

Original Research Article

Pleural fluid cholesterol level is an important parameter in differentiating exudative from transudative pleural effusions

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ABSTRACT

Background: The first important step is to decide whether the pleural effusion is transudate or exudates by Light's criteria. Light's criteria can misclassify 25% of pleural transudates as exudates. Pleural fluid cholesterol level can differentiate transudates from exudates as a single parameter instead of multiple parameters used in Light's criteria. Measurement of pleural fluid cholesterol levels to differentiate transudative effusions from exudative effusions.

Methods: Consecutive 60 cases of pleural effusion were taken in the study. Pleural fluid analysis was done for parameters of Light's criteria along with pleural fluid cholesterol levels. First exudative and transudative effusion was classified by Light's criteria. Other clinical and relevant biochemical tests were done to arrive in the final etiological diagnosis and data were collected and analysed. Pleural fluid cholesterol levels was correlated to Light's criteria.

Results: Total 60 cases of pleural effusion were there in the study. There were 43 exudative and 17 transudative effusions. Mean cholesterol level was 64.2 ± 7.5 mg/dl in exudative effusions and 26.05 ± 8.01 mg/dl in transudates. Pleural fluid cholesterol was ≥ 55 mg/dl in 43 cases of exudates and < 55 mg/dl in 17 cases of transudates.

Conclusions: Pleural fluid cholesterol level of ≥ 55 mg/dl had similar sensitivity and specificity to Light's criteria and as a single important parameter to differentiate exudative from transudative pleural effusion.

Keywords: Exudates, Cholesterol level, Differentiation, Pleural fluid, Transudates

INTRODUCTION

The mean amount of pleural fluid (PF) present in normal state is as small as 8.4 ± 4.3 ml. Fluids that enter the pleural space can originate in the pleural capillaries, the interstitial space of the lungs, the intrathoracic lymphatics, intrathoracic blood vessels, or the peritoneal cavity. Pleural fluid is usually absorbed through the lymphatic vessels in the parietal pleura by means of stomata in the parietal pleura, through the alternative transcytosis. Pleural effusion (PE) is a pathological state often develops in patients with thoracic or systemic diseases and if properly not diagnosed and treated early, herald a serious prognosis.¹ Various pathophysiologic mechanisms increase the amount of pleural fluid by

increasing the rates of pleural fluid formation exceeding the rates of pleural fluid absorption.² The presence of pleural effusion enables a physician to obtain a sample of pleural fluid easily and with a systematic analysis of the pleural fluid, in conjunction with the clinical features and ancillary laboratory data, a clinician should be able to arrive at a presumptive or definite diagnosis in approximately 90% of the cases. The first important step is to decide whether the effusion is a transudate or exudate by Light's criteria. The differential diagnoses of transudates are limited and usually discernible from the clinical presentation, but the differential diagnosis of exudates poses a more difficult challenge for the clinicians. Transudates are caused by increased hydrostatic pressure, (e.g. Heart failure), decreased oncotic pressure (e.g.

Hypoproteinemia). Increased negative intrathoracic pleural pressure (e.g. Atelactesis) or movement of ascetic fluid through the diaphragm (e.g. Hepatic hydrothorax). In contrast exudates are due to increased capillary permeability and or impaired lymphatic drainage which results from proliferative (e.g. malignancy), or inflammatory (e.g. Parapneumonic or Tuberculosis).² The use of certain pleural fluid test such as differential leukocyte counts, glucose, total proteins, albumin, LDH, Cholesterol, PH, Amylase, ADA, and tumor markers for malignancy helps to narrow the differential diagnosis of an exudates.³

In 1972 Light RW et al compared the various parameters of pleural fluid and label the pleural fluid into exudates and transudates called the Light's criteria.⁴ An exudative pleural effusions meet one or more of the following criteria, with 99% sensitivity and 98% specificity are

- Pleural fluid proteins divided by serum protein quotient or ratio of >0.5 .
- Pleural fluid lactate dehydrogenase (LDH) divided by serum LDH >0.6 .
- Pleural fluid LDH $>2/3^{\text{rd}}$ (67%) of the upper limit normal of the serum LDH.¹ Whereas transudative pleural effusion meets none.

Patients with congestive heart failure with pleural effusion are often on chronic diuretic use have been classified as exudates in 29% of cases by Light's criteria by using pleural fluid proteins/serum proteins ratio of >3.1 gm/dl and can be correctly classified by using serum albumin/pleural fluid albumin gradient of >1.2 gm/dl. Similarly in patients with cirrhosis of liver with hydrothorax misdiagnosed as exudates by Light's criteria in 18% of cases and correctly diagnosed by pleural fluid albumin/serum albumin gradient of <0.6 .² Light's criteria can identify 98% of pleural exudates correctly and misclassify 25% of transudates as an exudates, which can be correctly diagnosed by serum albumin /pleural fluid albumin gradient of ≥ 1.2 gm/dl as an exudates and <0.4 gm/dl as transudates.⁵ In 60-70% cases of all PE the aetiology was primarily due to diseases of respiratory system or elsewhere is known and is called secondary PE and in about 30-40% cases of PE the aetiology is not known and called primary PE or labelled as idiopathic or indeterminate.⁶

The cut-off values of biochemical tests on pleural fluid and their usefulness in differential diagnosis of pleural fluid has been suggested.⁷ As RBC count $=10 \times 10^9/\text{L}$, Leukocyte count $=10 \times 10^9/\text{L}$, percentage of neutrophils or lymphocytes $>50\%$. Protein $=50$ gm/dl, glucose $=60$ mg/dl, PH $=7.2$, LDH $=100$ IU/L, ADA $=40$ U/L, Amylase $=100$ U/L, Cholesterol $=60$ mg/dl. In $1/6^{\text{th}}$ of transudates contain blood tinged; grossly bloody fluid suggests malignancy, trauma, or pulmonary embolism. Nearly 90% PE contain $10 \times 10^9/\text{L}$ leukocytes were parapneumonic. In TB PE 73% have protein content ≥ 50 gm/dl. In $\geq 90\%$ of PE had ADA >40 U/L suggesting

TB or parapneumonic effusion. In $1/3^{\text{rd}}$ PE with amylase level 100 U/L have underlying malignancy. A low PH, glucose suggests parapneumonia, TB or malignancy. Pleural fluid cytology can diagnose 94% of malignancy, along with low glucose. The concentration of cholesterol in pleural space is increased by the degeneration of leukocytes and erythrocytes, which contain large amount of cholesterol and vascular leakage from increased permeability due to inflammation.⁸ Other possible mechanisms are, pleural cholesterol derived from plasma, as some 70% of plasma cholesterol is bound to low density, high molecular lipoproteins (LDL) and the rest to HDL or very high density lipoproteins (VLDL), and the increased permeability of pleural capillaries in pleural exudates would allow plasma cholesterol to enter the pleural cavity. Next other possible explanation are cholesterol is synthesized themselves by pleural cells for their own needs and extra hepatic synthesis of cholesterol is now known to be much more greater than was once thought, depends on the metabolism with needs of the cells and is in dynamic equilibrium with cholesterol supply by LDL and cholesterol removal by HDL.^{9,10} Elevated cholesterol levels in pleural fluid exudates seem to be independent of serum levels.⁸ Various studies using cut-off pleural fluid cholesterol levels ranging from 47mg/dl to 60mg/dl with sensitivity ranging from 73%-96% and specificity ranging from 81-100% in comparison to Light's criteria sensitivity range of 99% and specificity of 98%. The reason to select the cut-off value of pleural fluid cholesterol level of ≥ 55 mg/dl (1.16 mmol/L) in this study was that this cut-off value eliminates the possibility of being equivocal to transudates and exudates has been used to improve the accuracy of differentiating transudative and exudative effusions with sensitivity of 97% and specificity of 100%.¹¹⁻¹³

Pleural fluid cholesterol level used as criteria to differentiate exudative and transudative pleural effusion and comparison to Light's criteria.

METHODS

It was a prospective and observational comparative study. Total 60 adult cases of pleural effusions were consecutively diagnosed by detail clinical history, physical examination and radiological imaging i.e. x-ray chest, Ultrasonography and CT scan as needed were taken in the study in the indoor department of medicine of VSSIMSAR, Burla during November 2014 to 2016 after approval of institutional ethic committee. With consent from patients and or patient's care taker, pleural fluid was aspirated with aseptic condition for analysis according to Light's criteria along with pleural fluid cholesterol levels for all samples. By applying Light's criteria, there were 43 samples diagnosed to be exudative and 17 samples as transudative in nature. Pleural fluid cholesterol was estimated at the same time by cholesterol oxidase peroxidase enzymatic method (Boehringer – Mannheim) and reference value of ≥ 55 mg/dl was

considered as cut-off value for exudates and $< 55\text{mg/dl}$ was considered as transudates. Other cytological and biochemical tests were done as needed for aetiological diagnosis. The validity of cholesterol level $\geq 55\text{mg/dl}$ as exudates was compared with diagnosis of exudates by Light's criteria.

RESULTS

Out of total of 60 cases, 48 were male and 12 were female patients and 47(80%) were aged >30 years. There

were 43 exudates and 17 were transudative effusions as per Light's criteria. The aetiology in exudative effusions was Tubercular in 28, Parapneumonic in 10, malignancy in 3, and connective tissue diseases in 2 cases. In transudative effusions, 11 were due to congestive cardiac failure and 6 were due to hepatic hydrothorax.

On pleural fluid analysis and parameters findings, (Table 1) pleural fluid cholesterol was $<55\text{mg/dl}$ in 18 cases and $\geq 55\text{mg/dl}$ in 42 cases.

Table 1: Pleural fluids parameters findings.

Pleural fluid examination	Parameter	Tubercular	Non-tubercular	Transudates
Appearance	Straw yellow	22	11	17
	Haemorrhagic	6	4	0
Protein level (gm/dl)	<3	0	1	16
	≥ 3	28	14	1
LDH level (IU/L)	$\geq 2/3^{\text{rd}}$ ULN of serum	19	11	0
	$< 2/3^{\text{rd}}$ ULN of serum	9	5	17
Pleural fluid/ serum protein ratio	<0.5	0	1	13
	≥ 0.5	28	14	4
Pleural fluid/ serum LDH ratio	<0.6	0	1	17
	≥ 0.6	28	14	0
Cells	Lymphocytic	26	4	0
	Polymorphonuclear	2	11	17
	Malignant cells	0	0	0
AFB staining of pleural fluid	+ve	6	0	0
Cholesterol(mg/dl)	<55	0	1	17
	≥ 55	28	14	0
Glucose (mg/dl)	≥ 50	14	7	11
	< 50	14	8	6
Culture for M. Tuberculosis	+ve	8	0	0
ADA(U/L)	≥ 50	26	2	0
	< 50	2	13	17

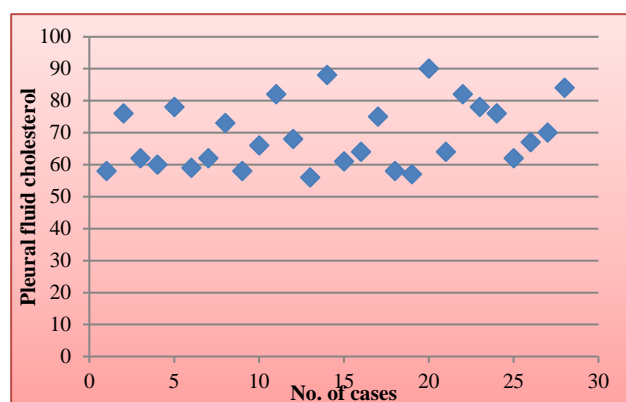


Figure 1: Pleural fluid cholesterol levels in non-tubercular exudates.

The mean level of pleural fluid cholesterol was $64.2 \pm 7.5\text{mg/dl}$ in non-tubercular exudates (ranges 56-

78mg/dl) (Figure 1). In Tubercular pleural effusion it was $69.07 \pm 10.2\text{mg/dl}$ (ranges of 56-90mg/dl) (Figure 2).

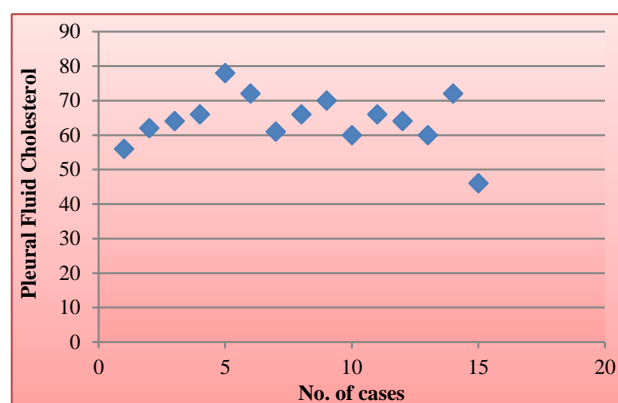


Figure 2: Pleural fluid cholesterol levels in tubercular exudates.

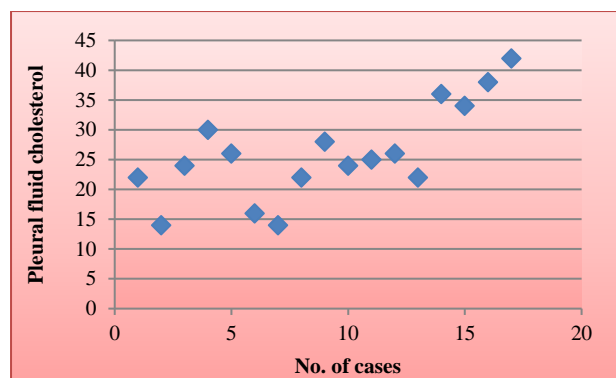


Figure 3: Pleural fluid cholesterol levels in transudates.

The mean cholesterol was 26.05 ± 8.01 mg/dl in transudates with range of 14-42 mg/dl ($P = 0.00001$) (Figure 3). In comparison of exudates and transudates according to pleural fluid cholesterol levels, 42 cases of

exudates had ≥ 55 mg/dl and < 55 mg/dl in 17 cases of transudates and only one with exudates. When considering pleural fluid /serum cholesterol ratio of 42 cases of exudates had > 0.3 , and < 0.3 in 17 cases of transudates and only one with exudates. As per pleural cholesterol levels in this study it was similar to Light's criteria. Pleural fluid LDH $\geq 2/3^{\text{rd}}$ upper limit of normal serum was found in 30 cases of exudates and $< 2/3^{\text{rd}}$ upper limit of normal serum in 14 cases of exudates and 17 cases of transudates. The pleural fluid /serum LDH ratio of < 0.6 in 17 cases of transudates and only 1 cases of exudates and ≥ 0.6 in 42 cases of exudates only.

Pleural fluid total protein was ≥ 3 gm/dl in 42 cases of exudates and in 1 case of transudate and < 3 gm/dl in 16 cases of transudates and 1 case with exudates. The pleural fluid /serum protein ratio of < 0.5 was present in 13 cases of transudates and 1 cases of exudates and it was ≥ 0.5 in 42 cases of exudates and 4 cases of transudates.

Table 2: Statistical comparison of pleural fluid parameters of light's criteria with pleural fluid cholesterol levels.

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P value
Light's criteria	100	94.44	97.67	100	< 0.00001
PCHOL	100	94.44	97.67	100	< 0.00001

(PPV= Positive predictive value. NPV =Negative predictive value)

Pleural fluid ADA was ≥ 50 IU/L in 28 cases of exudates (26 TB and 2 non-TB) and none in transudates and it was < 50 IU/L in 15 cases of exudates and in 17 cases of transudates.

According to Light's criteria in this study, there were 42 cases with true exudates and false negative was 0 and true transudates were 17 and false positive transudate was one, thus Light's criteria correctly diagnosed 42 out of 43 cases of exudates and all cases of transudates (Table 2).

DISCUSSION

Carr DT et al reported that pleural fluid protein content of ≥ 3.0 gm% suggest exudative pleural effusion, but not always differentiate transudates.¹⁴ Light et al suggest that ratio of pleural fluid to serum protein of ≥ 0.5 was suggestive of exudative effusion.⁴ In present study 71.66% cases had protein content of > 3 gm% and 76.66% had pleural fluid /serum protein ratio of ≥ 0.5 . In this study 4 (25.30%) cases of transudates due to congestive heart failure had ratio of > 0.5 and classified as exudates (pseudo exudates) may be due to chronic diuretic use.

Light et al opined that, pleural exudates have LDH levels > 200 IU/L and in their study 71% patient's pleural LDH had > 200 IU/L and pleural LDH/Serum LDH ratio of < 0.6 , correctly diagnosed all transudates except in one case of malignant exudates.⁴ In present study 32 exudates

were of TB and 2 cases were non-TB exudates had ADA activity of > 50 IU/L and did not correlate with exudative or transudative effusion.

In this study, pleural fluid Cholesterol cut-off value of ≥ 55 mg/dl, 17 (100%) cases of transudates had value of < 55 mg/dl and 28 tubercular exudates and one case of malignant exudates had > 55 mg/dl. Thus, in our study a sensitivity of 100% and specificity of 94.44% for exudative pleural effusions. Our study was comparable to many other published studies. Burgess et al reported that, Light's criteria were most accurate in 93% and sensitivity of 98% and specificity of 83%.¹⁵ They also found that Light's criteria misclassified 19 transudates as exudates, of which 13 (68%) were correctly classified by serum to pleural fluid albumin gradient of ≥ 1.2 gm/dl and with pleural fluid cholesterol cut-off value of ≥ 47 mg/dl had sensitivity of 73% and specificity of 85%. Porcel JM reported that Light's criteria identified 98% pleural exudates and misclassified 25% pleural transudates as exudates.⁵ Costa M et al taking pleural fluid cholesterol cut-off level of ≥ 45 mg/dl had sensitivity of 90% and specificity of 100% versus Light's criteria of 98% and 82% respectively.¹⁶ Gil SV et al with cut-off cholesterol value of 54 mg/dl had found sensitivity and specificity of 96% and 92% respectively versus Light's criteria with 100% and 65%.¹⁷ Valdes A et al with cholesterol level of ≥ 55 mg/dl had sensitivity of 91% and specificity of 100% and with pleural fluid cholesterol/serum cholesterol ratio

of 0.3 was 92.5% sensitivity and 87.6% specificity and the number of misclassification was less than other parameters i.e. pleural cholesterol versus pleural LDH.¹⁸ Hamm H et al with pleural cholesterol cut-off Value of $\geq 60\text{mg/dl}$ correctly diagnosed exudates in 95% cases with sensitivity of 92% and specificity of 100% versus Light's criteria with 100 and 71% respectively.¹³

CONCLUSION

Pleural fluid cholesterol cut-off level of $\geq 55\text{mg/dl}$ is an important parameter that suggest exudative and $<55\text{mg/dl}$ suggest transudative pleural effusions and similar to Light's criteria in regards to sensitivity and specificity as a single parameter in comparison to consideration of multiple parameters in Light's criteria. It may be used as a single parameter to differentiate exudates from transudates in resource poor conditions and as a cross check to Light's criteria.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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