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The Evaluation of the Light Parameters and Pleural Fluid Cholesterol to Determine the Differences Between Exudative and Transudative Pleural Discharge

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Abstract

Background: *Pleural effusion occurs when an imbalance between pleural fluid production and absorption leads to the accumulation of excess fluid in the pleural cavity. Pleural effusions are commonly classified into two types: transudative or exudative, depending on the underlying mechanism of fluid formation. While transudates typically result from systemic factors like heart failure or liver cirrhosis, exudates are usually caused by local factors, such as infection, malignancy, or inflammation. Differentiating between transudates and exudates is essential for selecting the correct treatment strategy. Light's criteria, which are based on pleural fluid and serum protein and lactate dehydrogenase (LDH) levels, are frequently used to differentiate between the two. However, these criteria have limitations and often require additional tests to accurately diagnose the etiology. Recently, pleural fluid cholesterol analysis has emerged as a reliable diagnostic tool that can effectively differentiate exudative effusions from transudative ones, potentially reducing the need for multiple tests and invasive procedures.* ***Materials and Methods:*** *This prospective study involved 80 patients with diagnosed pleural effusion. All effusions were categorized as either transudative or exudative based on their clinical presentation and etiological analysis. Light's criteria were applied for the initial classification, and pleural fluid cholesterol levels were measured for each case. The diagnostic performance of pleural fluid cholesterol in identifying exudative effusions was evaluated by calculating its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal pleural fluid cholesterol threshold for differentiating exudates.* ***Results:*** *Pleural fluid cholesterol levels demonstrated a high degree of accuracy in identifying exudative effusions, with a sensitivity of 97.84% and a precision of 98.12% (P < 0.0001). The negative predictive value was found to be 93.61%, and the positive predictive value was 98.89%. ROC curve analysis yielded an area under the curve (AUC) of 0.857, with a pleural fluid cholesterol cut-off of 52 mg/dL being the most effective threshold for differentiation. These findings suggest that pleural fluid cholesterol is a highly reliable marker for diagnosing exudative effusions, with performance metrics superior to those of Light's criteria.* ***Conclusion:*** *Pleural fluid cholesterol analysis offers a more accurate and practical method for identifying exudative pleural effusions compared to Light's criteria. The high sensitivity and specificity of cholesterol testing reduces the need for multiple blood tests and invasive procedures, thereby streamlining the diagnostic process. Incorporating cholesterol measurement into routine clinical practice could greatly improve the diagnosis and treatment of pleural effusions, especially in situations where the cause is unclear. Further studies with larger sample sizes are recommended to validate these findings and assess their applicability in diverse patient populations.*

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INTRODUCTION

The mesothelium consists of parietal and visceral layers that are lubricated by a thin layer of fluid, aiding their movement against each other. As a result, these spaces are not classified as true cavities by default; they require the presence of gas or fluid to be considered as such. A discharge is the accumulation of more fluid than is typical in a serous cavity. It is divided into three categories: pericardial, pleural, and peritoneal, depending on where it is collected. Pleural effusion refers to the buildup of fluid within the pleural space. There are two types of effusions: (1) transudative, caused by elevated venous pressure, and (2) exudative, caused by increased capillary permeability. Distinguishing between transudative and exudative pleural effusion causes is crucial as it aids in both diagnosis and treatment [1]. The criteria for differentiating between transudative and exudative pleural effusion were established. It is based on the following factors: ratios of pleural fluid protein to serum protein >0.3, ratios of pleural fluid LDH to serum LDH >0.8, and pleural fluid LDH >1/4th of the upper limit of serum LDH [2]. But other researchers were unable to replicate the same findings; instead, applying Light's criterion, a specificity of just 80–95% was discovered. Furthermore, transudative effusion was mistakenly diagnosed as exudative effusion in 38% of patients. High protein transudative pleural effusions may occur in situations like heart failure receiving diuretic medication [3]. Comparing pleural fluid cholesterol to Light's criteria, few patients are incorrectly classified [4].

In a meta-analysis, pleural effusion was categorized as exudative if at least one of the following criteria was met.

i. Protein in the pleural fluid >3.5 gm/dL
ii. Cholesterol in the pleural fluid >32 mg/dL (5.31 mmol/L)
iii. LDH in pleural fluid >1/4th of the serum upper limit [5].

It is hypothesized that vascular permeability and deteriorating cells produce cholesterol found in pleural fluid. Though the precise cause of the elevated cholesterol levels in pleural exudates remains uncertain, two theories have been put forth [6]. It is now understood that extrahepatic cholesterol synthesis is significantly higher than previously believed, varying according to the metabolic demands of cells and maintaining a dynamic balance with cholesterol provided by LDL and removed by HDL. Secondly, pleural cells synthesize cholesterol to meet their own requirements. Moreover, cholesterol levels in the pleural cavity increase due to the breakdown of leukocytes and erythrocytes [7]. The second explanation suggests that pleural cholesterol originates from plasma, where cholesterol is primarily bound to high molecular weight LDL, while the remaining serum cholesterol is bound to VLDL or HDL. In patients with pleural exudates, increased permeability of pleural capillaries allows plasma cholesterol to enter the pleural cavity. Measuring pleural cholesterol levels above 38 mg/dL (2.25 mmol/L) has been used to improve the accuracy of distinguishing between transudative and exudative effusions. This cutoff value for pleural fluid cholesterol was selected to minimize overlap between transudates and exudates [8, 9].

Methods

Eighty eligible patients with pleural effusion, who presented to the hospital between June 2022 and May 2023, were selected for this descriptive study. The study received approval from the ethics committee, and informed consent was obtained from all participants.

Excel cholesterol kits that were examined on an 'ERBA EM 240 machine' were used to estimate cholesterol levels.

Accumulation of Solutions

- Every aseptic measure was done.

- Two vials were used to collect the samples: one for cytology in EDTA and the other for biochemistry in a simple vial.
- Samples were processed instantly.

Case Distribution

Eighty (80) cases of pleural effusion were included in the current study over a 12-month period, from June 2022 to May 2023. Fluid samples of various kinds were taken from the IPDs and OPDs of the medical and critical care units.

The Basis

Cholesterol ester hydrolase is a protein that decomposes cholesterol esters, resulting in the release of free cholesterol molecules and fatty acids. Cholesterol oxidase converts pre-existing cholesterol into cholestenone and hydrogen peroxide in addition to the cholesterol produced by the previously described process. When peroxidase and H_2O_2 are present, chromogen is oxidized to produce a red color complex that can be measured at 450 nm. This color does not change for an hour unless it's in exposure to sunlight.

Estimating Cholesterol Level

One tube has the label 'blank' (A). Test (T) labels and codes were placed on the remaining tubes based on the quantity of pleural fluid samples, while one extra tube was labeled as standard (S). 1 (cc) of the cholesterol reagents was added to each tube once it had reached room temperature. 15 micro-liters of standard cholesterol were added to tube S and 15 micro-liters of distilled water were added to tube A. Add 15 micro-liters of the T-labeled supernatant from the pertinent fluid sample. Every tube was maintained at 37° C for a duration of 15 minutes. Every reading was recorded after standard calibration.

Quantitative Statistics

Data was entered into an MS Excel spreadsheet, summed up, averages and variances were determined, and additional data analysis was carried out.

Criteria for the Research

To assess the effectiveness of using pleural fluid cholesterol alone, compared to Light's criteria, in diagnosing exudative pleural effusion.

Criteria for Inclusion

The patients met the following inclusion criteria:

1. Age greater than 18.
2. Consent from the patients.
3. Patients who have an exact diagnosis of the etiology of the pleural effusion, either transudative or exudative.

Criteria for Exclusion

The following were the patients' exclusion criteria:

1. Patients unwilling to take part in the research.
2. Patients without a clear clinical diagnosis.
3. Patients who have already received a diagnosis are undergoing therapy.
4. Age < 18 years.

Results

Eighty patients with definitive clinical diagnoses who met the study's eligibility requirements were enrolled, of whom forty cases (40%) were exudates and forty cases (40) were transudates. The study found that tubercular effusion was the most common type of pleural effusion. It was responsible for 40

(35.0%) of the 80 cases. The second most frequent cause, accounting for 15.34% of cases, was lung cancer. Parapneumonic effusion came in second at 9.49% (12), followed by empyema thoracis at 8.35% (9). The rest of the exudative effusions included pancreatic pleural effusion (6 cases), splenic abscess (5 cases), and chylothorax (3 cases). Additionally, 40 cases, accounting for 25.43%, were transudates. The current investigation revealed that the average plasma cholesterol level (mg/dL) for exudates was 75.32 ± 41.66 and for transudates it was 15.17 ± 24.51. Out of 80 instances (40 exudates and 40 transudates based on the etiological diagnosis), the protein ratio (pleural fluid/serum) was observed.

Identified 40 cases as exudates and 40 cases as transudates; 40 cases were classified as exudates and 40 cases as transudates by the LDH ratio; 40 cases were recognized as exudates and 40 cases as transudates by the plasma cholesterol. The results showed that the pleural fluid protein/serum protein ratio had an 78.33% sensitivity and an 92% specificity; the pleural LDH/serum LDH ratio has an 80.24% sensitivity and a 92.32% specificity; and the pleural fluid cholesterol has an 85.62% sensitivity and a 98.12% specificity for distinguishing between exudative and transudative pleural effusion. Each of these parameters has a significant P-value of less than 0.0001. A study using a cut-off of 45 mg/dl for pleural fluid cholesterol revealed that the study's receiver operating characteristic (ROC) analysis revealed the following: sensitivity (97.95%), specificity (95.23%) ($P < 0.0001$), area under the curve (0.986), positive predictive value (97.95%), and negative predictive value (95.23%).

Rustogi et al.'s study produced comparable findings when they conducted a ROC analysis of pleural fluid cholesterol with a cutoff of 45 mg/dL (Figure 1). The results indicated a sensitivity of 98.18%, specificity of 95.65% ($P < 0.0001$), area under the curve of 0.969, positive predictive value of 96.4%, and negative predictive value of 97.8%, respectively.

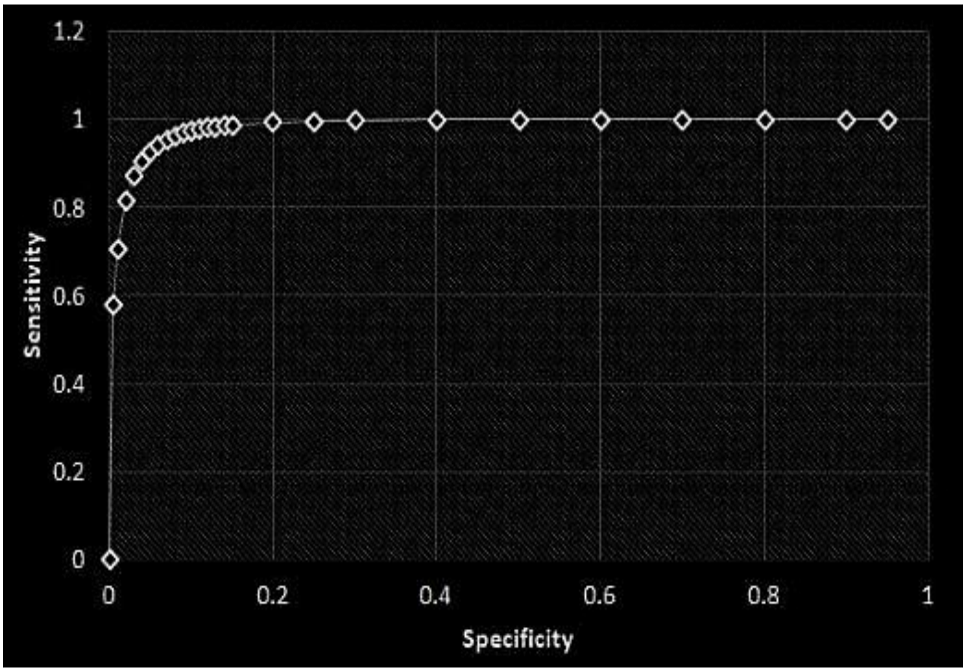

Figure 1. Pleural cholesterol's sensitivity and specificity curve.

Plotting sensitivity (true positive rate) against specificity (false positive rate) for various cutoff points creates a receiver operating characteristic (ROC) curve. Each point on the ROC curve represents a combination of sensitivity and specificity for a specific decision threshold. An ROC curve that approaches the upper left corner signifies a test with perfect discrimination, meaning it achieves 100% sensitivity and 100% specificity with no overlap between distributions. A test with higher overall accuracy will have its ROC curve closer to this ideal corner. This ROC curve has a p-value of less than 0.0001, an area of 0.986 (SD 0.0105), and a 95% confidence interval ranging from 0.965 to 1.007.

DISCUSSION

Because pleural fluid cholesterol testing does not necessitate concurrent blood collection, it is less cumbersome in clinical settings and offers an advantage over Light's criteria for differentiating between transudates and exudates 45 mg/dL should be the threshold for pleural fluid cholesterol in order to distinguish between transudates and exudates [10]. Out of the 80 patients included in this study, 40 had transudates and 40 had exudates, all based on the clinical diagnosis. Lung cancer is the second most frequent cause of pleural exudates, following tuberculosis. This observation aligns with a study conducted in India, where tuberculosis is highly prevalent [11]. It has been found that measuring pleural cholesterol levels above 45 mg/dl increases the precision of the distinction between transudative and exudative effusion [12].

The study results show that pleural fluid cholesterol with a cutoff of >45 mg/dL exhibits the following characteristics: sensitivity of 97.95%, specificity of 95.23%, positive predictive value of 97.95%, and negative predictive value of 95.23%, for exudate identification. It appears that elevated cholesterol levels in exudates are unrelated to serum levels [13]. The study, using pleural cholesterol values >55 mg/dl and pleural/serum cholesterol values >0.3 to define exudative effusion led to a reduction in incorrect classification, with sensitivity of 93%, specificity of 100%, positive predictive value (PPV) of 100%, and accuracy of 95.2% [14, 15]. A sensitivity of 95%, specificity of 95%, PPV of 97.6%, and accuracy of 95.2% were obtained using Light's criteria. For patients with congestive heart failure receiving diuretics, pleural fluid cholesterol was particularly effective in differentiating between exudative and transudative pleural effusions [16, 17].

CONCLUSION

By utilizing pleural fluid cholesterol as an alternative to several tests and simultaneous blood sampling, patients might avoid incurring costs associated with confirming an exudative pleural effusion, as per Light's criteria.

Consent

The author(s) have gathered and maintained the patients' written permission in accordance with international or university norms.

Ethical Approval

Written ethical approval has been gathered and kept by the author(s) in accordance with international or university norms.

Competing Interests

Authors have declared that no competing interests exist.

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