

The Diagnostic Values of Protein to Lactate Dehydrogenase Ratio in Serum and Pleural Fluid in Exudate Pleural Effusions

Zahra Hadizadeh Talasaz¹, Shahrzad M.Lari¹, Reza Basiri¹, Mohammad Towhidi¹, Davood Attaran^{*2}, Amir Asnaashari¹, Zahra Javid-Arabshahi³

¹ Pulmonologist, COPD Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

² Pulmonologist, Cardio- Thoracic Surgery & Transplant Research Center, Emam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

³ Resident of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

ARTICLE INFO

ABSTRACT

Article type:

Original Article

Introduction: Different etiologies of pleural effusion are diagnosed based on serum and pleural fluid characteristics. The aim of this study was to assess and compare the serum and pleural fluid protein to lactate dehydrogenase (Pr/LDH) ratio in exudative pleural effusions.

Article history:

Received: 25 March 2013

Revised: 29 April 2013

Accepted: 29 June 2013

Materials and Methods: This study was conducted on 60 patients with exudative pleural effusion including: 20 cases with parapneumonic, 20 cases with Tuberculosis (TB), and 20 cases with malignancy. The serum and pleural Pr/LDH were measured and compared among 3 groups.

Keyword:

Exudative

Malignancy

Pleural Effusion

Tuberculosis Parapneumonic

Results: The mean age of the patients was 55±19SD (years) and male to female ratio was 36/24. There was no statistically significant difference in mean age of the patients among 3 groups (p=0.08). There were statistically significant differences in serum and pleural Pr./LDH ratios among groups (p=0.04 and p= 0.1, respectively). Additionally the comparisons of serum and pleural Pr./LDH ratios between malignancy and tuberculosis groups were significant (p=0.02 and p=0.001, respectively). The serum and pleural Pr./LDH ratios were higher in TB group.

Conclusion: The results of our study showed that serum and pleural Pr./LDH ratio can be used in differentiating the etiology of exudative pleural effusion, but needs to be confirmed by larger study.

Introduction:

Thoracentesis as a simple procedure permits to easily sample the pleural fluid for determining the cause of pleural effusion. An important point in approach to the cause of pleural effusion is separating the exudative from transudative pleural effusion. The traditional Light's criteria have been used as a good starting step in this way (1) Based on Light's criteria the presence of

at least one of the following three criteria, defines the exudative pleural effusion (1): pleural fluid protein (Pr.) to serum Pr. greater than 0.5, pleural fluid lactate dehydrogenase (LDH) to serum LDH greater than 0.6, and pleural fluid LDH greater than two-thirds of the normal upper limit. It must be noted that alternative diagnostic criteria are also

*Corresponding author: Davood Attaran, Cardio-Thoracic Surgery & Transplant Research Center, Emam Reza Hospital, Mashhad, Iran, Tel: +98 -511- 801 2742, Fax: +98 -511- 843 1252, E-mail: attarand@mums.ac.ir, © 2013 mums.ac.ir All rights reserved. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

exist which can be used in especial settings (2-4).

By determining the exudative pleural effusion, the effort should be performed to define the common possible underlying disease including: pneumonia, tuberculosis (TB), malignancy, and pulmonary thromboembolism (1). For better determining the cause of exudative pleural effusion, several parameters have been proposed by previous studies like pH, amylase level, antinuclear antibody (ANA) level, rheumatoid factor level, adenosine deaminase (ADA), and lipid analysis (5-7). But indeed, it is not cost-effective to order these tests in routine work-up of pleural effusion (8). Besides the consideration of traditional Light's criteria, the total concentration of pleural fluid Pr. has been introduced for differentiating the cause of exudative pleural effusion; means that protein level above 5.0 g/dL is suggestive for the diagnosis of tuberculous pleurisy (9). Since the Light's criteria is the most common way for diagnosing the type of pleural effusion, in this study we aim to evaluate the diagnostic value of Pr/LDH ratio in different cause of exudative pleural effusion.

Materials and Methods:

This was a cross-sectional study performed in Ghaem hospital, Mashhad, Iran from April 2011 until April 2012. This study was approved by our Ethical Committee in accordance with the ethical standards of Helsinki declaration in Mashhad University of Medical Sciences, Mashhad, Iran. We obtained informed consent form all patients prior to assess their inclusion criteria for enrollment in this study. The patients with age more than 18 years old and measurable pleural effusions (>10 mm on lateral decubitus chest x-ray) were included in this study. Also thoracentesis performed by pulmonary specialist for all included patients on the first day of enrollment.

The patients with coagulation disorders (platelet count less than 10000 cu/mm), and lower than 10 mm of pleural effusions were excluded. All demographic information and clinical symptoms were recorded. Pleural fluid samples were obtained and cytological studies were performed in our biochemistry department and pathology laboratory. Pleural fluid samples were immediately analyzed for glucose, LDH, protein and cell count. Also, 5 cc non-fasting blood was obtained from each patient for measuring serum Pr. and LDH. The transudative and exudative pleural effusion diagnosis was based on Light's criteria (1). Malignancies were confirmed by evaluation of pleural cytological and biopsy (closed needle biopsy or thoracoscopy). Subsequently a total of 60 patients were analyzed and divided into three group; Parapneumonic effusion (20 cases), TB effusion (20 cases), and malignant effusion (20 cases). The Pr./LDH ratio was calculated in 3 groups and compared among them. The data were analyzed using SPSS 11.5 (SPSS Inc, Chicago, IL, USA). All data were checked for normality by Kolmogorov-Smirnov test (K-S test). Descriptive statistics and compare means (one sample t test and paired sample t test) were also used. P-value less than 0.05 was considered significant. Numerical data are expressed as mean \pm SD or as proportions of the sample size. One way ANOVA for analysis of different variables in pleural fluid of three studied groups were performed.

Results:

The main characteristics of patients are shown in Table 1. As shown in Table 1, there were no significant differences in mean pleural and serum protein and LDH among groups. In malignant group, 13 cases (65%) were secondary to bronchogenic carcinoma and 7 (35%) due to metastasis from other organs. There

was no case of TB empyema. Serum and pleural fluid Pr/LDH ratio were calculated in 3 groups as shown in Table 2 and the mean value was compared among groups by one-way ANOVA test. There were statistically significant differences in serum and pleural indexes among groups as shown in Table 2. Since

differentiation of two common causes of lymphocytic dominant exudative pleural effusion is important and by cell differentiation one can easily discriminate the parapneumonic pleural effusion from lymphocytic pleural effusion, we compared the serum and pleural Pr/LDH ratios between malignancy and TB groups.

Table 1: The clinical and pathophysiological parameters in patients with exudative pleural effusion

Parameter	All patients (60)*	Malignancy (20)*	Tuberculosis (20)*	Parapneumonic (20)*	P value**
Age (years)	55±19	66±10	45±19	53±19	0.08
Male/Female	36/24	12/8	11/9	14/6	0.1
Pleural Pr.(g/dl)	4.34±0.72	4.04±0.54	4.60±0.75	4.35±0.75	0.07
Serum Pr.(g/dl)	5.9±0.68	5.9±0.62	5.7±0.72	4.9±0.57	0.08
Pleural LDH (IU)	438±102	478±75	423±107	416±102	0.45
Serum LDH(IU)	603±110	653±76	578±94	581±93	0.09

* Data are presented as mean ± SD.

** P value<0.05 was considered significant.

Pr: Protein, g/dl: gram/deciliter,

LDH: Lactate dehydrogenase,

IU: International Unit

Table 2: The mean serum and pleural Pr./LDH ratio in malignant, tuberculosis, and parapneumonic groups

	Malignancy	Tuberculosis	Parapneumonic	P value**
Serum Pr./LDH	0.009±0.001*	0.010±0.002*	0.011±0.002*	0.04
Pleural Pr./LDH	0.008±0.001*	0.011±0.003*	0.011±0.004*	0.01

*Data are presented as mean ± SD.

** P value < 0.05 was considered significant.

Pr: Protein, LDH: Lactate dehydrogenase.

In Fig.1, the comparison of mean pleural Pr./LDH between malignant and TB pleural effusion, is shown that was

statistically significant (p= 0.001). Additionally, the comparison of serum Pr./LDH between malignant and TB pleural effusion is shown in Fig.2 (p= 0.02)

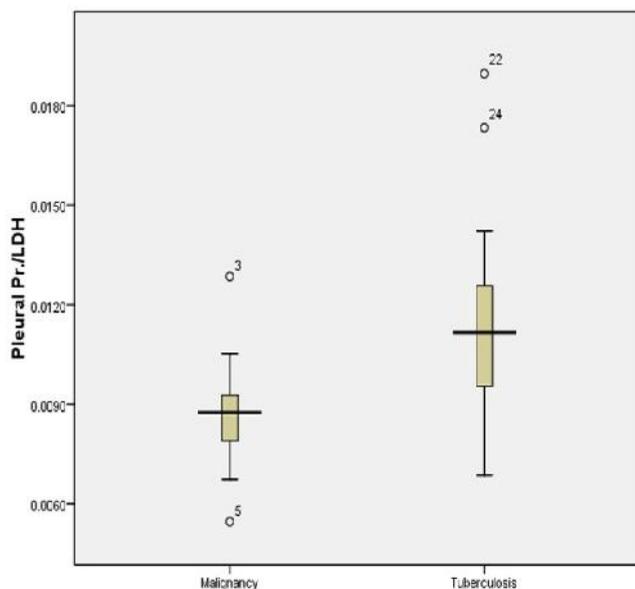


Figure.1: The comparison of mean pleural Pr/LDH ratio between malignant and tuberculosis groups ($p=0.001$)

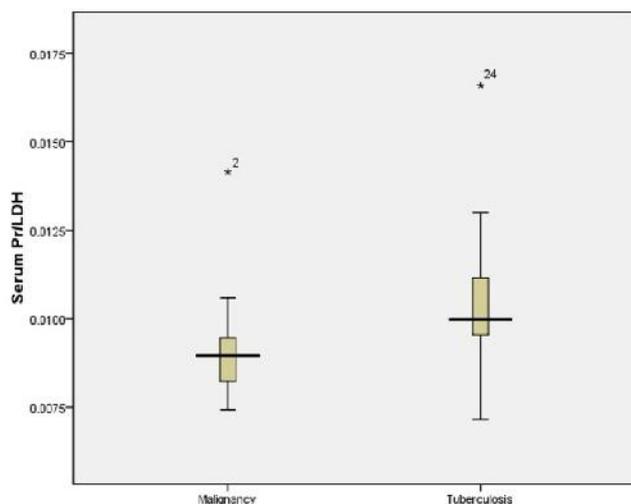


Figure.2: The comparison of mean serum Pr./LDH ratio in malignant and tuberculosis groups ($p=0.02$)

Dicussion:

Since diagnosing the different causes of exudative pleural effusions has a pivotal role a proposed index (Pr/LDH) was evaluated in 3 groups of exudative pleural effusions means; tuberculosis, malignancy, and parapneumonic effusions. We found a statistically significant difference in pleural Pr/LDH ratio among these groups. Interestingly, the pleural Pr/LDH ratio was

significantly higher in TB comparing the malignant pleural effusion. Differentiating the parapneumonic pleural effusions from other causes of exudative pleural effusions is simple.

By measuring the white blood cells count and differentials in pleural fluid, the pattern of the fluid; neutrophil or lymphocyte dominant; will be determined. It is now well accepted that in some instances the differentiation of lymphocyte dominant exudative pleural effusion is challenging especially in cases suspicious to malignancy or tuberculosis.

During previous decades several pleural markers have been proposed for better differentiation of exudative pleural effusions (5-8). QiAn and colleagues showed that pleural vascular endothelial growth factor (VEGF) was significantly higher in malignant comparing TB pleural effusions (10). Additionally pleural interferon gamma, ADA, and low c-reactive protein have proposed as useful markers for diagnosing TB pleural effusions (11-13). To our knowledge, this was the first study that evaluate the pleural Pr/LDH ratio in different exudative pleural effusions. We found that this ratio is significantly higher in TB comparing to malignant pleural effusion. As in every pleural effusion, generally Light's criteria is used, therefore the access to the proposed index is completely feasible. On the other hand, it is cost-effective comparing to other biomarkers. Previous studies have shown that LDH and related isoenzymes are elevated in malignant pleural effusion (14,15). Alternatively pleural protein greater than 5 g/dl is frequently encountered in TB pleural effusion which is probably due to systemic inflammatory response to mycobacterium (9). Although it must be considered that sometimes confounding factors like age (especially in parapneumonic pleural effusion) and diuretic therapy may interfered with this index (9,16). This study has some limitations. First and foremost was small

sample size. For strengthen our theory about the value of this index for differentiating the common causes of exudative pleural effusions, we need to continue this study with more cases. Secondly, we considered the 3 common causes of exudative pleural effusion in our study. By extending the causes of exudative pleural effusion (like pulmonary thromboembolism, connective tissue disease, ...) and evaluating the index, the results would be more interesting.

Conclusion:

As differentiating the different causes of exudative pleural effusion, especially lymphocytic dominant type, is an important step in management of patients with pleural effusion, in this study we proposed serum and pleural indexes. We found statistically significant differences in mean serum and pleural Pr/LDH among parapneumonic, malignancy, and tuberculosis groups. Additionally the comparison of aforementioned indexes between malignancy and tuberculosis groups were significant.

Acknowledgments:

This study was financially supported by Mashhad University of Medical Sciences, Mashhad, Iran (code number: 900658). The authors wish to thank to Gh.Zareh and H.Sadraei for their wonderful assistance in performing the study.

Conflict of interests:

The authors have no conflict of interests.

References:

1. Light RW. The Light criteria: the beginning and why they are useful 40 years later. *Clin Chest Med*. 2013;34:21-6.
2. Romero-Candeira S, Fernández C, Martín C, Sánchez-Paya J, Hernández L. Influence of diuretics on the concentration of proteins and other components of pleural

transudates in patients with heart failure. *Am J Med* 2001;110:681-686.

3. Burgess LJ, Maritz FJ, Taljaard JJF. Comparative analysis of the biochemical parameters used to distinguish between pleural transudates and exudates. *Chest* 1995;107:1604-1609.

4. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. *Chest* 1997;111:970-980.

5. Sherr HP, Light RW, Merson MH, Wolf RO, Taylor LL, Hendrix TR. Origin of pleural fluid amylase in esophageal rupture. *Ann Intern Med* 1972;76:985-986.

6. Walker WC, Wright V. Rheumatoid pleuritis. *Ann Rheum Dis* 1967;26:467-474.

7. Winslow WA, Ploss LN, Loitman B: Pleuritis in systemic lupus erythematosus: Its importance as an early manifestation in diagnosis. *Ann Intern Med* 1958;49:70-88.

8. Branca P, Rodriguez RM, Rogers JT, Ayo DS, Moyers JP, Light RW. Routine measurement of pleural fluid amylase is not indicated. *Arch Intern Med* 2001;161:228-232.

9. Light RW. Clinical manifestations and useful tests. *Pleural Diseases*, 5th ed. Baltimore: Lippincott Williams & Wilkins 2007. p. 75-7.

10. Qian Q, Zhan P, Sun WK, Zhang Y, Song Y, Yu LK. Vascular endothelial growth factor and soluble intercellular adhesion molecule-1 in lung adenocarcinoma with malignant pleural effusion: correlations with patient survival and pleural effusion control. *Neoplasma* 2012;59:433-439.

11. Daniil ZD, Zintzaras E, Kiropoulos T, Papaioannou AI, Koutsokera A, Kastanis A, et al. Discrimination of exudative pleural effusions based on multiple biological parameters. *Eur Respir J* 2007;30:957-964.

12. Krenke R, Safianowska A, Paplińska M, Korczyński P, Dmowska-Sobstyl B, Bogacka-Zatorska E, et al. Pleural fluid interferon-gamma (IFN-gamma) measurement as a diagnostic tool in tuberculous pleurisy. *Pneumonol Alergol Pol* 2008;76: 237-245.
13. Lee SH, Lee EJ, Min KH, Hur GY, Lee SY, Kim JH, et al. Procalcitonin as a diagnostic marker in differentiating parapneumonic effusion from tuberculous pleurisy or malignant effusion. *Clin Biochem*. 2013;6: Epub ahead of print
14. Augoff K, Grabowski K. Significance of lactate dehydrogenase measurements in diagnosis of malignancies. *Pol Merkur Lekarski* 2004;17:644-647.
15. Kotyza J, Havel D, Kulda V, Bunatová K, Pesek M. Differentiated expression of the lactate dehydrogenase subunit M in pleural fluids of neoplastic aetiology. *Scand J Clin Lab Invest* 2009;69:73-78.
16. Zarogiannis SG, Tsilioni I, Hatzoglou C, Molyvdas PA, Gourgoulianis KI. Pleural fluid protein is inversely correlated with age in uncomplicated parapneumonic pleural effusions. *Clin Biochem* 2013;46:378-80.