Comparative analysis of pleural fluid cholesterol levels against light's criteria in differentiating exudative and transudative pleural effusions

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Abstract
Background: Pleural effusion is a very common clinical presentation encountered by a chest physician and may be a transudate or an exudate. In recent years pleural fluid cholesterol have been proposed for separation of transudates from exudates, and present study was aimed to study levels of Cholesterol levels in pleural fluids of varied etiologies. **Material and Methods:** Present study was single-center, prospective, comparative, parallel-group, observational study, conducted in patients age $\geq$ 14 years, evaluated on OPD basis and/or admitted with definite clinical diagnosis and pleural effusion evidenced by radiological imaging giving written informed consent for thoracocentesis. **Results:** In present study, 180 patients with pleural effusion were studied majority were from 30-40 years (22.2 %), males (70.6%), had right sided pleural effusion. According to clinical diagnosis 155 (86.1%) patients had exudative pleural fluid and 25 (13.9%) patients had transudative pleural effusion. According to one of light's criteria (ratio of pleural fluid protein to serum protein more than 0.5 as exudative pleural effusion) 152 (84.4 %) patients had exudative and 28 (15.6 %) had transudative pleural effusion. While based on another Light's criteria (pleural fluid LDH more than or equal to 200 IU suggestive of exudative pleural effusion). 143 (79.4 %) had exudative and remaining 37 (20.4 %) had transudative pleural effusion. Pleural fluid cholesterol > 40 mg/dl was considered as exudative pleural fluid, 149 (82.7 %) had exudative pleural effusion and 31 (17.3 %) had transudative. We compared mean values of pleural fluid protein, protein ratio, LDH and pleural fluid cholesterol between exudates and transudates, we noted highly significant difference between them (P value of < 0.001). Majority of the patients were of tubercular origin with no. of patients being 89 (49.4%) followed by synpneumonic effusion with 28(15.6%) patients and patients with malignant effusion being 24 (13.3%). The cut of value of pleural fluid cholesterol less than 40 mg/dl was highest with sensitivity of 95.8 and specificity of 93.7 with positive predictive value of 99.71 and negative predictive value of 82.34. **Conclusion:** Measuring pleural fluid cholesterol is simple and cost effective, it has better sensitivity, specificity and PPV in differentiating transudates and exudates, avoids simultaneous estimation of four parameters as required by Light's criteria.
Keywords: pleural effusions, pleural fluid cholesterol, Light's criteria, exudative, transudative.

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INTRODUCTION

Pleural effusion is a very common clinical presentation encountered by a chest physician. A correct diagnosis of underlying disease is essential for management of pleural effusion. It can be due to diseases of the pleural membrane or due to diseases of thorax or abdominal organs. Pleural effusion may be a transudate or an exudate.[1] Transudates are mostly due to congestive heart failure, and liver cirrhosis. Exudative pleural effusion is formed because of damaged capillary beds by inflammation and injury to the lung, the pleura or adjacent tissues.[2] Pleural effusions are

due to varied etiological factors [2]; hence the differential diagnosis is wide, which makes the physician difficult to come to the diagnostic conclusion without extensive investigation.[3] Therefore, the first step in the evaluation of pleural effusion after diagnostic thoracocentesis is to differentiate between transudate and exudates, which narrows down the diagnosis, and avoid further unnecessary investigation. Light's criteria misidentifies a transudative effusion as an exudative pleural effusion in as many as 25% of cases.[1] Various biochemical tests have been investigated to differentiate pleural effusion into exudates and transudates as pleural fluid cholesterol, serum-effusion albumin gradient, pleural fluid to serum bilirubin concentration ratio, pleural fluid acute phase proteins, and pleural fluid cholinesterase.[4,5,6] In recent years pleural fluid cholesterol have been proposed for separation of transudates from exudates, the tests that indicate a pleural exudate have included a pleural fluid cholesterol greater than 60 mg/dl[7] or greater than 45 mg/dl.[8] Present study was aimed to study levels of Cholesterol in pleural fluids of varied etiologies as well as evaluate diagnostic efficacy with Light's criteria as compared to level of pleural fluid cholesterol in order to differentiate between transudates and exudates.

MATERIAL AND METHODS

Present study was single-center, prospective, comparative, parallel-group, observational study, conducted in department of Respiratory Medicine, at MGM Hospital and Medical college, Aurangabad, Maharashtra, India. Study duration was of 2 years (August 2012 to Oct 2014). Study was approved by institutional ethical committee.

Inclusion criteria: Patients age ≥ 14 years, evaluated on OPD basis and/or admitted with definite clinical diagnosis and pleural effusion evidenced by radiological imaging giving written informed consent for thoracocentesis.

Exclusion criteria: Patients not willing and not giving written informed consent for thoracocentesis.

Informed consent was obtained from all subjects who fulfill the inclusion criteria for study. Details such as age, gender, clinical history, examination and diagnosis. relevant investigations as chest X-ray(P-A view) ,USG (Chest and abdomen), CECT (Chest), laboratory investigations (Complete blood count, ESR, peripheral smear, Random blood sugar ,RFT, LFT, Serum Cholesterol, S LDH, serum electrolytes), investigations specific to pleural fluid (Protein, sugar, LDH, Microscopy ,Cytology, Culture and gram stain) were noted in case record proforma. All patients underwent a diagnostic thoracocentesis under aseptic precautions, pleural fluid was collected in empty plain and EDTA vacutainers and centrifuged and cell free supernatant was aliquoted. Venous Blood samples will be collected in plain vacutainers by venepuncture with aseptic precautions and the serum will be aliquoted and stored at -20^0C until assayed. Venous Blood and pleural fluid underwent total Protein estimation (Biuret method), LDH estimation (by two point calorimetric method) and cholesterol estimation (by Boehringer-Mannheim enzymatic method CHOD PAP). Etiology of the pleural effusion was established by thorough history, clinical examination, blood investigations, radiological evidence (chest X-ray, USG chest, CECT) FNAC, cytology, histopathology, bronchoscopy, 2-D ECHO, CT guided biopsy to establish etiology, response to treatment and follow up The Statistical software namely SPSS 17.0 was used for the analysis of the data. Microsoft Excel have been used to generate graphs, tables etc. Continuous variable was given as mean, $\pm$ SD. Categorical variable was given as Numbers and Percentage. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive value, Receiver Operating Characteristics (ROC) Curve was calculated. Variables between the groups was compared using the Student's t test and Analysis Of Variance (ANOVA).

RESULTS

In present study, 180 patients with pleural effusion were studied of which patient with age ranging between 30-40 years (22.2 %), followed by age group between 50-60 years (21.1 %). Out of the total 180 patients, predominant were males with 127 (70.6%) and females being 53 (29.4%). Majority had right sided pleural effusion with 92 (51.1%).

Table 1: General characteristics

General characteristics	Frequency	Percentage
Age (years)		
<20	11	6.1%
20-30	35	19.4%
30-40	40	22.2%
40-50	20	11.1%
50-60	38	21.1%
60-70	21	11.7%
70-80	12	6.7%
>80	3	1.7%

Gender		
Male	127	70.6%
Female	53	29.4%
Side of effusion		
Right sided	92	51.1%
Left sided	54	30.0%
Bilateral	34	18.9%

According to clinical diagnosis (history, clinical examination, radiological evidence, FNAC, cytology, histopathology, bronchoscopy, CT guided biopsy) 155 (86.1%) patients had exudative pleural fluid and 25 (13.9%) patients had transudative pleural effusion. According to one of light's criteria (ratio of pleural fluid protein to serum protein more than 0.5 as exudative pleural effusion) 152 (84.4 %) patients had exudative and 28 (15.6 %) had transudative pleural effusion. While based on another Light's criteria (pleural fluid LDH more than or equal to 200 IU suggestive of exudative pleural effusion). 143 (79.4 %) had exudative and remaining 37 (20.4 %) had transudative pleural effusion. Pleural fluid cholesterol > 40 mg/dl was considered as exudative pleural fluid, 149 (82.7 %) had exudative pleural effusion and 31 (17.3 %) had transudative.

Table 2: Distribution according to various criteria's

	Frequency	Percentage
Clinical (etiological) diagnosis		
Exudates	155	86.1%
Transudates	25	13.9%
Total	180	100%
Light's criteria (protein ratio)		
Exudates	152	84.4%
Transudates	28	15.6%
Light's criteria (LDH >200 IU)		
Exudates	143	79.4%
Transudates	37	20.6%
according to pleural fluid cholesterol		
Exudates	149	82.7%
Transudates	31	17.3%

We compared mean values of pleural fluid protein, protein ratio, LDH and pleural fluid cholesterol between exudates and transudates, we noted highly significant difference between them (P value of < 0.001).

Table 3: Mean values of pleural fluid protein, protein ratio, LDH and cholesterol

	Exudate (MEAN±SD)	Transudate (MEAN±SD)	P Value
PLEURAL FLUID PROTEINS	5.16±1.22	2.12±0.81	<0.001 (Highly Significant)
PROTEIN RATIO (g/l)	0.39±0.15	0.30±0.87	<0.001 (Highly Significant)
LDH (IU)	1297.21±3173.08	206.80±208.13	<0.001 (Highly Significant)
CHOLESTEROL mg/dl	82.51±91.08	31.16±12.21	<0.001 (Highly Significant)

Majority of the patients were of tubercular origin with no. of patients being 89 (49.4%) followed by synpneumonic effusion with 28(15.6%) patients and patients with malignant effusion being 24 (13.3%).

Table 4: Distribution according to varied etiologies and mean cholesterol levels

	Frequency	Percentage	Average pl. chol
ALL LIV	1	0.6%	17
Cardiomyo	5	2.8%	25.4
CCF	4	2.2%	31.25
CKD	6	3.3%	32.67
DKA	1	0.6%	34
HYPOPROT	2	1.1%	22
LIV CIRH	6	3.33%	39.4
MAL	24	13.3%	64.79
SUR	14	7.8%	61.14
SYN	28	15.6%	82.17
TB	89	49.4%	78.39
Total	180	100%	--

The cut of value of pleural fluid cholesterol less than 40 mg/dl was highest with sensitivity of 95.8 and specificity of 93.7 with positive predictive value of 99.71 and negative predictive value of 82.34.

Table 5: Pleural fluid Cholesterol cut off values at different sensitivity and specificity

Pleural fluid cholesterol	Sensitivity	1- Specificity	PPV	NPV
< 40 mg/dl	95.8	93.7	99.71	82.34
40 – 50 mg/dl	92.1	92.0	98.91	82.13
> 50 mg/dl	94.5	90.1	96.01	79.26

In present study, true exudates and true transudate identified by one of the light criteria i.e. ratio of pleural fluid protein to serum protein noted 149 patients as exudates and 6 patients were misclassified as transudates. Pleural fluid cholesterol with cut off value of 40 mg/dl identified 148 patients as exudates and 24 patients as transudates. 7 patients were misclassified as transudates and 1 patient was misclassified as exudates. Another criteria of light's i.e. pleural fluid LDH more than 200 IU, identified 141 patient as exudates and misclassified 14 patients as transudate.

Table 6: Number of subjects classified as true exudates and true transudate

	True Exudate	False Exudate	True Transudate	False Transudate
Light's criteria (Protein ratio)	149	6	25	
Pleural fluid cholesterol	148	7	24	1
LDH	141	20	19	

DISCUSSION

Pleural effusions present a common diagnostic problem to the pulmonary physician, even extensive diagnostic workup fail to identify its etiology in as many as 10-20% of all cases.[9,10,11] In 1972, Light et. al published a study in which exudative effusions could be distinguished from transudative effusions using both parameters with a high sensitivity and an acceptable specificity.[3] Still up to 30% of transudates are misclassified as exudates .This misclassification has severe consequences for the patient and can lead to additional diagnostic approaches, such as thoracocentesis with biopsy, surgery or thoracoscopy.[12,13] Light's criteria have been widely accepted so far, though some reports suggest that measuring cholesterol levels may be better or just as helpful.[7,8] The mean age in exudative group was 40.6 and mean age in transudative was 43.9 whereas the study done by Chander S et al.,[14] noted mean age of 39.8 +/- 18.1 years and 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 127 (70.6%) and female being 53 (29.4%) similar to the study done by Chander S et al.,[14] and not co-relating to the studies done before, Rogerio Rufino et al.,[16] found female percentage being 43%. Among the 155 exudative pleural effusions 87 were right sided, 52 were left sided and bi-lateral in 16 patients similar to observation made by R .Guleria, et al.[15] Etiological classification showed the predominant etiology in exudative pleural effusion being tubercular etiology with 89 (49.4%) patients followed by synpneumonic effusion with 28 (15.6%) patients , malignant pleural effusion 24(13.3%) ,14 (7.8%) patients due to surgical cause such as acute pancreatitis, liver abscess ,laparotomy etc. and 1 patient of chylothorax. This etiological observation is much similar to the other studies done in Asian continent where tubercular etiology was predominant. A. B Hamal et al.,[17] made similar observations pertaining to etiology and also study by C. K. Liam et al.,[18] showed similar results. In our study the mean of pleural fluid protein in exudative effusion was 5.16 +/ - 1.22 and 2.12 +/- 0.81 in transudates and P value on comparison between two groups was <0.001 which was highly significant, mean LDH in exudative and transudative effusions were 1297.21 and 206.8 respectively. The mean pleural fluid cholesterol was 82.51 in exudates and 31.16 in transudates and difference was highly significant which was almost similar to the studies done by. A. B Hamal et al. ,[17], Chander S et al.,[14] where the mean pleural fluid cholesterol was 35.6% in transudates and 80.3 %in exudates. The cut-off value of pleural fluid cholesterol was taken with different concentrations of cholesterol in pleural fluid, pleural fluid concentration of 40mg /dl showed highest sensitivity and specificity i.e. 95.8 % and 93.7 % respectively with PPV and NPV being 99.71 % and 82.34% respectively. ROC curve was generated by plotting a graph between sensitivity and 1-specificity. The levels of pleural fluid cholesterol with cut off of 40 mg/dl with this assay gives good sensitivity and specificity, which may serve as good marker for the differentiation of exudates and transudates. Using the Light's criteria namely ratio of pleural fluid protein to serum protein, 149 patients were identified as true exudates and 24 as true transudates with accuracy of 96.1 % and 96 % respectively. It misclassified 6 as transudates and 1 as exudates. Another Light's criteria namely LDH level in pleural fluid more than 200 IU identified 141 as true exudates and 19 as true transudates with accuracy of 90.96% and 76% respectively.it misclassified 11 exudates as transudates and 6 transudates as exudates which was high. Similar observations were noted by Mehdi Keshmiri et al.,[19] A.B Hamal et.al.,[17] Chander S et al.,[14] Using the cut off value of 40mg /dl of pleural fluid cholesterol 148 patients were identified as exudates and 24 were transudates. It misclassified 7 (4.51%) exudative pleural effusion as transudative pleural effusion

and only 1(4%) transudative pleural effusion as exudative pleural effusion. It showed 95.48 % accuracy in identifying exudative pleural effusion and 96 % accuracy in identifying transudative pleural effusion. This result is very much similar to the studies done before where pleural fluid cholesterol is at par with Light's criteria in differentiating exudative and transudative pleural effusion. The previous studies on pleural fluid cholesterol by Chander S et al.,[14] found that taking cut off value of 60 mg/dl for PCHOL 2.3% of exudates were misclassified, Ham et al.,[20] found it to be 4.8% with dividing line of 55mg/dl and 6.7% by Valdes et al.,[21] with cut off of 55 mg/dl. Compared to Light's criteria, pleural fluid cholesterol is almost equal or at par in differentiating exudates from transudates. Light's criteria had almost same sensitivity compared to cholesterol in our study and we found that Light's criteria had slightly higher specificity compared to pleural fluid cholesterol.

CONCLUSION

In present study we found that pleural fluid cholesterol with the cut off of 40 mg/dl was useful marker in differentiating exudates from transudates apart from Light's criteria, total protein, and LDH. Measuring pleural fluid cholesterol is simple and cost effective, it has better sensitivity, specificity and PPV in differentiating transudates and exudates, avoids simultaneous estimation of four parameters as required by Light's criteria.

REFERENCES

1. Garcia-Pachon E, Padilla-Navas I, Sanchez JF, Jimenez B, Custardoy J. Pleural fluid 1996;110:97-110.
2. Storey DD, David DE, Coles DT. Pleural effusion: a diagnostic dilemma. JAMA 1976;236:2183-6.
3. Light RW, MacGregor MI, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77:507-13.
4. Valdes L, Pose A, Suarez J, Gonzalez-Juanatey JR, Sarndeses A, Jose ES et al. cholesterol: A useful parameter for distinguishing between pleura exudates and transudates. Chest 1991;99:1097-102.
5. Roth BJ, O' Meara TF, Cragun WH. The serum-effusion albumin gradient in the evaluation of pleural effusion. Chest 1990;98:546-9.
6. Calikoglu M, Sezer C, Unlu A, Kanik A, Tamer L, Calikoglu L. Use of acute phase proteins in pleural effusion discrimination. Tuberkuloz ve Toraks Dergisi 2004;52(2):122-9.
7. Valdes L ,Pose A, Suarez J ,et al. .Cholesterol: a useful parameter for distinguishing between pleural exudates and transudates. Chest 1991;99:1097-1102.
8. Costa M ,Quiroga T, Cruz E. Measurement of pleural fluid cholesterol and lactate dehydrogenase. A simple and accurate set of indicators for separating exudates from transudates. Chest 1995;108:1260-1263.
9. Wardman AG et .al; The diagnosis of pleural effusions;are cancer markers really useful. Med PED Oncol 1984;12,68-71.
10. Hirsch A et .al; Pleural effusions; Laboratory tests in 300 cases. Thorax 1979 ;34;106-12.
11. Light R W: Disorders of pleura.In ;Wilson JD,Braunwald E et .al(eds), Harrisons's 13th edn ,vol Pp 1229-34,1994.
12. Hooper C et .al ; Investigation of a unilateral pleural effusion in adults; BTS pleural diseases guideline 2010. Thorax 2010;65
13. Romero-Candeira S et.al; The separation of transudate with particular reference to the protein gradient. Curr Opin Pulm Med 2004; 0; 294-8.
14. Chander S et.al; Cholesterol in pleural effusions: A parameter to distinguish exudates and transudates. Lung India Nov 1998 (p113-114).
15. R .Guleria et . al; Role of pleural fluid cholesterol in differentiating transudative from exudative pleural effusion; National medical journal India 2003;16:64-69.
16. Rogerio Rufino; Pleural Cholesterol to the diagnosis of Exudative Effusion: The Open Respiratory Medicine Journal 2014,8,14-17.
17. A. B. Hamal et al; Pleural Fluid cholesterol in differentiating Exudative and Transudative Pleural Effusion; journal of pulmonary medicine vol. 23 2013.
18. C.K.Liam et.al "Causes of pleural exudates in a region with a high incidence of tuberculosis", Respirology,vol 5 no 1;pp33-38,2000.
19. Mehdi Keshmiri et .al; Use of Cholesterol in the differentiation of exudative and transudative pleural effusion; Medical journal of the Islamic republic of Iran nov 1997:vol 11.
20. Hamm H, et al: cholesterol in pleural effusions –a diagnostic aid. Chest 92:296-302, 1987.
21. Valdes L, et al.; cholesterol: a useful parameter for distinguishing between pleural exudates and transudates. Chest 99:1097-1102,1991.

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