Diagnostic Value of Pleural Fluid Cholesterol versus Pleural Fluid Protein / Serum Protein Ratio to Differentiate Exudative from Transudative Pleural Effusion

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Abstract: *The classification of pleural effusion is usually done on the basis of Light's criteria as per which an exudative pleural effusion meets one of the following criteria - a) Ratio of protein in pleural fluid and serum >0.5 b) Ratio of LDH in pleural fluid to serum >0.6 c) Pleural fluid LDH > 2/3rd upper limit of serum LDH. But studies have observed that about 25% of transudative pleural effusions are misclassified as exudative using Light's criteria. The present study was conducted to determine the diagnostic value of pleural fluid cholesterol in differentiating transudative from exudative pleural effusion in comparison to Pleural fluid/Serum protein ratio.* <u>*Material and methods*</u>*: The present study was conducted on 50 patients with definite clinical diagnosis and pleural effusion evidenced by radiological imaging in department of Medicine, Guru Nanak Dev Hospital attached to Govt. Medical College, Amritsar. Each patient was investigated for routine investigations, Chest X - ray P. A. view, Pleural fluid protein and Pleural fluid cholesterol.* <u>*Results*</u>*: Out of 50 patients, 32 patients had transudative pleural effusion and 18 had exudative pleural effusion according to etiology. Using 0.5 as a cut off, pleural fluid protein/serum protein classified 42 as exudative and 8 as transudative pleural effusion. Using a cut off of 50 mg/dL, pleural fluid cholesterol classified 37 as exudative and 13 as transudative pleural effusion. The sensitivity, specificity, PPV, NPV and accuracy were found to be higher with pleural fluid cholesterol.* <u>*Conclusion*</u>*: Pleural fluid cholesterol is a good diagnostic tool to determine the type of pleural effusion. There is no need of simultaneous blood sampling reducing the cost and discomfort to the patient.*

Keywords: Pleural effusion, pleural fluid protein to serum protein ratio, pleural fluid cholesterol.

1. Introduction

A pleura is a serous membrane that folds back on itself to form a two layered membranous pleural sac.[1] Normally the pleural space contains less than 15 ml of pleural fluid.[2] The fluid functions as a lubricant and also prevents the collapse of lungs.[3] A pleural effusion is said to be present when there is an excess quantity of fluid in the pleural space.[4]

Pleural fluid accumulates when pleural fluid formation exceeds the pleural fluid absorption.[5] The lymphatics have the capacity to absorb 20 times more fluid that is formed normally.[6] As there are openings in the diaphragm and the pressure in the pleural cavity is less than the peritoneal cavity, pleural fluid accumulation can occur if there is free fluid in the peritoneal cavity.[7]

The common symptoms of patients with pleural effusion are dry cough, chest pain and breathlessness.[8]

When the patient is found to have pleural effusion, an effort should be made to determine its etiology. The first step is to determine whether the effusion is a transudative or an exudative.[9] Common causes of transudative effusion are congestive heart failure, cirrhosis of liver, nephrotic syndrome & hypoproteinemia.[10] Common causes of exudative pleural effusion are: Pulmonary tuberculosis, pneumonia, neoplasms and Pulmonary embolism.[11]

Initially a pleural fluid protein level of 3.0g/dl was used as a cut off to differentiate between transudative from exudative.[12]

Light et al. in 1972 found criteria to have sensitivity and specificity of 99% and 98%, respectively, for differentiating transudative and exudative pleural effusions. Exudates meet at least one of the following criteria, whereas transudative pleural effusions meet none.[11]

Light's criteria:
1) Ratio of protein in pleural fluid and serum >0.5
2) Ratio of LDH in pleural fluid and serum >0.6
3) Pleural fluid LDH >2/3rd of upper limit of serum LDH.[11]

Heffner et al.2002[13] have identified pleural effusion of exudative type with at least one of the following criteria.
1) Pleural fluid protein >2.9 gm/dL.
2) Pleural fluid cholesterol >45 mg/dL (1.16 mmol/L).
3) Pleural fluid LDH >2/3rd of upper limit of serum[13]

The cause of the increased cholesterol concentration is unknown, but two hypotheses are available[14]:

a) Cholesterol production by different cells has been recognized and it is possible that destruction of white and red blood cells in pleural effusion can cause an increase in the fluid cholesterol level.

b) Increased pleural permeability causes cholesterol concentrations to increase.

Present study was conducted to assess the usefulness of pleural fluid cholesterol in differentiating exudative and transudative pleural effusion. The diagnostic value of pleural fluid cholesterol was compared to pleural fluid protein/ serum protein ratio in differentiating between transudative and exudative pleural effusions.

2. Material and Methods

The present study was conducted on 50 patients with definite clinical diagnosis and pleural effusion evidenced by radiological imaging in department of Medicine, Guru Nanak Dev Hospital attached to Govt. Medical College, Amritsar after obtaining approval from Institutional Ethics Committee, Govt. Medical College, Amritsar and written informed consent from the patient.

Detailed clinical history and physical examination including detailed chest examination of each patient was recorded.

Each patient was investigated for CBC, LFT, RFT, Serum electrolytes and Chest X - ray PA view. HRCT chest was performed in certain cases. Diagnostic thoracentesis was performed in each patient and the pleural fluid was analyzed for proteins, cholesterol and culture and sensitivity. The ratio pf pleural fluid protein to serum protein was calculated and a cut off of 0.5 was used to differentiate between transudative and exudative pleural effusions. A cut off value of 50 mg/dL was used for pleural fluid cholesterol as a criteria to distinguish between transudative and exudative pleural effusion.

Interpretation of Results of Pleural Fluid/Serum Protein Ratio	
<0.5	Transudative Pleural Effusion
>0.5	Exudative Pleural Effusion

Interpretation of Results of Pleural Fluid Cholesterol	
<50 mg/dl	Transudative Pleural Effusion
>50 mg/dl	Exudative Pleural Effusion

3. Results

Demographic characteristics
The majority of the patients were males being 28 (56%) and the females 22 (44%). The mean age of patients was 49.56 years. The majority of the patients were with age ranging between 51 to 60 years (36%) followed by age group of 41 to 50 years (24%). The mean age of the patients with exudative pleural effusion was 44.24 years and those with transudative pleural effusion was 52 years.

Comorbidity
The most common comorbidity noted was Hypertension which was present in 18 patients (36%) followed by Diabetes mellitus in 12 patients (24%) and CVD in 10 patients (20%).

Etiology
The most common cause of pleural effusion was found to be tuberculosis in 23 (46%) followed by heart failure in 12 (24%) and malignancy in 6 (12%). Other less frequent causes of pleural effusion were Liver cirrhosis in 4 (8%), pneumonia with parapneumonic effusion in 3 (6%) and nephrotic syndrome in 2 (4%). According to the etiology, 32 (64%) patients had exudative pleural effusion and 18 (36%) had transudative pleural effusion.

Table 1: Distribution of patients according to Pleural fluid to Serum protein ratio

Protein Ratio	Frequency	Percent
>0.5	42	84.0
<0.5	8	16.0

42 patients (84%) had a protein ratio > 0.5 and 8 patients (16%) had a protein ratio < 0.5.

Table 2: Distribution of patients according to Pleural fluid Cholesterol

Pleural Fluid Cholesterol	Frequency	Percent
>50 mg/dL	37	74.0
<50 mg/dL	13	26.0

37 patients (74%) had pleural fluid cholesterol > 50 mg/dl and 13 patients (26%) had pleural fluid cholesterol < 50 mg/dl.

Table 3: Factors for identifying Exudative and Transudative Pleural Effusions

Parameter	Specificity	Sensitivity	PPV	NPV	Accuracy	P: value
Protein Ratio	86%	89%	92%	76%	89%	<0.0001
Fluid Cholesterol	98%	95%	99%	88%	96%	<0.0001

The practicality of each of the factors for recognizing exudate and transudate were evaluated in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and p - value. It is seen that Protein ratio has a sensitivity of 89%, specificity of 86%, PPV of 92%, NPV of 76% and accuracy of 89% and Fluid cholesterol has a sensitivity of 95%, specificity of 98%, PPV of 99%, NPV of 88% and accuracy of 96% for differentiating exudative and transudative pleural effusion. All these parameters have a significant p - value that is <0.0001.

Using Pleural fluid protein/Serum protein ratio cut - off of 0.5, 42 patients (84%) were diagnosed to have exudative pleural effusion and the rest of the 8 patients (16%) were diagnosed to have transudative pleural effusion. Using Pleural fluid cholesterol level of 50 mg/dl as a cut - off, 37 patients (74%) were diagnosed to have exudative pleural effusion and 13 patients (26%) were diagnosed to have transudative pleural effusion. p value of < 0.001 was obtained implying statistically significant difference between exudative and transudative pleural effusion. The mean Pleural fluid cholesterol in exudative pleural effusions was 81.34 mg/dl and in transudative pleural effusions was 25.12 mg/dl. The mean Pleural fluid protein was 5.12 g/dl in exudative pleural effusions and 3.25 g/dl in transudative

pleural effusions. The sensitivity, specificity, PPV, NPV and accuracy were 89%, 86%, 92%, 76% and 89% respectively with Pleural fluid/Serum protein ratio while the same parameters were found to be higher with pleural fluid cholesterol being 95%, 98 %, 99%, 88% and 96% respectively.

4. Discussion

In present study, 50 patients with pleural effusion were studied consisting of both males and females. According to final diagnosis, 32 (64 %) patients had exudative and 18 (36 %) had transudative Pleural effusion. The mean age in exudative group was 44.24±6.56 years and mean age in transudative was 52.56±4.36 years whereas the study done by R. Guleria et al.[15] shows mean age of patients with transudative effusion was 40±15.9 years and of those with exudative pleural effusion was 43.5±17.5 years. There was male predominance with 28 (56%) and female being 22 (44%) similar to the study done by Rogerio Rufino et al.[16] which found female percentage being 43%. The most common comorbidities in patients with effusion in the study were hypertension (36%), diabetes (24%) and CVD (20%).

Etiological classification showed that the most frequent cause of exudative effusion in this study was tuberculosis in 23 (46%) patients followed by heart failure in 12 (24%) and malignancy in 6 (12%). Other less frequent causes of effusion were Liver cirrhosis in four of them (8%) and pneumonia with para - pneumonic effusion in 3 of them (6%). Similarly, in a study by Hamal et al.[17] it was seen that tubercular effusion was the most common pleural effusion. It counted 21 out of 62 cases (33.9%). Carcinoma lung was the second most common cause accounting for 14.5%.

On statistical analysis, the mean of pleural fluid protein in exudative effusion was 5.12± 1.26 g/dL and 3.25± 1.12 g/dL in transudates and p - value = 0.001 which means statistically significant difference between two groups. The mean pleural fluid cholesterol was 81.34 mg/dL in exudates and 25.12 mg/dL in transudates and difference was highly significant which was comparable to other studies. In study by Chandler et al.,[18] the mean pleural fluid cholesterol was 35.6 mg/dL in transudates and 80.3 mg/dL in exudates. In study by Majhi et al.,[19] the mean Pleural fluid cholesterol level was 64.2 ± 7.5 mg/ dL in exudative effusions and 26.05± 8.01 mg/dL in transudative effusions. In study by Rugerio Rufino et al.,[16] the mean pleural cholesterol level in exudates was 90.39 mg/dL.

In our study, 37 patients (74%) were diagnosed to have exudative pleural effusion and 13 patients (26%) were diagnosed to have transudative pleural effusion using fluid cholesterol while 42 patients (84%) were diagnosed to have exudative pleural effusion and 8 patients (16%) were diagnosed to have transudative pleural effusion using fluid protein/serum protein ratio (protein ratio). p - value was 0.56, which means there is no significant difference between protein ratio and fluid cholesterol in differentiating exudative from transudative pleural effusion.

In a study on 53 patients by Dhandapani et al.[20] 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. The pleural fluid cholesterol (cut - off >60 mg/dL) gave a higher specificity (100%) and positive predictive value (100%) but a lower sensitivity (82.93%) and negative predictive value (63.16%). A study by Hamal et al, [17] on 62 cases of pleural effusion demonstrated that Pleural fluid cholesterol concentration had a sensitivity of 97.7 % and specificity of 100% for differentiating transudative and exudative pleural effusion. The pleural fluid protein / serum protein ratio had a sensitivity of 81.4% and specificity of 82.6%. Rugerio Rufino et al.[16] in their case series of 100 consecutive patients used a pleural fluid cholesterol cut - off of more than 50 mg/ dL and demonstrated a sensitivity of 97.22%, a specificity of 85.71%, a positive predictive value of 98.59% and a negative predictive value of 75%. The study by Leers et al.[21] had an accuracy of 82%, sensitivity of 76% and specificity of 98%. Using pleural fluid cholesterol whereas Light's criteria gave an accuracy of 98%, sensitivity of 98% and specificity of 95%. Costa et al.[22] showed a sensitivity of 99% and specificity of 98% in their study using pleural fluid cholesterol cut - off of 45 mg/dL. The Light's criteria identified exudates with a sensitivity of 99% and a specificity of 82%. A study by Gautam et al.[23] showed that both Light's criteria and Heffner[13] criteria had a sensitivity of 100% however specificity was 71.43% and 64.29% respectively which is far less than that of pleural fluid cholesterol (85.71%). Using pleural fluid cholesterol levels at a cut - off point of greater than 60 mg/dL for distinguishing transudates and exudates, the sensitivity was 98%, specificity, positive predictive value (PPV) and negative predictive value (NPV), were 100 percent in a study conducted by Patel and Chaudhary.[24] A study by Ambresh and Mulimani[25] showed that Pleural fluid cholesterol had a sensitivity of 97.8%, specificity of 100% and an accuracy of 98.3 %. In study by Guleria et al, [15] a cut off value of > 60 mg/ dL pleural fluid cholesterol was taken and a sensitivity of 88% with a specificity of 100% and an accuracy of 92% was demonstrated. The results were superior to the Light's criteria which showed a sensitivity of 98% and specificity of 80%.

In our study, the sensitivity, specificity, PPV, NPV and accuracy using pleural fluid cholesterol cut off of 50 mg/dl were 95%, 98, 99%, 88% and 96% respectively whereas using protein fluid protein/serum protein ratio were 89%, 86%, 92%, 76% and 89% respectively

These studies were also comparable with the findings in our study. Compared to Pleural fluid/Serum protein ratio, pleural fluid cholesterol is almost equal or at par in differentiating exudative pleural effusion from transudative pleural effusion. We found that Pleural fluid cholesterol had a higher sensitivity and specificity than pleural fluid/serum protein ratio.

5. Conclusion

Measuring pleural fluid cholesterol is a simple and cost effective method. There is no need of simultaneous blood sampling reducing the cost and patient's discomfort. Based on the results of this study and review of research done by

other authors, it can be concluded that Pleural fluid cholesterol is a good diagnostic tool to determine the type and etiology of effusion.

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