

Use of Pleural fluid C-Reactive Protein & Comparison with Light's Criteria to Differentiate between Transudative and Exudative Pleural effusion

Atul Rajkondawar¹, Imran Shaikh²

ABSTRACT

Introduction : Pleural effusion is a common medical problem with the diagnostic dilemma. This study was conducted to determine if C- Reactive Protein (CRP) level in pleural fluid is a better diagnostic tool in differentiating exudative and transudative pleural effusion & to compare with the parameters of modified Light's criteria.

Material and Methods : A Cross-Sectional study of 116 patients was conducted during the study period (November 2017 to October 2019). Patients with Unilateral Pleural effusion were included. Values of pleural fluid CRP and Light's criteria were then used to differentiate between transudative and exudative fluid. In this study Light's criteria used defines a pleural effusion as exudative if at least one of the following criteria exists. The ratio of pleural fluid to serum protein greater than 0.5. The ratio of pleural fluid to serum LDH greater than 0.6 and Pleural fluid LDH greater than two-thirds of the upper limits of normal serum value, however the fluid is considered as transudative if all of the above are absent. The Pleural fluid CRP level more than 10 mg/dl was considered as exudative effusion.

Results : Considering Pleural fluid CRP level ≥ 10 mg/dl for exudative effusion; 76 (83.51%) exudates were correctly classified as exudates. On evaluating the individual parameters of Light's Criteria: for the ratio of pleural protein to serum protein > 0.5 ; 83 (91.20%) exudates were classified as exudates. While for pleural fluid to serum Lactate Dehydrogenase (LDH) ratio > 0.6 ; 68 (74.72%) exudates were classified as exudates and Pleural fluid LDH greater than two-thirds of the upper limits of normal serum value; 64 (70.33%) exudates were classified as exudates.

Conclusion : With the classifying threshold of CRP ≥ 10 mg/dl has almost similar sensitivity, specificity, positive predictive value, and negative predictive value compared with Parameters of Light's criteria. Measurement of this single parameter can add better results in differentiating exudates from transudates.

Introduction :

A pleural effusion is a collection of fluid abnormally present in the pleural space, usually resulting from excess fluid production and/or decreased lymphatic absorption. On the basis of pathophysiology pleural effusion are classified into transudative and exudative effusion. Transudates are due to alteration of hydrostatic and colloidal-osmotic pressure in pleural capillaries. While Pleural exudates are secondary to alteration of capillary permeability or lymphatic obstruction.

In cases with transudative pleural effusion, the diagnosis is usually made without any difficulties but exudative pleural effusion requires a careful differential diagnosis that includes Parapneumonic effusion, tuberculosis, and metastatic cancers which

are found to be the cases in a large number of patients.

Light's criteria have been universally accepted than any other criteria for differentiating transudates from exudates as a gold standard test for decades until now.¹²

According to Light's criteria (Light, et al. 1972), a pleural effusion is likely exudative if at least one of the following exists¹ :

- The ratio of pleural fluid to serum protein greater than 0.5
- The ratio of pleural fluid to serum LDH greater than 0.6
- Pleural fluid LDH greater than two-thirds of the upper limits of normal serum value

The fluid is considered a transudate if all of the above are absent.

Light's criteria have a sensitivity and specificity of 99% and 98% but over the last few years, many workers noted even Light's criteria misclassify

¹Associate Professor, ²Junior Resident,
Department of Medicine, Government Medical College, Nagpur

Address for Correspondence -

Dr. Imran Shaikh
E-mail : imran.sk94@gmail.com

Received on 5th December 2019

Accepted on 20th December 2019

significant percentage of the transudative pleural effusions as Exudative effusion.¹³

Normal CRP in the serum of healthy individuals is less than 10 mg/dl. Blood levels of CRP are known to rise rapidly from normal baseline levels to as high as 50 mg/dl in infections and inflammations. CRP in pleural fluid >10 mg/dl correlates more to exudative effusions and > 30mg/dl correlates more to parapneumonic effusion with high sensitivity and specificity.⁴

Pleural fluid CRP, this single test is easy, cost-effective and avoids the need for simultaneous other blood and pleural fluid examinations in differentiating transudates from exudates. Hence, In this study, we investigated the diagnostic usefulness of pleural fluid CRP levels and compared them with the light's criteria for discriminating exudative from transudative effusion.

Aim and Objectives :

- To determine the usefulness of pleural fluid CRP levels and comparing light's criteria for differentiating exudative from transudative effusion.

Materials and Methods :

After obtaining Institutional Ethics Committee approval and written informed consent from all the patients or their relatives, Cross-Sectional study of patients admitted in the wards of Hospital during the period of two years (November 2017 to October 2019) was performed.

A total of 116 patients of pleural effusion were included in our study. Detailed history, clinical examination along with radiological investigations such as chest X-ray,USG thorax, USG abdomen, and HRCT chest were done.

Clinically, pleural effusion associated with congestive cardiac failure and liver cirrhosis were considered transudates and all other effusions were considered exudates.

The patients were categorized into different groups based on clinical diagnosis (i.e., etiological diagnosis) as follows (1) Pleural effusions due to congestive cardiac failure (2) Effusion due to

Cirrhosis (3) Parapneumonic pleural effusions (4) Malignant pleural effusion (5) Tubercular effusion (6) Effusion due to Nephrotic syndrome, etc.

Patients with unilateral pleural effusion underwent thoracentesis. 10 ml of pleural fluid was obtained by maintaining all aseptic precautions in the hospital. The pleural fluid sample obtained was sent immediately to the laboratory for analysis. If the analysis of these samples was not feasible immediately, it was refrigerated until analysis was done within 24 hours of sample collection. The pleural fluid was analyzed for total cells, differential cell counts, total protein, LDH and CRP level along with simultaneous serum sample for total protein, albumin. Then Pleural fluid CRP and Light's criteria were used for distinguishing between pleural exudates and transudates.

Inclusion criteria :

- Unilateral Pleural effusion whose cause was unknown
- Age group between 17-88years
- Patients who gave consent for being part of this study.

Exclusion criteria :

- Bilateral pleural effusions
- Pregnant women

Statistical Analysis :

Collected data were entered into the Microsoft Excel spreadsheet. Tables and charts were prepared with the help of Microsoft Windows 10, Word and Excel. Continuous variables were presented as Mean \pm SD. Continuous variables (serum protein in gram, pleural fluid protein in gram, serum LDH, pleural fluid LDH, and pleural fluid CRP) were compared between transudative and exudative effusion by performing an independent t-test. Categorical variables were expressed in frequency and percentages. Categorical variables were compared by performing a chi-square test. For a small number, the Fisher exact test was used wherever applicable. Predictive values (sensitivity, specificity, PPV, and NPV) were calculated for different study parameters to differentiate transudative and exudative. Kappa

statistic was performed for agreement between the type of pleural effusion and different pleural fluid. $P < 0.05$ was considered as statistical significance. Statistical software STATA version 14.0 was used for data analysis.

Observations and Results :

A total of 116 patients with unilateral pleural effusion were enrolled in this study. After the study, it was found that Maximum patients were from the age group of 21-30 years. The most common presenting symptom was poor appetite. Tuberculosis was found to be the main etiological agent for pleural effusion followed by malignancy. (Table 1)

On the basis of etiological (clinical classification), amongst the 116 pleural effusions, 91 (78.45%) were exudates and 25 (21.55%) were transudates. (Figure 1)

On applying Light's Criteria :

- 1) The ratio of pleural protein to serum protein more than 0.5 correctly classified 83 (91.20%) exudates, whereas 1 exudate was classified falsely as transudates and 24 out of 25 transudates were correctly classified as transudates. This criterion had a sensitivity, specificity, positive predictive value and negative predictive values of 91.20%, 96.0%, 98.81%, and 75.0% respectively with a significant p value of < 0.001 . The kappa value was 0.51. (Table 4,5)
- 2) The ratio of pleural fluid to serum LDH ratio more than 0.6 correctly classified 68 (74.72%) exudates as exudates, whereas 2 exudates were classified falsely as transudates and 24 out of 25 transudates were correctly classified as transudate, This criterion had a sensitivity, specificity, positive predictive value and negative predictive values of 74.72%, 92.0%, 97.14%, and 50.0% respectively with a significant p value of < 0.001 . The kappa value was 0.46.

- 3) Pleural fluid LDH greater than two-thirds of the upper limits of normal serum value correctly classified 64 (70.33%) exudates as exudates whereas 2 falsely classified as transudates and 23 out of 25 transudates were correctly classified as transudate. This criterion had a sensitivity, specificity, positive predictive value of and a negative predictive value of 70.33%, 92.0%, 96.97%, and 46.0% respectively with a significant p value of < 0.001 . The kappa value was 0.40.

On applying Pleural fluid CRP level = 10 mg/dl :

This criterion correctly Classified 76(83.51%) exudates as exudates whereas, 6 transudates out of 25 were misclassified as exudates, i.e 19 out of 25 transudates were correctly classified as transudate. This criterion had sensitivity, specificity, positive predictive value and negative predictive value of 83.51%, 76.0%, 92.68%, and 55.88% respectively with a highly significant p value of < 0.0001 . The kappa value was 0.59.

Considering Pleural fluid CRP > 30 mg/dl for exudative effusion, this criterion correctly classified 3 (3.29%) exudates as exudates and all transudates as transudates but misclassified 88 exudates as transudates this criterion had sensitivity, specificity, PPV and NPV as 3.29% ,.100%,100% and 22.12% respectively with a p value of 0.17 which was not significant.

Figure 1 : Distribution of cases according to clinical classification

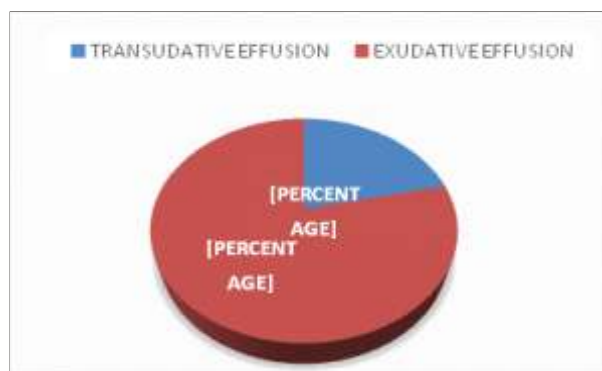


Table 1 : Etiological classification (clinical classification) of pleural effusion

Causes	Frequency	Percent
CHF	9	7.76
Hepatic hydrothorax	6	5.17
Renal hydrothorax	9	7.76
Tubercular	54	46.55
Malignant	30	25.86
Parapneumonic effusion	3	2.59
Others	5	4.31

Table 2 : Mean value of Pleural fluid CRP and different parameters of Light's criteria in transudative and exudative effusion.

	Transudative		Exudative		P-value
	Mean	SD	Mean	SD	
Serum protein in gram	5.86	0.95	5.64	0.94	0.3262, NS
Pleural fluid protein in gram	1.08	0.51	3.28	0.92	<0.0001, HS
Serum LDH	88.92	41.09	285.59	135.02	<0.0001, HS
Pleural fluid LDH	50.2	51.63	251.01	153.56	<0.0001, HS
Pleural fluid CRP	8.40	4.27	17.00	6.43	<0.0001, HS

Table 3 : Comparison of Pleural CRP and Light's criteria in differentiating transudative and exudative pleural effusion

Total (116)	Pleural fluid CRP level more than 10 mg	Light's criteria		
		The ratio of pleural fluid Protein more than 0.5	The ratio of pleural fluid LDH more than 0.6	Pleural fluid LDH more than 2/3 of the upper limit of normal SLDH
Transudative Effusion (25)	19	24	24	23
Exudative Effusion (91)	76	83	68	64

Table 4 : Predictive values of the different parameters of Light's criteria and pleural fluid CRP in differentiating exudative from transudative effusion

	Sensitivity	Specificity	PPV	NPV	Accuracy
Pleural fluid more than 0.5 times of serum proteins.	91.20%	96.0%	98.81%	75.0%	92.24%
Pleural fluid more than 0.6 times serum LDH	74.72%	92.0%	97.14%	50.0%	78.45%
Pleural fluid more than 2/3 of upper limit of serum LDH	70.33%	92.0%	96.97%	46.0%	75.0%
CRP more than 10	83.51%	76.0%	92.68%	55.88%	81.90%
CRP more than 30	3.29%	100%	100%	22.12%	24.14%

Table 5 : Kappa statistic in pleural fluid CRP and different parameters of Light's criteria in differentiating transudative and exudative effusion

	Kappa value	Z-value	P-value
Pleural fluid more than 0.5 times of serum Proteins.	0.5109	10.77	<0.0001, HS
Pleural fluid more than 0.6 times serum LDH	0.4699	8.64	<0.0001, HS
Pleural fluid more than 2/3 of the upper limit of serum LDH	0.4037	6.04	<0.0001, HS
CRP more than 10	0.3908	0.3908	<0.0001, HS
CRP more than 30	0.0145	0.92	0.1788, NS

Discussion :

Pleural effusions occur in different diseases: Transudative pleural effusions like Congestive heart failure, Nephrotic syndrome, Cirrhosis of the liver, Peritoneal dialysis, Superior vena cava obstruction, Myxedema, Urinothorax and Exudative pleural effusions in infectious, metastatic, Pulmonary embolization, Neoplastic disease, Mesothelioma, etc. The clinical features play an important role in identifying the pathogenesis, the first step in the proper and adequate diagnosis of pleural effusion is correctly classifying it into exudative and transudative types by analysis of the pleural fluid for appropriate management.

Distribution of types of effusion :

On the basis of clinical classification of the 116 pleural effusion samples studied in this study, 91 (78.45%) pleural effusion were exudates and 25 (21.55%) pleural effusion samples were transudates which was comparable with the study by Thapa et al⁵ in Nepalese population, among the 86 pleural effusion samples studied, 73 (85%) pleural effusions were exudates and 13 (15%) pleural effusion samples were transudates.

Distribution according to etiology of effusion :

Tuberculosis was found to be the main etiological agent for pleural effusion 54 (46.55%) followed by malignancy 30 (25.86%), while parapneumonic effusion was the least common causative agent for pleural effusion 3 (2.59%). Tuberculosis was also the main etiological agent in males 50 (43.10%), Malignant pleural effusion 13 (11.20%) was the commonest cause of pleural effusion in females.

In India tubercular effusion is the commonest cause of all exudative effusions. This is also found in the observation of different studies from India by Maldhure et al⁶ where they showed that the tubercular effusions constitute 66% of the effusions, malignancy 15%, and parapneumonic effusion 4.8%.

Light's criteria :

Using different parameters of Light's Criteria, the study showed that 83 (91.20%), 68 (74.72%) and 64 (70.33%) exudates were correctly classified as exudate with pleural protein to serum protein ratio of > 0.5, pleural fluid to serum LDH ratio > 0.6 and pleural fluid LDH > 2/3rd of the upper limit of normal serum level, respectively. These figures could possibly be due to high proportions of tubercular pleural effusion, which gives exudative characteristics on laboratory evaluation of the pleural fluid biochemical parameters.

Pleural fluid protein ratio more than 0.5 times correlated well with the clinical diagnosis in this study as compared to the pleural fluid to serum LDH more than 0.6 and more than the upper limit of normal LDH with better sensitivity, specificity, and predictive values.

Pleural fluid CRP :

The higher mean value for the CRP level was found in parapneumonic effusion i.e 35 mg/dl. The lower mean value for CRP level was noted for hepatic hydrothorax i.e, 5.45 mg/dl. Mean values of Pleural fluid CRP in transudative and exudative effusion were 8.40 ± 4.27 and 17 ± 6.43 having significant p value < 0.0001, while in a study by Turay et al⁷

means in transudative effusion and exudative effusion were 14.9 ± 4.5 and 35.5 ± 4.9 . (**Table 2**)

Of the 43 Tubercular effusion fluid i.e. clinically defined exudates in this study, 44 (81.48%) TB effusion were correctly classified as exudates by the criteria of CRP level > 10 mg/dl, which was set as a cut-off value for discrimination of exudates and transudates. While 10 samples were misclassified as transudates by this criterion. This criterion had sensitivity values of 83.51% accuracy 91.80% with a significant p value of < 0.001 .

Among the 3 Parapneumonic effusion cases studied in this study, 3 were classified correctly as exudates by the criteria of CRP level > 10 mg/dl, which was set as a cutoff value for discrimination of exudates and transudate.

Conclusion :

With classifying threshold of CRP > 10 mg/dl only 76 of 91 clinically defined exudates were correctly classified as exudates and showed the sensitivity of 83.51% and misclassified 6 transudates as exudate. The result has almost similar sensitivity, specificity, positive predictive value, and negative predictive value compared with Parameters of Light's criteria. Measurement of this single parameter can add better results in differentiating exudates from transudates as well for identifying parapneumonic effusions and identifying tubercular pleural effusion. However, larger population-based multicenter studies needed to be done to reach a definitive conclusion.

References :

1. Light RW, Macgregor MI, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med.* 1972;77(4):507-513. doi:10.7326/0003-4819-77-4-507
2. Daniil ZD, Zintzaras E, Kiropoulos T, et al. Discrimination of exudative pleural effusions based on multiple biological parameters. *Eur Respir J.* 2007; 30 (5) : 957-964. Doi:10.1183/09031936.00126306
3. Iqbal M, Jaffery T, Shah SH. Isolated pleural fluid lactic dehydrogenase level: a cost effective way of characterizing pleural effusions. *J Ayub Med Coll Abbottabad.* 14 (2):2-5.
4. Castaño Vidriales JL, Amores Antequera C. Use of pleural fluid C-reactive protein in laboratory diagnosis of pleural effusions. *Eur J Med.* 1(4):201-207.
5. Thapa J, Basnet A, Sapkota K, Thapa AB. Use of Pleural Fluid C-Reactive Protein and Comparison with Light's Criteria to Differentiate Exudative from Transudative Pleural Effusions in Nepalese Population. Vol 2.; 2017.
6. Ranga Raja Rao M, Mohan Babu K, Lakshmi Navya C. AETIOLOGICAL STUDY OF PLEURAL EFFUSION BY CONVENTIONAL METHODS -ITS CLINICAL PRESENTATION ALONG WITH RADIOLOGICAL, BIOCHEMICAL AND CYTOLOGICAL CORRELATION OF 60 CASES OF PLEURAL EFFUSION. *J Evol Med Dent Sci.* 2016;5(52):3420-3424. doi:10.14260/jemds/2016/790
7. Turay ÜY, Yildirim Z, Türköz Y, et al. Use of pleural fluid C-reactive protein in diagnosis of pleural effusions. *Respir Med.* 2000. Doi:10.1053/rmed.1999.0759