Journal of Advances in Medicine and Medical Research

Volume 35, Issue 22, Page 28-33, 2023; Article no.JAMMR.106204
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

A Comparative Study between Pleural Fluid Cholesterol and Light's Criteria in Differentiating Exudative and Transudative Pleural Effusion

Aarjuv Majmundar [a++*], Harshita H. Nouni [a++], Vaibhav Mehta [a++], Sucheta J. Lakhani [b#], Jitendra D. Lakhani [a#] and Shubham Darda [a++]

[a] Department of Medicine, SBKS MI and RC, SVDU, Vadodara, India.
[b] Department of Microbiology, SBKS MI and RC, SVDU, Vadodara, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2023/v35i225242

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/106204

Original Research Article

Received: 25/07/2023
Accepted: 27/09/2023
Published: 03/10/2023

ABSTRACT

Background/Aims: When the production and buildup of pleural fluid overwhelm its absorption, pleural effusion develops. Pleural effusions are classified as either exudates or transudates based on their pathogenesis. In order to treat the patient rationally, it is critical to make an appropriate etiological diagnosis. Discrimination between transudates and exudates using Light's criteria may require additional testing, however employing pleural fluid cholesterol makes diagnosis possible with only pleural fluid analysis.

[++] PG Resident;
[#] Professor;
**Corresponding author: E-mail: aarjuv1996@gmail.com;*

Materials and Methods: This comparative study included 140 patients with pleural effusions. Pleural effusions were determined to be transudative or exudative based on etiological diagnosis. The sensitivity, specificity, positive predictive value, and negative predictive values of each test for the diagnosis of an exudative effusion were assessed.
Results: The pleural fluid cholesterol levels showed a sensitivity of 97.95%, a specificity of 95.23% ($P < 0.0001$), a positive predictive value of 97.95% and a negative predictive value of 95.23%. The ROC curve analysis (receiver operating characteristic curve) of pleural fluid cholesterol with a cut-off of 45 mg/dl showed an area under the curve of 0.986.
Conclusions: The pleural cholesterol level can be utilized as a biomarker to identify an exudative effusion and replace Light's criteria. It also eliminates the need for simultaneous blood sampling.

Keywords: Cholesterol; exudative effusion; pleural effusion.

1. INTRODUCTION

"The parietal and visceral layers of the mesothelium are separated by a thin layer of fluid for lubrication that facilitates the movement of the two layers against each other. Therefore, these cavities are not called true cavities, the presence of gas or fluid converts them into true cavities.

The collection of more than the normal amount of fluid in a serous cavity is called an effusion. It is classified based on the location where it gets collected i.e., pericardial, pleural and peritoneal. The fluid collected in the pleural cavity is called pleural effusion. Effusions can be classified into two types i.e. (1) transudative due to increased venous pressure and (2) exudative due to an increase in capillary permeability. It is important to differentiate between transudative and exudative causes of pleural effusion which helps in diagnosis as well as treatment" [1]. "In 1971 Light et al. devised a criterion having high sensitivity and specificity of 99% and 98% respectively for differentiating transudative and exudative pleural effusion (ratio of pleural fluid protein by serum protein >0.5; ratio of pleural fluid LDH by serum LDH >0.6; pleural fluid LDH >2/3rd of upper limit of serum LDH)" [2]. "However other researchers were not able to reproduce similar results instead a specificity of only 70-86% was found using Light's criteria. Also, 25% of patients with transudative effusion were wrongly tagged as exudative effusion. Transudative pleural effusions could have high protein in cases such as heart failure on diuretic therapy" [3]. Pleural fluid cholesterol misclassifies fewer cases compared to Light's criteria [4]. From a meta-analysis done by Heffner et al. in the year 2002, pleural effusion was identified as an exudative type by at least one of the following conditions.

i. Pleural fluid protein >2.9 gm/dL.
ii. Pleural fluid cholesterol >45 mg/dL (1.16 mmol/L).
iii. Pleural fluid LDH >2/3rd of the upper limit of serum [5].

"Pleural fluid cholesterol is hypothesised to be produced by degenerating cells and increased vascular permeability. Two hypotheses have been proposed, albeit the exact reason for the elevation in cholesterol levels in pleural exudates is unknown. According to the first, the pleural cells themselves produce cholesterol for their own needs (extrahepatic synthesis of cholesterol is now known to be much greater than that was previously thought of, which depends on the metabolic needs of cells, and is in dynamic equilibrium with cholesterol supply by LDL and cholesterol removal by HDL)" [6]. "Furthermore, the degradation of leukocytes and erythrocytes raises the levels of cholesterol in the pleural cavity" [7]. "The second possible theory is that pleural cholesterol originates from plasma; plasma cholesterol is primarily bound to low-density, high molecular weight lipoproteins (LDL), with the remaining serum cholesterol bound to very low-density lipoproteins (VLDL) or HDL. Pleural exudate patients have increased pleural capillary permeability, which would allow plasma cholesterol to enter the pleural cavity. The choice of 45 mg/dL (1.16 mmol/L) as the cutoff value for pleural fluid cholesterol was made in order to avoid being ambiguous between transudates and exudates, and measurement of pleural cholesterol >45 mg/dL (1.16 mmol/L) has been used to increase the accuracy of discriminating between transudative and exudative effusions" [8].

2. METHODOLOGY

In this descriptive study, 140 eligible patients with pleural effusion coming to Dhiraj General Hospital between the period of May 2021 to May 2022 were selected. The study was approved by the ethics committee and informed consent was taken. Cholesterol estimation was done using

Excel cholesterol kits analyzed on the “ERBA EM 360 machine”.

2.1 Collection of Fluids

1. All aseptic precautions taken.
2. Samples were collected in two vials– one in EDTA for cytology & another one in plain vial for biochemistry.
3. Samples were processed immediately.

2.2 Case Allocation

In the present study, 140 cases of pleural effusion were taken for a span of 12 months i.e., from May 2021 to May 2022. Various fluid samples were collected from OPDs and IPD’s of Medical and Critical care units.

2.3 Principle

Cholesterol ester hydrolase breaks down cholesterol esters to release free cholesterol molecules and fatty acids. There is pre-existing cholesterol that, along with the cholesterol created by the aforementioned reaction, is oxidized by cholesterol oxidase into cholestenone and hydrogen peroxide. Chromogen in the presence of H2O2 and peroxidase is oxidized to a red colour complex that can be read at 520 nm. Unless placed in direct sunlight, this colour remains stable for two hours.

2.4 Procedure for Cholesterol Estimation

- 1 tube was marked "blank" (B).
- One additional tube was marked as standard (S).
- The remaining tubes were given test (T) labels and codes depending on the number of pleural fluids samples.
- After bringing the cholesterol reagent to room temperature, 1 cc of reagent was poured into each tube. 10 microliters of distilled water were poured to tube B, and 10 microliters of standard cholesterol into tube S. Add 10 microliters of the relevant fluid sample's supernatant, labelled as T. All the tubes were kept at 37° C for 10 minutes. After calibrating using a standard, each reading was noted.

2.5 Statistical Analysis

The data was formulated in MS - Excel spreadsheet, data summarized, frequencies & means calculated, and further data analysis was performed.

2.6 Objectives of the Study

To compare the efficacy of pleural fluid cholesterol alone compared to Light’s criteria for the diagnosis of exudative pleural effusion.

2.7 Inclusion Criteria

The inclusion criteria for the patients were as below:

1. Age ≥ 16 years,
2. Patients giving consent,
3. Patients with a definite etiological diagnosis of causes leading to either transudative or exudative pleural effusion.

2.8 Exclusion Criteria

The exclusion criteria for the patients were as below:

1. Patients not willing to participate in the study,
2. Age < 16 years,
3. Patients without definite clinical diagnosis,
4. Patients previously diagnosed and already on treatment.

3. RESULTS AND DISCUSSION

A total of 140 patients with definite clinical diagnoses, eligible for the study, were included in which 71.42% (100) cases were exudates, and 28.57% (40) cases were transudates. It was seen that tubercular effusion was the most common pleural effusion in the study. It accounted for 49 out of 140 cases (35.0%). Carcinoma lung was the second most common cause accounting for 11.42% (16), followed by parapneumonic effusion at 8.57% (12), empyema thoracis at 6.42% (9), remaining % of exudative effusion comprised of pancreatic pleural effusion (6), splenic abscess (5) and chylothorax (3). Transudates counted for 28.57% (40 cases).

In the present study, it was found that the mean plasma cholesterol level (mg/dL) was 84.21 ± 34.85 for exudates and 23.24 ± 12.28 for transudates.
It was seen that out of 140 cases (exudates 100 and transudates 40 according to etiological diagnosis), protein ratio (pleural fluid/ serum)

identified 86 cases as exudates and 54 cases as transudates; LDH ratio identified 91 cases as exudates and 49 cases as transudates, while plasma cholesterol identified 98 cases as exudate and 42 cases as transudates. It was seen that the pleural fluid protein/serum protein ratio had a sensitivity of 84.44% and specificity of 80%; the pleural LDH/serum LDH ratio has a sensitivity of 90.32% and specificity of 85.10%, and pleural fluid cholesterol with a sensitivity of 97.95% and specificity of 95.23% for differentiating exudative and transudative pleural effusion. All these parameters have a significant *P* value that is, <0.0001.

Table 1. Causes of exudative pleural effusion

Causes of exudative pleural effusion	Number	Percentage (%) of total patients
Tubercular effusion	49	35.00%
Neoplasia	16	11.42%
Parapneumonic effusion	12	08.57%
Empyema thoracic	09	06.42%
Others	14	10.00%

Table 2. Comparison of various pleural fluid parameters

Parameters	Sensitivity	Specificity	PPV	NPV	*P* value
Protein ratio (Pleural fluid/Serum)	84.44%	80.00%	88.37%	74.07%	<0.0001
LDH ratio (Pleural fluid/Serum)	90.32%	85.10%	92.30%	81.63%	<0.0001
Pleural fluid Cholesterol	97.95%	95.23%	97.95%	95.23%	<0.0001

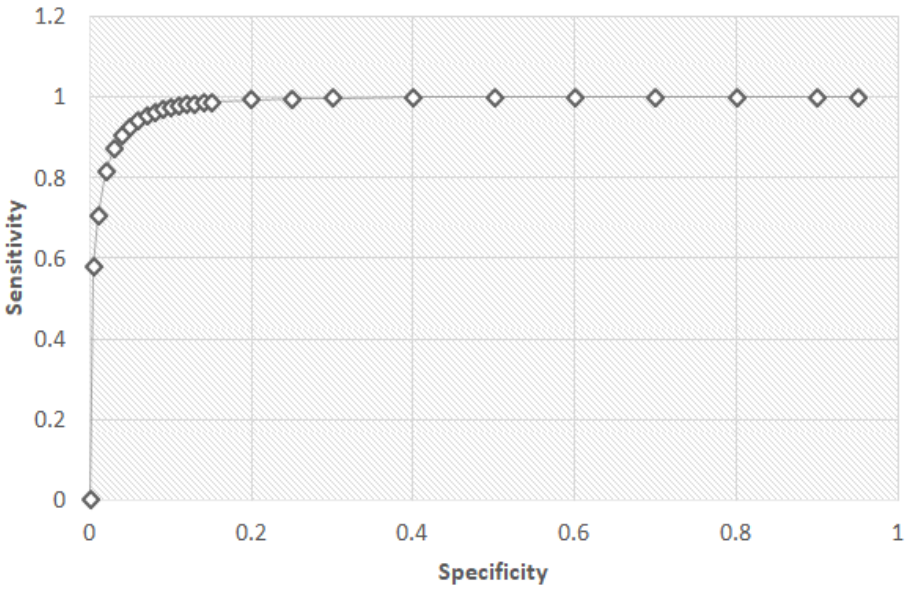

Fig. 1. Curve of the sensitivity and specificity of pleural cholesterol

In a Receiver Operating Characteristic (ROC) curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (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 a 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 the overall accuracy of the test. This ROC curve has an area of 0.986 (SD 0.0105), a confidence interval of 95% (0.965-1.007), and p< 0.0001.

Receiver operating characteristic (ROC) analysis of pleural fluid cholesterol with a cut-off of 45 mg/dl showed a sensitivity (97.95%), specificity (95.23%) ($P < 0.0001$), area under curve 0.986, positive predictive value and negative predictive value of 97.95% and 95.23%, respectively.

Similar results were found in a study done by Rustogi et al who plotted a ROC analysis of pleural fluid cholesterol with a cut-off of 45 mg/dl which showed a sensitivity (98.18%), specificity (95.65%) ($P < 0.0001$), the area under curve 0.969, positive predictive value and negative predictive value of 96.4% and 97.8%, respectively [9].

4. DISCUSSION

"Pleural fluid cholesterol is superior to Light's criteria for the differentiation of transudates and exudates and is less cumbersome in the clinical setting as it does not require simultaneous blood sampling. A cut-off value of pleural fluid cholesterol for differentiating transudates and exudates should be 45 mg/dL" [10]. "In this study, a total of 140 patients, 40 with transudates and 100 with exudates were considered according to the clinical diagnosis. The most frequent cause of pleural exudates is tuberculosis followed by lung cancer which is similar to the result of a study done in Malaysia where there is a high incidence of tuberculosis" [11]. "Measurement of pleural cholesterol >45 mg/dl has been used to improve the accuracy of differentiating transudative and exudative effusion" [8]. "In this study, the sensitivity, specificity, positive predictive value, and negative predictive value of the pleural fluid cholesterol (cut-off >45 mg/dl) were 97.95, 95.23, 97.95 and 95.23%, respectively, for identifying exudates. Elevated cholesterol levels in exudates seem to be independent of serum levels" [12]. "The findings in a study done by Mehdi Kashmiri et al showed taking a value of pleural cholesterol >55 mg/dl and pleural/serum cholesterol >0.3 to define exudative effusion resulted in less erroneous classification with a sensitivity of 93%, a specificity of 100%, a positive predictive value (PPV) of 100% and an accuracy of 95.2%. Light's criteria yielded a sensitivity of 95%, a specificity of 95%, and a PPV of 97.6% with an accuracy of 95.2%. Using pleural fluid cholesterol in differentiating exudate from transudate was especially useful in patients with congestive heart failure who received diuretics" [13].

5. CONCLUSION

Assessment using pleural fluid cholesterol can spare patients from having to pay for multiple tests used in Light's criteria to confirm an exudative pleural effusion, as well as from simultaneous blood sampling.

CONSENT

As per international standards or university standards, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sharma V, Sharma R, Arora P, et al. Study of cholesterol levels in ascitic fluid to differentiate malignant from nonmalignant effusion. J. Evolution Med. Dent. Sci. 2020;9(26):1903-1907.
2. Light RW, Macgregor MI, Luchsinger PC, Ball WC., Jr. Pleural effusions: the diagnostic separation of transudates and exudates. *Annals of Internal Medicine.* 1972;77(4):507–513.
3. Chakko SC, Caldwell SH, Sforza PP. Treatment of congestive heart failure.Its effect on pleural fluid chemistry. Chest 1989;95(4):798–802.
4. Valdes L, Pose A, Suarez J, et al. Cholesterol: a useful parameter for distinguishing between pleural exudates and transudates. Chest. 1991;99(5):1097–1102.
5. Heffner JE, Sahn SA, Brown LK. Multilevel likelihood ratios for identifying exudative pleural effusions. Chest. 2002;121(6):1916–1920.
6. Spady DK, Dietschy JM. Sterol synthesis in vivo in 18 tissues of the squirrel monkey, guinea pig, rabbit, hamster, and rat. Journal of Lipid Research. 1983;24(3): 303–315.

7. Brown MS, Goldstein JL. Receptor mediated control of cholesterol metabolism .*Science.* 1976; 191(4223):150-154.
8. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Chest. 1997;111(4):970–980.
9. Rustogi N, Gupta H. Pleural fluid cholesterol: A promising marker to differentiate transudates and exudates. Indian J Respir Care 2021;10: 326-9.
10. Dhandapani S, Reddy S, Rajagopalan R. Differentiating pleural effusions: Criteria based on pleural fluid cholesterol. Eurasian Journal of Pulmonology. 2016;18:76-79.
11. Liam CK, Kim-Hatt LIM, Wong CMM. Causes of pleural exudates in a region with a high incidence of tuberculosis. Respirology. 2000;5(1):33–38.
12. Hamm H, Brohan U, Bohmer R, Missmahl HP. Cholesterol in pleural effusions-a diagnostic aid. Chest. 1987;92: 296-302
13. Mehdi Keshmiri, Mojtaba Hashemzadeh. Use of cholesterol in the differentiation of exudative and transudative pleural effusion. Medical Journal of Islamic Republic of Iran. 1997;11(3):187-190

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/106204