levels in a very short period may provide a more useful screening tool compared to other strategies.

Keywords: transudate-exudate, pleural lactate

Özet

Çalışmamız, plevral efüzyonlu hastalarda transüda ve eksüdayı ayırt etmenin güvenilirliğini ve geçerliliğini belirleyerek plevral laktat düzeylerini değerlendirmeyi amaçladı.1 Temmuz 2017 ile 31 Ocak 2018 tarihleri arasında bir üniversite hastanesine başvuran ve plevral efüzyon tanısı alan hastalar üzerinde yapılan prospektif, gözlemsel bir çalışmadır. Transüda ve eksüda plevral sıvı sınıflandırması Light kriterlerine göre yapılmıştır. Çalışma grubu pevral effüzyonlu toplam 169 hastadan oluştu [99 (% 58.6) erkek ve 18-93 yaş arası (ortalama ± SS, 64.6 ± 16.1 yıl)]. Hastaların 44'ü (% 26) eksüda ve 125'i transüda olarak değerlendirildi. Laktatın ortanca değeri eksüda hastalarda 3.20 mmol / L (min-maks: 0.90-14.3) ve transüda hastalarda 1.85 mmol / L (min-maks: 0.90-4.70) idi ve her ikisinin karşılaştırılmasında anlamlı farklılık saptandı. (z: 5.894; p <0.001). Plevral laktat seviyeleri ile plevral LDH, plevral LDH / serum LDH ve plevral protein / serum protein oranları arasında pozitif bir korelasyon tespit edildi. En yüksek duyarlılık ve özgüllük için plevral sıvı laktat düzeyinin kestirim değeri 2.0 olarak belirlendi (duyarlılık:% 85, özgüllük:% 64, AUC: 0.799). Plevral sıvıda laktat seviyelerinin ölçümü, transüda ve eksüda sıvısının ayrımı için yararlı olabilir. Ayrıca laktat seviyesinin çok kısa sürede tespiti diğer stratejilere göre daha kullanışlı bir tarama aracı olarak kullanılabilir.

Anahtar Kelimeler: transuda-eksuda, plevral laktat

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1. Introduction

Pleural effusion is one of the common pulmonary emergencies (1). It is defined as an accumulation of abnormal fluid in the pleural space and may occur for many different causes (2). The incidence of pleural effusion, which can occur as a complication of various diseases, is 3-5 cases per 1000 people per year (3) and the mortality rate is 0.3 per 100.000 (4). Etiology varies according to many factors like age, living area, and the quality of the diagnostic and therapeutic methods. Although many advances are made in the medical field and new diagnostic tools have emerged, about 20% of the cases cannot be diagnosed (5). The first step in the etiologic diagnosis of a pleural effusion is to differentiate a transudate from an exudate. A delayed etiological diagnosis can be associated with higher morbidity and mortality therefore the determination of pleural fluid characteristics is important for management and treatment. The pleural fluid analysis yields important diagnostic information in pleural effusions. If pleural fluid is detected as exudate, additional tests are required to determine the etiology, if the fluid is transudate, further diagnostic procedures are not required and a treatment plan is made according to the underlying disease (6). The most commonly used method for determining pleural fluid characteristics is Light's criteria, which is based on the pleural fluid and serum protein-LDH measurements (7). Despite its high sensitivity, Light's criteria are not sufficient for the diagnosis of all pleural fluids. Therefore, in addition to Light's criteria, different parameters have been used recently, such as serum-pleural fluid albumin gradient (8), pleural fluid cholesterol level (9), Costa criteria (10), Köktürk formula (11). Pleural lactate is one of them, but the number of studies in the literature is limited to a few (12-15).

The aim of this study is to investigate the diagnostic accuracy of the measurement of lactate level in pleural effusion and assess the validity and reliability of the pleural fluid characteristics by using Light's criteria.

2. Materials and Methods

Study design and setting

This prospective study was conducted in patients who were admitted to University Health Practice and Research Hospital (Emergency Service and Chest Diseases Clinics) between July 1, 2017, and January 31, 2018. One hundred sixty-nine patients with pleural effusion were included in the study. The study was conducted in accordance with the revised Declaration of Helsinki and was approved by the Research Ethics and Review Board of the University Medical Center (Reference Number-Date: 03-29.06.2017). Also, written permission has been obtained by all participants. For the recruitment of patients, the following inclusion criteria were used: age 18 years or older, patients with pleural effusion and patients who underwent thoracentesis. Exclusion criteria were: pregnant, traumatized, unable to perform thoracentesis and bleeding diathesis. Pleural effusion was confirmed by a thorough physical examination and a postero-anterior or lateral chest radiograph and ultrasonography. Pleural fluid classification into transudates and exudates was made according to Light's criteria

Data source and collection

Information on socio-demographics (age, gender, level of education, etc.), past medical history, comorbidities, drug history, vital signs were recorded.

After obtaining the written consent from patients, thoracentesis was performed and pleural fluid was analyzed for biomarkers (protein, albumin, LDH and lactate). Simultaneous blood sample protein, LDH and albumin levels were also obtained. In the study, the thoracentesis procedure was performed with ultrasound (USG). Pleural fluid removal with USG was performed by trained doctors with static and dynamic methods according to the clinical condition of the patient. Fluid obtained by thoracentesis

was taken into biochemistry tube for protein, albumin, glucose, cholesterol, LDH, and heparinized insulin injector for pleural fluid lactate level and pH. Lactate and ph values were analyzed with the ABL800 BASIC blood gas device. Pleural fluid protein, LDH, glucose, cholesterol and albumin levels were analyzed in the biochemistry laboratory with the device named Cobas 6000 C501. Protein, LDH, glucose, cholesterol and albumin levels from venous blood samples obtained simultaneously were studied in the biochemistry laboratory with the Cobas 6000 C501 device.

Statistical analysis

Data were analyzed using IBM SPSS (version 20.0). A Chi-square test was used for univariate analyzes to determine the variables associated with pleural fluid characteristics. The Shapiro-Wilk test was used to test the normal distribution of the non-categorical data obtained from the pleural fluid analysis. Mann-Whitney U test was used for comparison of the pleural fluid characteristics and measurement data. To differentiate transudate-exudate, the predictive value of pleural lactate levels (by accepting Light's criteria as a standard), predictive value and area under the ROC curve (AUC) were calculated by using the MedCalc (v18.2.1) software. According to predictive value for pleural lactate level, pleural fluid levels of patients were re-classified as transudate and exudate. Then, sensitivity (a/a+c), specificity (d/d+c), positive predictive value (a/a+b), negative predictive value (d/d+c) and accuracy ratio (a+d/a+b+c+d) were calculated according to Light's criteria (16). Later, the definitive diagnoses of the patients were recorded on the questionnaire and sensitivity-specificity of the Light's criteria were calculated according to these definitive diagnoses.

3. Results

A total of 169 patients, [99 (58.6%) male and ageing 18-93 years (mean ± SD, 64.6 ± 16.1 years)] were included in the study. Most commonly seen comorbidities were chronic diseases in 86 (50.3%), malignancy in 50 (29.4%), CHF in 29 (17.1%), CRF in 12 (7%), chronic liver disease (CLD) in 4 (2.3%) cases. Used drugs were diuretics in 29.6%, antibiotics in 5.9% and beta-blockers in 26.6% of cases.

According to Light's criteria, 44 (%26) of the patients were evaluated as transudate and 125 (%74) as exudate. In the relationship between pleural fluid content and variables; exudative pleural effusion was observed in patients younger than 60 years (p=0.036), having a high fever (p=0.045), transudative pleural effusion was observed in patients with a past medical history of CHF and CRF (p≤0.0001, p=0.003, respectively). Comparison of characteristics according to pleural fluid content Table 1.

Table 1. Comparison of demographic, vital signs, comorbidities and drug use according to pleural fluid characteristics

Characteristics		n (%)	Quality of pleural fluid		Statistical analysis x^2 ; p
			Transudate n: 44 (%)	Exudate n: 125 (%)	
Age group (year)	≤59	47 (27.8)	7 (14.9)	40 (85.1)	6.663; 0.036*
	60-69	38 (22.5)	8 (21.1)	30 (78.9)	
	≥70	84 (49.7)	29 (34.5)	55 (65.5)	
Gender	Male	70 (41.4)	24 (24.2)	75 (75.8)	0.206; 0.650*
	Female	99 (58.6)	20 (28.6)	50 (71.4)	
SBP	Normal	43 (25.4)	8 (18.6)	35 (81.4)	1.177; 0.232*
	Abnormal	126 (74.6)	36 (28.6)	90 (71.4)	
Pulse	Normal (60-100 beat/ min)	81 (47.9)	23 (28.4)	58 (71.6)	0.245; 0.620*
	Abnormal	88 (52.1)	21 (23.9)	67 (76.1)	
RR	Normal (12-20 resp/min)	54 (32.0)	13 (24.1)	41 (75.9)	0.044; 0.834*

	Abnormal	115 (68.0)	31 (27.0)	84 (73.0)	
Body temperature	Normal (36,5-37,5ºC)	151 (89.3)	43 (28.5)	108 (71.5)	0.045**
	Abnormal	18 (10.7)	1 (5.6)	17 (94.4)	
CHF/CRF/CLD	Present	38 (22.5)	18 (13.7)	113 (86.3)	42.939; <0.001*
	Absent	131 (77.5)	26 (68.4)	12 (31.6)	
Malignancy	Present	50 (29.6)	10 (20.0)	40 (80.0)	0.935; 0.334*
	Absent	119 (70.4)	34 (28.6)	85 (71.4)	
Chronic disease	Present	86 (50.9)	30 (34.9)	56 (65.1)	6.214; 0.013*
	Absent	83 (49.1)	14 (16.9)	69 (83.1)	
Diuretic use	Present	50 (29.6)	26 (52.0)	24 (48.0)	22.981; <0.001*
	Absent	119 (70.4)	18 (15.1)	101 (84.9)	
B blocker use	Present	45 (26.6)	22 (48.9)	23 (51.1)	5.056; <0.0001*
	Absent	124 (73.4)	22 (17.7)	102 (82.3)	
Antibiotic use history	Present	10 (5.9)	0 (0.0)	10 (100.0)	0.065**
	Absent	159 (94.1)	44 (27.7)	115 (74.0)	

** Chi-Squared test **Fisher's Exact Test , SBP: Systolic blood pressure, RR: Respiratory rate, CHF: Chronic Heart Failure, CRF: Chronic Renal Failure, CLD: Chronic Liver Disease*

Comparison of pleural protein and LDH, albumin gradient, plasma protein and LDH ratio between transuda and exuda fluids are given in Table 2.

Table 2. Parameters used for differentiating transudates and exudates

Parameters		**Quality of Pleural effusion**		**Statistical analysis**
		Transudate n (%)	Exudate n (%)	**x^2; p**
Pleural protein	<3 g/dl	26 (59.1)	5 (4.0)	62.316; <0.001
	≥3 g/ dl	18 (40.9)	120 (96.0)	
Pleural LDH	<200 IU	42 (95.5)	26 (20.8)	72.355; <0.001
	≥200 IU	2 (4.5)	99 (79.2)	
Albumin gradient	<1.2	4 (9.1)	77 (61.6)	33.881; <0.001
	≥1.2	40 (90.9)	48 (38.4)	
PSPR/S_PR	<0.5	32 (72.7)	9 (7.2)	72.526; <0.001
	≥0.5	12 (27.3)	116 (92.8)	
PSLDH/S_LDH	<0.6	42 (95.5)	26 (20.8)	72.355; <0.001
	≥0.6	2 (4.5)	99 (79.2)	

After pleural fluid differentiating according to the Light criteria, the median value of lactate was 3.20 mmol/L (min-max: 0.90-14.3) in exudate patients and 1.85 mmol/L (min-max: 0.90-4.70) in transudate patients, and a significant difference was detected in the comparison of both (z: 5.894; p<0.001).

There was a positive correlation between pleural lactate levels and pleural LDH, pleural LDH/serum LDH and pleural protein/serum protein ratios (Table 3).

Table 3. Correlation between lactate and Light cirteria parameters

	Pleural LDH level r; p	**Pleural LDH/serum LDH ratio r; p**	**Pleural protein/serum protein ratio r; p**
Pleural lactate level	**0.656; 0.000**	**0.611; 0.000**	**0.419; <0.001**

The predictive value of pleural fluid lactate level was determined to be 2.0 for the highest sensitivity and specificity [sensitivity: 85%, specificity: 64%, positive likelihood ratio: 2.3 (CI: 1.6-3.5), negative likelihood ratio: 0.24 (CI: 0.1-0.4), the area under the curve: 0.799 (CI: 0.7-0.9)] (Table 4, Figure 1).

Table 4. Comparison of lactate for differentiating transuda exuda

	Cutt-off value	Sensitivity %	Spesificity %	LR (+) CI	LR (-) CI	AUC CI
Pleural Lactate level	2.0 mmol/L	85	64	2.33 (1.6-3.5)	0.24 (0.1-0.4)	0.799 (0.7-0.9)***

: CI= %95 confidence interval; AUC: Area Under Curve

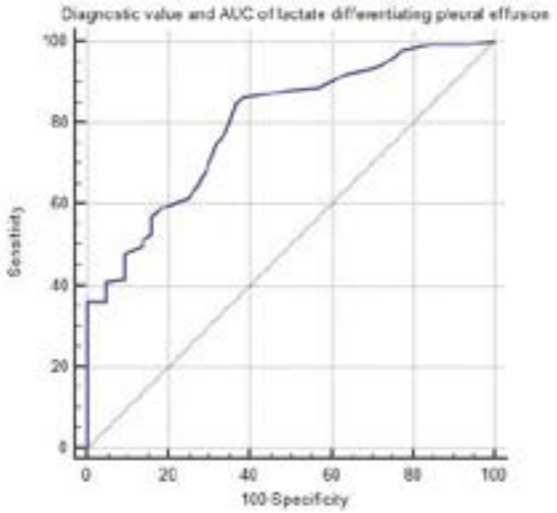

Figure 1.

4. Discussion

The results of our study show that the diagnostic parameters of Light's criteria are strongly positively correlated with pleural lactate levels. The best advantage of lactate levels measurements is that the result can be achieved in a very short time after the invasive thoracentesis procedure. These advantages may be important in septic cases due to pneumonic effusion where a prompt treatment decision is required. Therefore this potentially enables rapid decision-making at the time of the initial diagnosis. However, further investigations are needed to differentiate between these two groups.

Increased production or decreased absorption causes pleural fluid accumulation and its pathophysiology changes depending on the underlying disease. History and physical examination of a patient with pleural effusion can give an idea of the nature of the fluid. Then, diagnosis can be confirmed with parameters obtained by thoracentesis. Various parameters are used to differentiate transudative and exudative pleural effusion, but there is no exact method of sensitivity and specificity (17, 18). Light's criteria, although more than 40 years have passed, is accepted as the standard and the first step in discrimination of transudate and exudate (19). Different studies reported different sensitivity-specificity values for the Light's criteria (20, 21). The decrease in specificity rather than the sensitivity of Light's criteria

suggests that this can be changed with any modification.

Lactate is the end product of the anaerobic metabolism of pyruvate, catalyzed by lactate dehydrogenase and can be measured using a blood gas analyzer. Several recent studies evaluated lactate levels in biologic fluids such as ascites, pleural, synovial, and cerebrospinal fluid and its correlation to bacterial infections, empyema, autoimmune diseases, tuberculosis, hypovolemia and neoplastic diseases (12, 22-25). Lactate formation during infection is likely from bacterial metabolisms and results from high metabolic activities of the inflammatory cell population (26). However transudative pleural effusions are commonly caused by increased hydrostatic pressure or reduced plasma oncotic pressure, this may explain the low level of pleural lactate which is associated with minimal inflammatory and metabolic activities.

In their series of 118 cases, Yeo et al. Found that the mean lactate level of patients with transudative pleural fluid was lower than that of exudate fluids. With a ratio and cut-off value similar to our study, they found the cut-off value for pleural lactate as 2.50 mmol / L, the sensitivity as 77.78% and the specificity as 54.17% for the distinction between transudate and exudate (19).

Therefore we hypothesized that pleural fluid lactate can help us in differentiating exuda and transude in our patient. As a result, in our study pleural lactate level could be used in transudate-exudate discrimination, when the cut-off value of pleural lactate was taken as 2 mmol / L (Light's criteria were accepted as a standard) sensitivity was found to be 61.3% and specificity was found to be 86.4%.

Limitations

The present study has some limitations. First of all our study is single centered and our sample is small to clearly define the diagnostic role of lactate in pleural effusion and its real clinical use

5. Conclusion

Light's criteria are commonly used parameters in the differentiation of transudate-exudate. Pleural lactate measurement after thoracentesis is quickly and very easy and simple methods that can lead to the physicians working in emergency services. We concluded that pleural lactate could be useful in practice and can be used in the differential diagnosis. We also think that multicenter and more comprehensive studies may be useful in determining the role of pleural lactate in differentiating transudate exudate effusions.

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