Differentiating Pleural Effusions: Criteria Based on Pleural Fluid Cholesterol

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Abstract

Objective: To assess the efficacy of pleural fluid cholesterol in differentiating transudates and exudates as compared with Light's criteria.

Methods: Patients with pleural effusion during a 6-month period were enrolled in the study and underwent thoracentesis. Pleural fluid was analyzed for the levels of protein, lactate dehydrogenase (LDH), and cholesterol. Etiological diagnosis, which was established after considering clinical and biochemical factors, was the gold standard for comparison. Cut-off values for pleural fluid cholesterol were taken as 60 mg/dL and 45 mg/dL.

Results: A total of 53 patients were included for final analysis. Of them, 19 were with transudates and 34 with exudates in their pleural fluids. The sensitivity, specificity, positive predictive value, and negative predictive value of the pleural fluid cholesterol (cut-off >45 mg/dL) were 97.06%, 94.74%, 97.06%, and 94.74%, respectively, for identifying exudates. These values were differentiating better than those obtained by Light's criteria for pleural fluid cholesterol (cut-off >60 mg/dL) (p<0.0001). Combining pleural fluid protein with pleural fluid cholesterol (>45 mg/dL) gave a higher specificity (100%) and positive predictive value (100%) but a lower sensitivity (82.93%) and negative predictive value (63.16%).

Conclusion: Pleural fluid cholesterol is better than Light's criteria for the differentiation of transudates and exudates and is less cumbersome as it does not require a simultaneous blood sampling. Cut-off value of pleural fluid cholesterol for differentiating transudates and exudates should be 45 mg/dL. Further studies are warranted to assess the efficacy of the combination of pleural fluid protein and cholesterol as criteria for classifying effusions.

Keywords: Exudates, light's criteria, pleural fluid cholesterol, pleural fluid LDH, pleural fluid protein

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INTRODUCTION

The first step in the evaluation of a pleural effusion is to determine if it is a transudate or an exudate. After the initial classification, the course of treatment of a pleural effusion is decided. If the effusion is a transudate, no further investigation is necessary, and the effusion is managed by treating the primary cause (i.e., heart failure, liver failure). If the effusion is an exudate, then further investigations are required.

Light et al. (1) derived the Light's criteria for identifying transudates and exudates. The Light's criteria involve measurement of the serum and pleural fluid protein and lactate dehydrogenase (LDH) levels. A pleural fluid is classified as an exudate if one of the following three criteria is met:

i)   Ratio of pleural fluid protein to serum protein greater than 0.5.
ii) Ratio of pleural fluid LDH to serum LDH greater than 0.6.
iii) Absolute pleural LDH value greater than two-thirds of the upper limit of normal serum LDH.

The pleural fluid protein to serum protein ratio is an indication of the permeability of the capillaries from which pleural fluid is formed. The pleural fluid LDH is an indication of the degree of inflammation in the pleural space (1).

In the original study, a total of 150 patients with pleural effusions were evaluated, of which 2 patients were misclassified, which resulted in a sensitivity of 99% and a specificity of 98% for identifying exudates (1). Subsequent studies by Hirsch et al. (2) and Roth et al. (3) confirmed the high sensitivity of Light's criteria, but reported a lower specificity of 65%–85%. Pleural fluid cholesterol levels are high in exudates because of the presence of degenerating cells and increased vascular permeability. Hamm et al. (4) used a pleural fluid cholesterol level of 60 mg/dl and correctly identified 95% of the 62 pleural fluid samples.

Light's criteria require the simultaneous measurement of serum and pleural fluid protein and LDH, totaling to four biochemical variables, which is cumbersome. Therefore, we compared the robustness of the pleural fluid cholesterol method with Light's criteria in differentiating transudates and exudates. We also combined pleural fluid protein with cholesterol and evaluated its efficiency in differentiating exudates.

METHODS
This is a prospective study conducted in a medical college hospital located in Chennai, Tamil Nadu, India. Patients of both sexes who presented with symptoms suggestive of pleural effusion were admitted in the hospital. Pleural effusion was confirmed by thorough physical examination and a postero-anterior or lateral chest radiograph. In cases where loculation was suspected, an ultrasound of the thorax was performed. These patients underwent thoracentesis after providing informed written consent in the vernacular language. Thoracentesis was done by trained doctors with or without ultrasound guidance as deemed necessary. The pleural fluid was analyzed for cholesterol, protein, and LDH levels. Pleural fluid cholesterol was measured using the enzymatic colorimetric method. A simultaneous blood sample was drawn and analyzed for protein and LDH. Other tests like complete blood count (CBC), renal function test (RFT), liver function test (LFT), sputum gram stain, sputum culture, and Ziehl–Nielsen (ZN) staining were conducted. Pleural fluid adenosine deaminase (ADA) was measured in patients in whom tuberculosis was suspected. In addition, pleural fluid was sent for gram staining, culture, and ZN staining. Thoracoscopic (flex-rigid pleuroscope LTF-160, Olympus, Tokyo, Japan) pleural biopsy was done in patients suspected of having malignancy in whom the cytology was negative.

The diagnosis of the disease causing the effusion was confirmed based on the following criteria:

1. **Congestive heart failure:** presence of an enlarged heart with clinical or echocardiographic evidence of cardiac dysfunction. Patients suspected of having co-existent respiratory infections, pulmonary emboli, or persistence of the effusion after adequate treatment of the cardiac disorder were excluded.
2. **Liver cirrhosis:** clinical and laboratory evidence of hepatic damage with portal hypertension or hypoalbuminemia.
3. **Pleural malignancy:** cytological or histological demonstration of pleural involvement.
4. **Tuberculosis:** elevated adenosine deaminase levels and good response to antituberculous treatment with improvement in symptoms to anti-tuberculous treatment.

5. **Parapneumonic effusion:** clinically and radiologically confirmed pneumonia with no direct or indirect evidence of bacterial invasion of the effusion.

Effusions associated with congestive heart failure and liver cirrhosis were classified as transudates and the rest were classified as exudates. Patients with renal disease and pulmonary embolism were excluded.

The classification of pleural fluid into transudates and exudates was based on the etiological diagnosis and this was considered as the gold standard against which the Light's criteria and pleural fluid cholesterol were compared. The precise cut-off value for pleural fluid cholesterol was not confirmed in the reviewed literature. Therefore, two cut-off values were used for analysis: 45 mg/dL and 60 mg/dL.

Statistical Analysis
The study was approved by the ethics committee of the institute. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows version 21.0 software (IBM Corp. Armonk, NY, USA). The Student's t-test was used to analyze the continuous variables, and chi-square test for proportions. The level of significance was analyzed, in more than two variables, using chi-square trend p value. Groups with more than three categorical variables were analyzed using the one-way analysis of variance (ANOVA) test. A p value of <0.05 was considered to be significant. The area under the receiver operating characteristic (ROC) curve was used to determine the diagnostic values of pleural fluid cholesterol between the study groups.

RESULTS
A total of 60 patients were enrolled for the study. Of these, 7 were excluded because an etiological diagnosis could not be established in them. The remaining 53 patients were included for analysis.

Effusions due to congestive cardiac failure, chronic liver disease, and hypoalbuminemia were classified as transudates and tuberculosis, carcinoma, and parapneumonic effusions were classified as exudates. Based on the etiological diagnosis, 19 (35.84%) of the effusions were classified as transudates and 34 (64.15%) were classified as exudates. Among the transudate group, 13 were male and 6 were female. Among the exudate group, 26 were male and 8 were female. The average age of patients presenting with transudate was slightly higher at 55.84 compared with those presenting with exudates at 49.18. The etiological diagnosis among the transudate and exudate groups is shown in Figure 1.
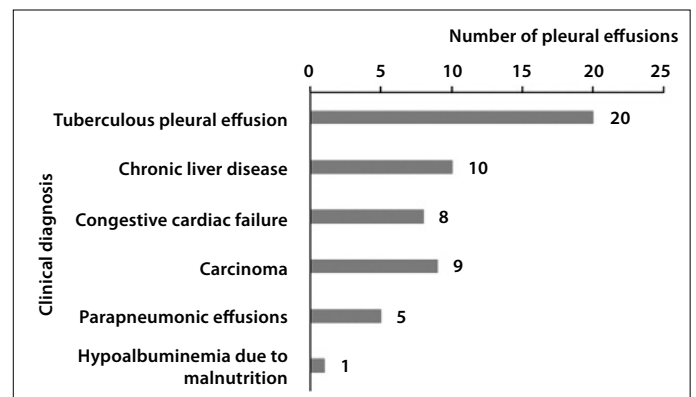

Figure 1. Etiological diagnosis of pleural effusions

The radiological presentation of the pleural effusion is shown in Table 1. In all, 8 (42.10%) of the transudative effusions were bilateral and 19 (55.88%) of the exudative effusions were right-sided.

The ROC curve analysis was performed to estimate the cut-off values of pleural fluid cholesterol for detecting exudates. With a cut-off value of 53 for exudates the sensitivity was 91.18% and specificity was 94.74%. The area under curve (AUC) was around 92% (p<0.0001) (Figure 2). When Light's criteria were applied, 9 of the transudates and 1 of the exudates were misclassified. On the other hand, when a pleural fluid cholesterol level of >60 mg/dL criteria was applied for defining an exudate, 1 transudate and 5 exudates were misclassified. When the cut-off was set as >53 mg/dL, 1 transudate and 3 exudates were misclassified. Pleural cholesterol cut-off of >45 mg/dl had the best discrimination resulting in misclassification of only 1 transudate and exudate (Table 2). Light's criteria misclassified 9 transudates, of which 1 was due to congestive heart failure and the other 8 were due to chronic liver disease. The exudate which was misclassified due to Light's criteria was due to carcinoma.

The sensitivity, specificity, positive predictive value, and negative predictive value of different criteria were calculated (Table 3) and compared with each other. We used a pleural fluid cholesterol level of >60 mg/dL as the cut-off for differentiating exudates and found that it was as good as Light's criteria. When we used >45 mg/dL as the cut-off, the pleural fluid cholesterol fared better than Light's criteria (p<0.0001).

We combined pleural cholesterol (>45 mg/dL) with pleural LDH (>200 IU/L) and used pleural protein (>3 g/dL) separately to calculate the indices for differentiating exudates. The combination of pleural fluid protein and pleural fluid cholesterol yielded the best results for sensitivity, specificity, positive predictive value, and negative predictive value at 82.93%, 100%, 100%, and 63.16%, respectively (p<0.0001) (Table 3).

DISCUSSION
In present study, we considered the etiological diagnosis as the gold standard and compared the efficacy of Light's criteria and pleural fluid cholesterol level in differentiating transudates and exudates. Light's criteria were designed to approach a 100% sensitivity and specificity for differentiating exudates. However, subsequent validation studies (2, 3) reported a lower specificity of 65%–85%. The reasons for this lower specificity are as follows: i) The original study by Light et al. (1)

Table 1. Radiological presentation of pleural effusion

	Transudate (n=19)	Exudate (n=34)
Right	6 (31.57%)	19 (55.88%)
Left	5 (26.31%)	10 (29.41%)
Bilaterally	8 (42.10%)	5 (14.70%)

Table 2. Misclassification of pleural effusion by applying Light's criteria and pleural fluid cholesterol level

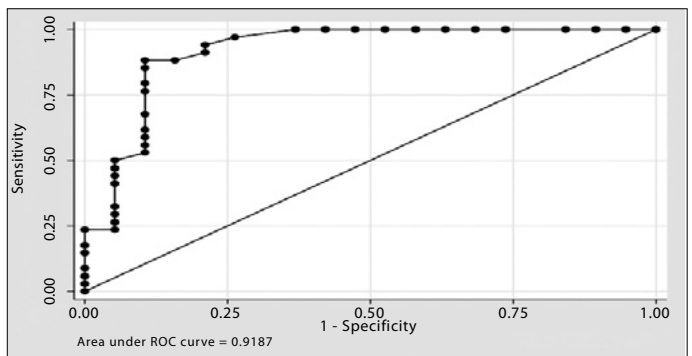|	Transudate (n=19)	Exudate (n=34)
Light's criteria	9 (47.36%)	1 (2.94%)
Cholesterol >60 mg/dL	1 (5.26%)	5 (14.70%)
Cholesterol >45 mg/dL	1 (5.26%)	1 (2.94%)
Cholesterol >53 mg/dL	1 (5.26%)	3 (8.82%)

Area under ROC curve = 0.9187

Figure 2. Curve of the sensitivity and specificity of pleural cholesterol. In a receiver operating characteristic (ROC) curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (1-specificity) for the different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair that corresponds to a particular decision threshold. A test with perfect discrimination (no overlap between the two distributions) has an ROC curve that passes through the upper left corner (100% sensitivity and 100% specificity). Therefore, the closer the ROC curve is to the upper left corner, the higher is the overall accuracy of the test. This ROC curve has an area of 0.918 (p<0.0001)

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value for various parameters and their combinations

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Light's criteria	78.57%	90.91%	97.06%	52.63%
Pleural fluid cholesterol >60 mg/dL	97.67%	78.26%	85.29%	94.74%
Pleural fluid cholesterol >45 mg/dL	97.06%	94.74%	97.06%	94.74%
Pleural fluid cholesterol >53 mg/dL	91.18%	94.74%	96.88%	85.71%
Pleural fluid protein + cholesterol	82.93%	100%	100%	63.16%
Pleural fluid LDH + cholesterol	82.05%	85.07%	94.12%	63.16%
LDH: Lactate dehydrogenase				

had rigorous inclusion criteria and hence the high specificity could not be replicated in subsequent studies on unselected populations, ii) The original recommendation to use an LDH value of 200 U/L decreased reproducibility because of differing assay techniques, and iii) Light's criteria uses multiple tests combined in an "or rule", thus increasing the likelihood of identifying a target condition. However, in doing so, it also increases the likelihood of incorrectly identifying other conditions (false positive result) and lowers the specificity (5).

In the original study by Hamm et al. (4), Light's criteria resulted in erroneous classification of 30% of 31 transudative effusions, whereas all the exudative effusions were correctly identified. Using a pleural fluid cholesterol level of 60 mg/dL as the cut-off value resulted in a misclassification of only 3 (5%) of the exudates as transudates. Quiroga et al. (6) used 45 mg/dL of cholesterol as the cut-off value in 80 patients and reported a sensitivity of 83% and a specificity of 100%. Hamal et al. (7) also used a pleural fluid cholesterol value of 45 mg/dL for the differentiation of pleural effusion. In their study, the application of Light's criteria misclassified 4 each of the exudates and transudates. Pleural fluid cholesterol was better as it misclassified only 1 each of the transudates and exudates with a sensitivity of 97.7% and specificity of 100%. In our study, we used 45 mg/dL as the cut-off, and the sensitivity and specificity were 97.06% and 94.74%, which was consistent with previous studies.

Heffner et al. (8) performed a meta-analysis in which they evaluated the complete data of the individual patients received from the primary investigators. The meta-analysis compared all the tests for pleural fluid differentiation by computing individual AUC generated by ROC analysis. The meta-analysis validated a pleural fluid cholesterol cut-off value of 45 mg/dL using ROC analysis and established a diagnostic accuracy with 89.0% sensitivity and 81.4% specificity. In addition to Light's criteria and pleural fluid cholesterol, Heffner et al. (8) also analyzed other methods for the classification of pleural fluid, such as pleural fluid to serum cholesterol ratio of >0.3, albumin gradient ≤1.2 g/dL and pleural fluid to serum bilirubin ratio of >0.6. The authors observed that triple test strategies had a better odds ratio than pair combinations, which were better than single tests in differentiating exudates. The exception was pleural fluid bilirubin which had the poorest discriminative properties.

In a meta-analysis conducted by Shen et al. (9) that included 20 studies and 3,496 subjects, the pleural cholesterol cut-off value in various studies ranged from 38 mg/dL to 65 mg/dL. The sensitivity (88%) and specificity (96%) of the pooled data were similar to those observed in our study. The authors recommended further studies to establish a correct cut-off for the pleural fluid cholesterol value.

The combination of pleural cholesterol concentration with pleural fluid protein and pleural fluid LDH has also been used to differentiate exudates from transudates. In 1995, Costa et al. (10) used a cut-off point of pleural fluid cholesterol as 45 mg/dL and combined it with pleural LDH >200 IU/L and identified exudates with a sensitivity of 99% and a specificity of 98%. Patel and Choudhury (11) combined pleural fluid cholesterol (≥60 mg/dL) with total protein (≥3 g/dL) and obtained a 100% sensitivity and specificity in identifying the exudates. In our study, the combination of pleural fluid cholesterol and pleural fluid protein produced better results than that of cholesterol with pleural fluid LDH (sensitivity 82.93% vs. 82.05% and specificity 100% vs. 85.07%).

CONCLUSION

Pleural fluid cholesterol with a cut-off value of >45 mg/dL is better than Light's criteria in the differentiation of exudative pleural effusions. The sensitivity and specificity of differentiation can be improved by combining pleural fluid cholesterol with pleural fluid protein. Both these criteria are better than the Light's criteria because they are cost-effective and do not require a simultaneous blood sampling for differentiation. In resource-limited settings, pleural fluid cholesterol can replace Light's criteria for classification of pleural effusion. The calculated power of the study is 97.1%. However, the study sample is small and these results need to be replicated in large-scale studies before recommending them for regular practice.

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