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ESTIMATION OF PLEURAL FLUID TOTAL CHOLESTEROL AS A DIAGNOSTIC AID IN PATIENTS WITH PLEURAL EFFUSION

General Medicine

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ABSTRACT

INTRODUCTION:- This study was conducted to assess the usefulness of pleural fluid cholesterol in differentiating exudative from transudative effusion and as a diagnostic aid in patients with pleural effusion.

METHOD:- In this Descriptive study we studied 100 cases with undiagnosed pleural effusion who were coming to OPD or IPD of Santokbha Durlabhji Memorial Hospital from July 2014 to March 2016. After cytological and biochemical analysis of pleural aspirate sample, it was classified as transudative or exudative according to light's criteria and final diagnosis with clinical diagnosis taken as gold standard for determining whether pleural effusion is exudative or transudative. Pleural cholesterol level was measured in all pleural fluid samples.

RESULTS:- In our study out of 100 patients 71 were exudative and 29 were transudative pleural effusion and included 68 male and 32 female patients with majority of the patients were in the age group of 21-30 years . most common etiological diagnosis for exudative effusion was tuberculosis(43% patients) followed by parapneumonic effusion(13% patients) and Malignancy (9% patients). In the transudative group, CHF (21% patients) was responsible for most of the cases. By using light's criteria we were able to classify all of the 71 exudates correctly (sensitivity of 100%) but it misclassified 8 transudates (all had CHF) as exudative effusion (specificity of 72.41%). After plotting ROC curves, the value of pleural fluid protein, pleural/serum protein ratio, pleural fluid LDH & Pleural/serum LDH ratio which could best differentiate exudative from transudative pleural effusion were ≥ 2.7 mg/dl(98.59% sensitivity, 96.55% specificity), ≥ 0.47(100% sensitivity, specificity), ≥396 IU/L (98.59% sensitivity, 86.21% specificity) & ≥0.555 (94.37% sensitivity, 89.66%specificity) . pleural fluid cholesterol level that would best differentiate exudative from transudative pleural effusion was found to be ≥53mg/dl (98.59%,sensitivity, 100%specificity). Pleural fluid cholesterol level had maximum positive correlation with pleural fluid protein. On comparing the diagnostic efficiency of various parameters for diagnosing exudative pleural effusion, we observed that pleural/serum protein ratio was most efficient and Pleural fluid cholesterol had the second best accuracy.

CONCLUSION:- We concluded that all the cases of transudative effusion which were misclassified by light's criteria were correctly diagnosed using pleural cholesterol hence when used together could lead to lesser misclassification of effusions. Pleural fluid cholesterol is in itself an efficient independent variable for diagnosing pleural effusions and does not require simultaneous measurement of other parameters in serum as required for light's criteria hence lowering the cost of diagnostic procedure.

KEYWORDS

Light's Criteria , Pleural Fluid Cholesterol, Roc Curve, Exudative , Transudative

INTRODUCTION

The lungs are a pair of spongy, air-filled organs located on either side of the chest (thorax). The pleural cavity is the pleural space between the two pleurae (visceral and parietal) of the lungs and normally contains a small amount of pleural fluid. Most fluid is produced by the parietal circulation (intercostal arteries) via bulk flow and reabsorbed by the lymphatic system. In a normal 70 kg human, a few milliliters of pleural fluid is always present within the intrapleural space.[1] A profound increase in the production of pleural fluid—or some blocking of the reabsorbing lymphatic system—is required for fluid to accumulate in the pleural space.[2]

Pleural effusions are generally classified as transudates or exudates, based on the mechanism of fluid formation and pleural fluid chemistry. In some cases, the pleural fluid may have a combination of both transudative and exudative characteristics.

The sensitivity and specificity of Light's criteria for detection of exudates have been measured in many studies and are usually reported to be around 98% and 80% respectively.[3] This means that although Light's criteria are relatively accurate, twenty percent of patients that are identified by Light's criteria as having exudative pleural effusion actually have transudative effusion.

Measuring cholesterol in pleural effusion could be a useful aid in diagnosis of a patient with pleural effusion. Pleural cholesterol level measurement is independent of serum cholesterol level and does not require any simultaneous serum sampling. Hence could be more efficient, easier and cost effective.we studied the pleural fluid total cholesterol as a diagnostic aid in patients with pleural effusion.

AIMS AND OBJECTIVES

To study Sensitivity and specificity of Pleural fluid cholesterol level for differentiating between Exudative and transudative pleural effusions and variation in cholesterol level in pleural fluid in various diseases. Also to measure correlation of pleural fluid cholesterol with pleural fluid protein and pleural fluid LDH levels.

MATERIAL AND METHODS

This study was conducted in Department of Medicine on patients coming to OPD or IPD of Santokba Durlabhji Memorial Hospital, Jaipur, who fulfill the inclusion criteria of the study. This was a Descriptive type of observational study from july 2014 to March 2016. Informed consent was obtained from patients or their legal surrogates and all patient information were kept confidential. Permission from institutional ethical committee was taken.Total 100 cases were taken and sample size was calculated at 95% confidence level assuming 93.2% efficiency of Pleural fluid Cholesterol in differentiating exudative and transudative types of pleural fluid as per previous studies results.All patients with undiagnosed pleural effusion of all age groups irrespective of sex were included in this study. Patients who have already undergone diagnostic thoracocentesis for the current illness before presenting to our hospital, diagnosed pleural effusion and those who did not give consent were excluded from the study.After cytological and biochemical analysis of pleural aspirate sample, it was classified as transudative or exudative according to light's criteria and final diagnosis with clinical diagnosis taken as gold standard for determining whether pleural effusion is exudative or transudative. Pleural cholesterol level was measured in all pleural fluid samples. Cholesterol was measured with reflectance spectrophotometry.Reagent Kit used is VITROS CHOL slide for all patients.

Data was entered in excel sheet to prepare master chart and subjected for statistical analysis. Quantitative data was summarized as mean and standard deviation (SD), while categorical data was summarized as percentages.One way ANOVA & post hoc Tukey HSD tests were used for analyzing quantitative data whereas Fischer exact test and Chi-square tests were used for analyzing categorical data. Pearson Correlation coefficients were calculated to assess correlation between quantitative variables. Sensitivity, Specificity , Negative predictive value, Positive predictive value and accuracy were calculated as per standard formulae. Receiver operating characteristic (ROC) curves were made to find out appropriate cut off values with highest sensitivity and specificity.P <0.05 was taken as significant.

MedCalc 12.2.1.0 version software was used for all statistical calculations.

OBSERVATION AND RESULTS

Total of 100 patients were included in our study out of which 68% of patients were males and 32% were females. Majority (19%) of patients were in the age group of 21-30 years with 16% males and 3% females.71% of the patients had exudative pleural effusion while 29% had transudative pleural effusion.

Tuberculosis(43 patients) was the most common etiology for exudative pleural effusion followed by pneumonia (13 patients) and Empyema (3 patients) while pulmonary embolism, rheumatoid arthritis and sepsis constituted one patient each .CHF (21 patient) was the most common condition responsible for transudative effusion while rest of the 8 patients in transudative group had hypoprotenemia (2 due to nephrotic syndrome, 1 due to cirrhosis of liver and other 6 due to various factors).

Table 1: Distribution of study participants according to type of fluid & type of disease

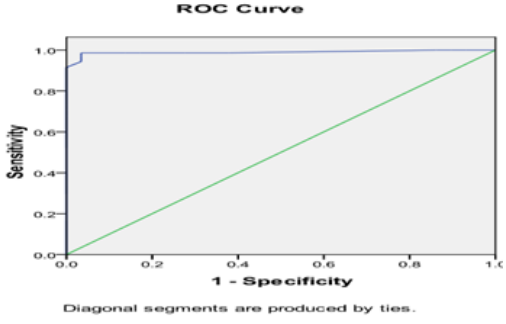
Clinical Diagnosis	Exudative		Transudative		Total	
	No.	%	No.	%	No.	%
CHF	0	0.00	21	72.41	21	21.00
Empyema	3	4.23	0	0.00	3	3.00
Hypoprotenemia	0	0.00	8	27.59	8	8.00
Malignancy	9	12.68	0	0.00	9	9.00
Pneumonia	13	18.31	0	0.00	13	13.00
Pulmonary Embolism	1	1.41	0	0.00	1	1.00
Rheumatoid Arthritis	1	1.41	0	0.00	1	1.00
Sepsis	1	1.41	0	0.00	1	1.00
Tuberculosis	43	60.56	0	0.00	43	43.00
Total	71	100.00	29	100.00	100	100.00

Chi-square = 100.000 with 8 degrees of freedom; P<0.001

The value of individual component of pleural fluid was obtained after plotting ROC curve, which could best differentiate exudative from transudative pleural effusion. Statistically significant AUC was found for different component of pleural fluid (p<0.001).

Table 2: ROC curve analysis of various pleural fluid components

	Area Under Curve	'p' Value	Exudative if	Sensitivity	1 – Specificity
Pleural fluid Cholesterol level	0.994	<0.001	≥53	0.986	0.000
Protein	0.989	<0.001	≥2.7	0.986	0.034
Pleural/Serum Protein ratio	1.000	<0.001	≥0.47	1.000	0.000
LDH	0.972	<0.001	≥396	0.986	0.138
Pleural/Serum LDH ratio	0.970	<0.001	≥0.555	0.944	0.103



In our study we used pleural fluid protein cut off value ≥ 2.7 mg/dl for diagnosing pleural effusion . 98.59% (70 patients) of exudative pleural effusion were correctly classified whereas in the transudative group 96.59% (28 patients) were correctly classified. similarly, pleural/serum protein ratio of ≥ 0.47 was correctly able to classify all exudative and transudative pleural effusion.Pleural fluid LDH of ≥ 396 IU/L could classify 98.59% (70 patients) of the exudative effusion correctly and 86% (25 patients) of transudative pleural effusion and by using pleural/serum LDH ratio cut-off of ≥ 0.555, 94.37% patients in exudative group & 89% patients in transudative group were correctly classified . Results were statistically significant (p<0.001) .

Table 3: Distribution of study participants according to type of fluid & Pleural fluid Cholesterol level

Pleural fluid Cholesterol level	Exudative		Transudative		Total	
	No.	%	No.	%	No.	%
Exudative if ≥53	70	98.59	0	0.00	70	70.00
Transudative if <53	1	1.41	29	100.00	30	30.00
Total	71	100.00	29	100.00	100	100.00

Fisher Exact Test P<0.001

We studied the distribution of study participants according to type of fluid & Pleural fluid Cholesterol level. In our study a pleural fluid cholesterol cut-off level of ≥ 53mg/dl was able to classify 98.59% (70 patients) of exudative effusion as exudative but one patient was misclassified as transudative. Whereas all of the transudative effusion were correctly classified by using the above cut-off value for pleural fluid cholesterol.Statistically significant (p<0.001) association was found between clinical diagnosis and diagnosis using pleural fluid cholesterol level of ≥ 53mg/dl for diagnosing exudative pleural effusion.

In our study using parameters of light's criteria all the exudative effusion (71 patients) were correctly classified but 27.59% patients of transudative effusion were misclassified as exudative. Statistically significant (p<0.001) association was found between clinical diagnosis and diagnosis using Light's criteria for diagnosing exudative pleural effusion.

Table 4: Diagnostic efficiency of various criteria

	Sensitivity	Specificity	PPV	NPV	Accuracy
Protein	98.59	96.55	98.59	96.55	98.00
Pleural/Serum Protein ratio	100.00	100.00	100.00	100.00	100.00
LDH	98.59	86.21	94.59	96.15	95.00
Pleural/Serum LDH ratio	94.37	89.66	95.71	86.67	97.00
Pleural fluid Cholesterol level	98.59	100.00	100.00	96.67	99.00
light's criteria	100.00	72.41	89.87	100.00	92.00

According to the above table our study shows that Pleural/Serum protein ratio had the highest accuracy (100%) for diagnosing exudative pleural effusion followed by pleural fluid cholesterol with accuracy of 99% whereas light's criteria was least accurate (92% accuracy).

We also studied the Correlation of Pleural fluid Cholesterol level with other parameters . In our study pleural fluid cholesterol level had maximum positive correlation with pleural fluid protein and minimum with pleural fluid LDH.

However, correlation of cholesterol with other parameters of pleural fluid was statistically significant (p<0.05).

On studying the level of mean cholesterol in pleural fluid in various diseases it was 48.81mg/dl CHF, 50mg/dl in hypoproteinemia, 62.33mg/dl in empyema while in malignancy it was 88.67mg/dl. In pneumonia mean cholesterol was 80.23mg/dl whereas in tuberculosis it was 81.60mg/dl.The difference between the mean cholesterol level in transudative effusion (CHF, Hypoproteinemia) and exudative effusion was statistically significant(p<0.05).

DISCUSSION

The most important step in evaluation of a patient with pleural effusion is diagnosing whether the effusion is exudative or transudative as the whole management of the patient depends on it. Although the light's criteria is highly sensitive for exudative effusions, it does misclassify approximate 20% transudative effusions as exudative. Light's criteria

also requires simultaneous measurement of serum level of protein and LDH which could be affected by many coexisting illnesses which the patient might have and it might affect the pleural/serum ratio of these factors leading to erroneous diagnosis.

Hence search for other parameters of pleural fluid which could help in diagnosis of type of pleural fluid led to the discovery of cholesterol as a useful factor in pleural fluid which could aid in the diagnosis. In 1987 Ham et al [4] investigated the usefulness of pleural fluid cholesterol and found that by using a cut-off value of 60mg/dl to separate the exudates from transudates, only 5% sample were incorrectly classified.

Our study was conducted to assess the usefulness of pleural fluid cholesterol in differentiating exudative from transudative effusion.

In our study of 100 patients, 71 were exudative and 29 were transudative pleural effusion and included 68 male and 32 female patients. The age group of 21-30 years constituted the maximum number of patients(19) with 16 male and 3 female candidates.

According to our study the most common etiological diagnosis for exudative effusion was tuberculosis(43% patients) followed by parapneumonic effusion(13% patients) and Malignancy (9% patients) which is almost similar to the findings in the study done by Anand patel et al [5] in which 50% patients had tuberculosis and 13.3% patients were of parapneumonic effusion while 16.7 % were of neoplastic etiology. Given the high prevalence of tuberculosis in our country it's not surprising to find it to be the most common etiology for exudative effusion. In contrast, the studies which were done in other countries, where tuberculosis is not so common, like one done by Gil suay et al [6], Valdes et al [7] and Romero et al [8], malignancy was the most common etiology for exudative effusion.

In the transudative group, CHF (21% patients) was responsible for most of the transudative effusions in our study which was also seen in studies done by Hamm et al [4] (41% patients), Romero et al [8] (10.4% patients), Anand patel et al [5](8.3% patients) where CHF was the most common etiology in the transudative group.

By using light's criteria we were able to classify all of the 71 exudates correctly (sensitivity of 100%) but it misclassified 8 transudates (all had CHF) as exudative effusion (specificity of 72.41%). The positive predictive value(PPV), negative predictive value(NPV) and accuracy of light's criteria in our study was 89.87%, 100% and 92% respectively. Statistically significant ($p<0.001$) association was found between clinical diagnosis and diagnosis using Light's criteria for diagnosing exudative pleural effusion in our study. These findings are similar to the studies done by Hamm et al [4], Ortega et al [9], Valdes et al [7], Romero et al [8] and Leers et al [10].

After plotting ROC curves, the value of pleural fluid protein which could best differentiate exudative from transudative pleural effusion was ≥ 2.7 mg/dl. Using this cut-off value only one of the exudate and one transudate was misclassified. The exudative effusion misclassified was parapneumonic and transudative effusion wrongly classified was due to CHF. The sensitivity, specificity, PPV, NPV and accuracy was 98.59%, 96.55%, 98.59%, 95.55% and 98% respectively. Hamm et al [4], Guleria et al [11] also observed that pleural fluid protein of ≥ 3mg/dl had best ability for diagnosing exudative pleural effusion. Similar finding was also seen in study done by Anand et al [5] .The value of pleural/serum protein ratio, after plotting ROC curves, for diagnosing pleural effusion was found to be ≥ 0.47. Using this cut-off all exudates and transudates were correctly classified thus achieving 100% sensitivity, specificity, PPV, NPV and accuracy. Statistically significant ($p<0.001$) association was found.

According to ROC curve, a pleural fluid LDH ≥396 IU/L had best discriminatory potential for diagnosing exudative pleural effusion. The sensitivity, specificity, PPV, NPV and accuracy was 98.59%, 86.21%, 94.59%, 96.15% and 95% respectively. Using this cut-off only 1 exudate and 4 transudates were misclassified. This is in contrast to the findings in the study done by Guleria et al [11] and Romero et al [8] where value of ≥135 IU/L and ≥280 IU/L respectively had best discriminatory ability. This variability of cut-off points thus noticed led Romero et al [8] to suggest that modification of these cut-off values according to the needs of one particular laboratory may improve specificity of the test without sensible loss in its capability to segregate exudates. Guleria et al [11] reported an improvement in their accuracy on using the modified cut-offs as compared to using classical light's criteria. Value of Pleural/serum LDH ratio which could best differentiate exudative from transudative effusion was ≥0.555 after plotting ROC curve. The sensitivity, specificity, PPV, NPV and accuracy was 94.37%, 89.66%, 95.71%, 86.67% and 97% respectively.

In our study the pleural fluid cholesterol level that would best differentiate exudative from transudative pleural effusion was found to be ≥53mg/dl. Using this cut-off only one exudative effusion was misclassified while all the transudates were correctly classified. The sensitivity, specificity, PPV, NPV and accuracy was calculated to 98.59%, 100%, 100%, 96.67% and 99% respectively. Statistically significant ($p<0.001$) association was found between clinical diagnosis and diagnosis using pleural fluid cholesterol for diagnosing exudative pleural effusion. The only exudate which was wrongly classified as transudate was due to empyema. Similar finding was also noticed by Valdes et al [7] who by using cut-off of 55mg/dl obtained sensitivity of 91%, specificity of 100%, PPV of 100%, 79% NPV and 93.2% accuracy in diagnosing exudative effusion. Gil suay et al [6] achieved sensitivity and specificity of 95.5% and 91.6% on using cut-off of 54mg/dl while Rufino R et al [12] by using cut-off at 50mg/dl observed sensitivity of 97.2% and specificity of 85.7%.

We also observed that pleural fluid cholesterol level had maximum positive correlation with pleural fluid protein (pearson correlation of 0.769) and minimum with pleural fluid LDH (pearson correlation of 0.202).However, correlation of cholesterol with protein , LDH and their pleural/serum ratio was statistically significant ($p<0.05$).

On comparing the diagnostic efficiency of various parameters for diagnosing exudative pleural effusion, we observed that pleural/serum protein ratio was most efficient . Pleural fluid cholesterol had the second best accuracy followed closely by Pleural fluid protein. Light's criteria was the least accurate.

Thus, the present study has shown that pleural fluid cholesterol has better diagnostic accuracy for diagnosing pleural effusion than light's criteria and similar finding was also noticed by Hamm et al [4], Valdes et al [7], Guleria et al [11], Pfalzer et al [13], Anand et al [5] and Rufino et al [12]. All the transudative effusions which were misclassified by light's criteria could be correctly diagnosed by pleural cholesterol. Given the fact that light's criteria requires measurement of protein and LDH both in pleural fluid and serum and it's lesser accuracy, measurement of pleural fluid cholesterol could be a simple, better, cost effective method for diagnosing pleural effusion and it also obviates the need for simultaneous serum sampling as required for light's criteria.

CONCLUSION

The present study was undertaken to determine the role of pleural fluid cholesterol in diagnosing pleural effusion. In this study all the cases of transudative effusion which were misclassified by light's criteria were correctly diagnosed using pleural cholesterol hence when used together could lead to lesser misclassification of effusions.Pleural fluid cholesterol is in itself an efficient independent variable for diagnosing pleural effusions and does not require simultaneous measurement of other parameters in serum as required for light's criteria hence lowering the cost of diagnostic procedure. Pleural fluid cholesterol has maximum positive correlation with pleural fluid protein with pearson correlation of 0.769.

Hence it can be concluded that measurement of pleural fluid cholesterol could be a simple, better, cost effective method for diagnosing pleural effusion and it also obviates the need for simultaneous serum sampling as required for light's.

BIBLIOGRAPHY

1. Widmaier, Eric P, Raff, Hershel, Strang, Kevin T. Vander's human physiology : the mechanisms of body function. 10 ed. Boston: McGraw-Hill; 2006.
2. Pleural cavity[internet]. 2014[cited 2014 May 28]. Available from: http://en.wikipedia.org/wiki/Pleural_cavity
3. Romero S, Martinez A, Hernandez L, Fernandez C, Espasa A, Candela A et al. Light's criteria revisited: consistency and comparison with new proposed alternative criteria for separating pleural transudates from exudates. Respiration; international review of thoracic diseases.2000; 67 (1): 18–23.
4. Hamm H, Brohan U, Bohmer R, Missmahl HP. Cholesterol in pleural effusions:a diagnostic aid. Chest 1987; 92: 296-302.
5. Anand K. Patel, Sushmita Choudhury. Combined Pleural fluid cholesterol and total protein in differentiation of exudates and transudates. The Indian Journal of Chest Diseases and allied sciences. 2013;55(1):21-23
6. Gil Suay V, Martínez Moragón E, Cases Viedma E,Perpiñá Tordera M, León Fábregas M, Sanchis Aldás J. Pleural cholesterol in differentiating transudates and exudates: a

prospective study of 232 cases. Respiration 1995; 62: 57-63.
7. L. Valdes, A. Pose, J. Suarez .Cholesterol: a useful parameter for distinguishing between pleural exudates and transudates. Chest. 1991; 99(5): 1097–1102.
8. Romero S, Candela A, Martín C, Hernández L, Trigo C, Gil J. Evaluation of different criteria for the separation of pleural transudates from exudates. Chest. 1993; 104(2): 399-404.
9. Ortega L, Heredia JL, Armengol R, Mir I, Romanillas T, Armengol J. The differential diagnosis between pleural exudates and transudates: The value of cholesterol. Med Clin . 1991; 96(10): 367-370 .
10. Leers MP, Kleinveld HA, Scharnhorst V. Differentiating transudative from exudative pleural effusion:should we measure effusion cholesterol?. Clin Chem Lab Med. 2007; 45(10):1332-1338.
11. Guleria R, Agarwal S.R, Sanjeev Sinha, Pande J.N, Anoop Misra. Role of Pleural fluid cholesterol in differentiating transudative from exudative pleural effusion. The National Medical Journal Of India. 2003;16(2):64-69
12. Rogerio Rufino, Bruna L, Renato Azambuja, Thiago Mafort, Jose Pugliese, Claudia Henrique. Pleural Cholesterol to the diagnosis of exudative effusion. Open Respir Med J. 2104; 8(1): 14-17.
13. Pfalzer B, Hamm H, Bröhan U, Beisiegel U, Ostendorf P. Cholesterol in pleural effusion:a diagnostic aid. Pneumologie. 1990; 44(1):180-181.