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The clinical utility of pleural fluid cholesterol as a parameter in differentiating exudative from transudative pleural effusion when compared to light's criteria

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ABSTRACT

Background: Pleural effusions are classified as exudate or transudate to guide clinical management. While Light's criteria have been the standard for this differentiation due to their high sensitivity, their lower specificity can lead to potential misclassification of transudates as exudates. This study evaluates the clinical utility of pleural fluid cholesterol compared to Light's criteria. **Aims and Objectives:** The aim of the study was to assess the clinical utility of pleural fluid cholesterol as a laboratory parameter in differentiating exudate from transudate pleural effusions. **Materials and Methods:** This cross-sectional study included 100 participants with pleural effusion. After baseline data collection and clinical examination, blood tests and pleural fluid analyses were conducted. McNemar's test compared the sensitivity, specificity, and diagnostic accuracy of pleural fluid cholesterol with Light's criteria. **Results:** Light's criteria showed a sensitivity of 98.39%, specificity of 84.21%, positive predictive value (PPV) of 91.04%, negative predictive value (NPV) of 96.97%, and diagnostic accuracy of 93%. Pleural fluid cholesterol (threshold >45 mg/dL) demonstrated a sensitivity of 91.94%, specificity of 97.37%, PPV of 98.28%, NPV of 88.10%, and diagnostic accuracy of 94%. The difference in specificity was statistically significant ($P<0.05$), while the difference in sensitivity was not. The overall diagnostic accuracy of pleural fluid cholesterol was similar to that of Light's criteria. **Conclusion:** Pleural fluid cholesterol has a higher specificity and similar diagnostic accuracy compared to Light's criteria. It effectively identifies transudates, reduces false positives for exudates, and can serve as a simple test to confirm the type of pleural, potentially minimizing invasive procedures.

Key words: Pleural fluid cholesterol; Light's criteria; Exudate; Transudate

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INTRODUCTION

Pleural effusion occurs when the amount of pleural fluid entering the pleural cavity (increased entry) exceeds the volume removed (decreased exit). Potential mechanisms by which pleural fluid can accumulate due to increased entry include conditions that increase systemic or pulmonary venous pressure and subsequently pulmonary capillary hydrostatic pressure (heart failure), decrease pulmonary capillary oncotic pressure (e.g., hypoalbuminemia in cirrhosis or nephrosis), conditions which increase the permeability of plasma membrane (inflammatory conditions, infections like pneumonia, malignancy) conditions which decrease pleural pressure (atelectasis), thoracic duct rupture (chylothorax) or diaphragmatic defects (hepatic hydrothorax). Decreased exit is associated with conditions that interfere with the absorption and clearance of pleural fluid through pleural lymphatics, like obstructed lymphatic flow due to infiltration by malignancy and conditions associated with limitation of respiratory motion (lung collapse, pneumothorax).[1]

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Pleural effusions were traditionally divided by clinicians into exudate and transudate. Exudates form due to inflammatory or malignant conditions such as pneumonia, tuberculosis (TB), or malignancy, increasing capillary permeability and allowing large molecules into the pleural space. Transudates occur when serum filters through pleural membranes due to imbalances in hydrostatic or oncotic pressure, typically linked with conditions like heart failure, cirrhosis with ascites, or nephrotic syndrome. This classification allowed clinicians to approach pleural effusion as exudates requiring additional invasive diagnostic testing or transudates, where the clinicians address the underlying issue and monitor for resolution.[2]

The Light's criteria proposed in 1972 used two biochemical parameters to classify an effusion as either exudate or transudate. Light's criteria were designed as a good screening test to approach 100% sensitivity. The study that established these criteria evaluated 150 patients with pleural effusions. Of these, only two patients were incorrectly classified, demonstrating a high sensitivity of 99% and specificity of 98% in identifying exudate.[3]

Subsequent research on Light's criteria confirmed that they are highly sensitive in identifying exudates, but they exhibit a lower specificity ranging from 65% to 85%.[4-7] About 25–30% of transudates can be misclassified as exudates, particularly those caused by conditions like heart failure where diuretics are used or when there is a high presence of erythrocytes (which release lactate dehydrogenase [LDH]) in the pleural fluid.[8,9] Despite their high sensitivity, Light's criteria may classify up to 10% of pleural effusions due to malignancy as transudates, although the exact reason for this is unclear.[10]

Hamm and colleagues introduced pleural fluid cholesterol in 1987 as a marker for identifying exudates after analyzing pleural effusion in 62 patients. The mean cholesterol levels were 94 mg/dL, 76 mg/dL, and 30 mg/dL in malignant, inflammatory, and transudate effusions, respectively. After using a cutoff of >60 mg/dL, the sensitivity was 90.32%, specificity was 100%, and diagnostic accuracy was 95% for the diagnosis of exudates. When Light's criteria were applied to the same set of patients, the sensitivity was 100%, specificity 70%, and diagnostic accuracy 85% to diagnose exudates. The exact mechanism of the increase in cholesterol levels in exudates is not known, but it is likely related to the breakdown of intrapleural cells with the release of cellular content of cholesterol or to increased capillary permeability, which allows cholesterol in the bloodstream to enter the pleural space.[11]

Valdes and colleagues used a cutoff value of pleural fluid cholesterol >55 mg/dL in 253 patients and reported a sensitivity of 91% and specificity of 100% in diagnosing exudate. In the same patients, pleural fluid LDH had a sensitivity of 67% and specificity of 95%. Using Light's criteria, the sensitivity was 94.6% and specificity was 78.4%. The mean pleural fluid cholesterol values were 28.5±12.8 mg/dL for transudates, 88.1±30 mg/dL for neoplastic exudates, 96.5±28 mg/dL for tuberculous exudates, and 88±35.9 mg/dL for the miscellaneous group (associated with pneumonia, pulmonary embolism, and connective tissue disorders).[12]

Costa et al., studied 180 patients with pleural effusion. When pleural fluid cholesterol cut-off of >45 mg/dL was used, the sensitivity was 90%, specificity was 100%, and diagnostic accuracy was 93%. When Light's criteria were applied sensitivity was 98%, specificity was 82% and diagnostic accuracy was 94%. Two exudates were misclassified as transudate, both due to complicated parapneumonic effusion. Nine transudates were misclassified as exudate, seven due to congestive heart failure (CHF), and two due to chronic liver disease (CLD). The exudates misclassified using Light's criteria were correctly classified using pleural fluid cholesterol, and all the transudates misclassified by Light's criteria were correctly classified by pleural fluid cholesterol. When Light's criteria were combined with pleural fluid cholesterol, the sensitivity was 100%, specificity was 94%, and diagnostic accuracy was 99%.[13]

Lépine et al., studied 399 patients who underwent pleural fluid analysis and compared various diagnostic parameters with Light's criteria. The highest sensitivity (97% with a confidence interval (CI) of 94–99%) and negative likelihood ratio (0.04 with a CI of 0.02–0.08) for detecting exudates were found in criteria that use pleural fluid LDH levels >0.6 times the upper limit of normal serum levels along with pleural fluid cholesterol levels >40 mg/dL. The overall accuracy of these criteria was comparable to Light's criteria.[14]

Guleria et al., studied 75 patients with pleural fluid cholesterol (cutoff value >60 mg/dL) and reported a sensitivity of 88% and specificity of 100% in detecting exudate with a diagnostic accuracy of 92%. These results were better than the reported sensitivity of 98 % and specificity of 80 % when Light's criteria were applied.[15]

Pleural fluid cholesterol has been used as a pleural fluid-only three-test combination approach along with pleural fluid protein and LDH. This obviates the need for blood tests which are often drawn simultaneously, and avoids duplicative use of highly correlated LDH criteria as in traditional Light's criteria.[7,9] It has also been used as a pleural fluid-only one test criteria, but the performance has been poor due to low sensitivity.[16]

The thresholds for interpreting pleural fluid test results are deliberately selected to maximize sensitivity in detecting exudative effusions, given their significant prognostic implications, such as in cases of malignancy or parapneumonic effusion. While it is desirable to use a test with high sensitivity like Light's criteria as a screening test, inadvertent misclassification of transudates as exudates can lead to additional diagnostic tests, potential overdiagnosis and treatments, unnecessary follow-ups, and psychological distress to patients who do not have the disease. In resource-limited settings, this can inflate healthcare expenses and strain available resources. A test with better specificity can potentially be used to confirm the presence of exudate and negate the need for additional testing, which may be invasive.

Aims and objectives

To assess the clinical utility of pleural fluid cholesterol as a laboratory parameter in differentiating exudate from transudate pleural effusions.

MATERIALS AND METHODS

Pleural fluid cholesterol cut-off values between 45 and 55 mg/dL have been used in various studies, with significant variability reported even within the same institution and research group over time.[7,17] Heffner and colleagues, in their meta-analysis of diagnostic tests used to differentiate exudative from transudative effusions, used a pleural fluid cholesterol value of >45 mg/dL based on ROC analysis.[7] Our study used a pleural fluid cholesterol cutoff of >45 mg/dL to classify the effusions as an exudate. We aimed to assess the diagnostic value of pleural fluid cholesterol as a laboratory parameter to differentiate exudative and transudative pleural effusion when compared to Light's criteria.

The study by Costa et al., which used a pleural fluid cholesterol cut-off of >45 mg/dL in 180 patients, found 23 discordant pairs (patient with different test results between the two tests). The proportion of discordant pairs was approximately 12.78%. To detect a 10% difference (effect size) in diagnostic parameters with 80% power and a 5% significance level, assuming a discordant pair proportion of 12.78%, it was calculated that approximately 100 patients would be needed.[13]

The study was conducted on 100 participants aged 18 years or older, admitted with pleural effusion in general medicine between the period of January 2021and December 2021. Participants were excluded if they presented with traumatic pleural effusion, renal failure with associated uremia, or pulmonary embolism. Participants were also excluded if they were pregnant or breastfeeding. Written informed consent was obtained from all participants or their legal representatives if they could not provide consent. The institutional ethics committee approved the study, and the procedures followed were per the Declaration of Helsinki.

After collecting baseline data, a clinical examination was conducted, and pleural effusions were categorized as exudative or transudative based on etiology. Effusions associated with CHF, liver cirrhosis, and nephrotic syndrome were classified as transudates, and the rest were classified as exudates.

The diagnosis of the etiology of the effusion was considered when the following conditions were met: CHF: The presence of an enlarged heart with clinical or echocardiographic evidence of cardiac dysfunction, and one or more of the following alterations: Elevated venous pressure, edema, tachycardia, or a ventricular gallop. Liver cirrhosis: Clinical and laboratory evidence of hepatic damage with portal hypertension or hypoalbuminemia; Nephrotic syndrome: The presence of heavy proteinuria (protein excretion >3.5 g/24 h), hypoalbuminemia (<3.5 g/dL), and peripheral edema. The diagnosis of tuberculous pleural effusion was established by demonstrating. Mycobacterium tuberculosis in pleural fluid or a pleural biopsy specimen. In the setting of high clinical suspicion for TB, a presumptive diagnosis of tuberculous pleural effusion was established in the setting of pleural fluid analysis with lymphocytic-to-neutrophil ratio >0.75 and adenosine deaminase >40 units/L or by demonstration of one or more caseating granulomas on pleural biopsy. Pleural effusion associated with pneumonia-parapneumonic effusion: Clinically and radiologically confirmed pneumonia with no direct or indirect evidence of bacterial invasion of the effusion; complicated parapneumonic effusion: Clinically and radiologically confirmed pneumonia with one or more of the following indicators of bacterial invasion of the effusion: Turbid pleural fluid with pH <7.20, pleural fluid white blood cell count >500 cells/mm^3, bacteria in Gram's stain smear or culture. Pleural effusion associated with malignancy: Cytologic and/or histologic evidence of malignant pleural effusion. The category "other exudates" encompasses those effusions caused by pancreatitis, collagen vascular disease, and various uncommon but well-documented causes of exudative pleural effusions.

According to Light's criteria rule, if at least one of the following three criteria is fulfilled, the fluid is defined as an exudate:[3]

1. Pleural fluid-to-serum protein ratio >0.5
2. Pleural fluid-to-serum LDH ratio >0.6
3. Pleural fluid LDH >0.67 (two-thirds) of the upper limit of the laboratory's normal serum LDH.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were estimated using 2×2 contingency tables with 95% CIs. Sensitivity was defined as the proportion of patients classified as exudate with the reference standard (etiologic classification) who tested positive by the index test (Light's criteria) or comparator test (pleural fluid cholesterol). Specificity was defined as the proportion of patients classified as transudate with the reference standard (etiologic classification) who tested negative by the index test (Light's criteria) or comparator test (pleural fluid cholesterol). McNemar's test for paired proportions was used to calculate McNemar's statistic and the associated p-value. Data were entered into an Excel sheet and analyzed using SPSS v21.0 operating on Windows 11.

RESULTS

Pleural fluid analysis was done for 100 patients. The mean age of participants was 50.28±15.85 years. Among the participants, 36 (36%) were female and 64 (64%) were male. As shown in Table 1, according to the causal disease and type of effusion expected, 62 (62%) pleural fluid samples were classified as exudates, and 38 (38%) were classified as transudates.

Table 2 shows the findings which were observed after applying Light's criteria and pleural fluid cholesterol as a single criterion. When Light's criteria were used 67% of samples were classified as exudates and 33% as transudates. Notably, one exudate was misclassified as a transudate, and six transudates were misclassified as exudates. When pleural fluid cholesterol was used a sole criterion, 58% were classified as exudates and 42% as transudates, with five exudates misclassified as transudates and one transudate misclassified as an exudate.

Table 3 presents the diagnostic performance of Light's criteria and pleural fluid cholesterol as compared to expected classification of effusion by etiology.

When Light's criteria were used, the sensitivity for diagnosing exudates was 98.39%, with a specificity of 84.21%. The PPV was 91.04%, and the NPV was 96.97%. The overall diagnostic accuracy was 93%. This indicates that Light's criteria are highly sensitive but have moderate specificity, potentially leading to some transudates being misclassified as exudates (false positives).

When pleural fluid cholesterol was used, the sensitivity for diagnosing exudates was 91.94%, with a specificity of 97.37%. The PPV was 98.28%, and the NPV was 88.10%. The overall diagnostic accuracy was 94%. These findings suggest that while pleural fluid cholesterol is slightly less sensitive than Light's criteria, it offers higher specificity, thereby reducing the likelihood of false-positive diagnoses.

We used McNemar's test for paired proportions to compare the diagnostic parameters from Light's criteria and pleural fluid cholesterol. While Light's criteria exhibited high sensitivity (98.39%), their lower specificity (84.21%) resulted in more false positives. In contrast, pleural fluid cholesterol, with slightly lower sensitivity (91.94%), offers significantly higher specificity (97.37%, P<0.05), making it a more reliable tool for identifying transudates. The

Table 1: Etiological classification of pleural fluid as exudate or transudate based on underlying primary disease (expected type of effusion)

Observed	Expected	Total
Exudate		
Pleural tuberculosis	27	62
Associated with pneumonia	16	
Malignancy	12	
Others	7	
Transudate		
CHF*	23	38
CLD⁺	12	
Nephrosis⁺⁺	3	
Total		100

*CHF: Congestive heart failure, ⁺CLD: Chronic liver disease, ⁺⁺Nephrosis - Nephrotic syndrome

Table 2: Classification of pleural fluid based on light's criteria and pleural fluid cholesterol

Observed	Expected	Observed	
		Light's criteria	Pleural cholesterol
Exudate			
Pleural tuberculosis	27	27	26
Associated with pneumonia	16	16	13
Malignancy	12	11	12
Others	7	7	6
Misclassified exudate			
CHF*	-	5	-
CLD⁺	-	1	1
Nephrosis⁺⁺	-	0	-
	62	67	58
Transudate			
CHF*	23	18	23
CLD⁺	12	11	11
Nephrosis⁺⁺	3	3	3
Misclassified transudate			
Pleural tuberculosis	-	-	1
Associated with pneumonia	-	-	3
Malignancy	-	1	-
Others	-	-	1
	38	33	42
Total	100	100	100

CHF: Congestive heart failure, ⁺CLD: Chronic liver disease, ⁺⁺Nephrosis - Nephrotic syndrome

Table 3: Comparison of operating parameters of light's criteria and pleural fluid cholesterol

Diagnostic parameter	Light's criteria (%)	95% CI	Pleural cholesterol (%)	95% CI	McNemar's statistic	P-value
Sensitivity	98.39	91.34–99.96	91.94	82.17–97.33	1.125	0.288
Specificity	84.21	68.75–93.98	97.37	86.19–99.93	5.0625	0.0245
PPV	91.04	82.98–95.50	98.28	89.16–99.75	-	-
NPV	96.97	82.01–99.56	88.10	76.12–94.50	-	-
Accuracy	93.00	86.11–97.14	94.00	87.40–97.77	0.1429	0.705

CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

difference in sensitivity between the two methods was not statistically significant, and both methods demonstrated similar overall diagnostic accuracy.

DISCUSSION

An early and clear indication of whether a pleural effusion is exudative or transudative is valuable in clinical practice, guiding subsequent diagnostic and treatment decisions. This cross-sectional study assessed the diagnostic value of pleural fluid cholesterol as a lab parameter to differentiate exudative and transudative pleural effusions. We compared it to the traditional Light's criteria. Both diagnostic methods resulted in misclassifications.

When classification based on the application of the criteria of Light et al. is compared with the etiologic classification (expected), considered as the gold standard, one of the exudates was classified as transudate, and six of the transudates were misclassified as exudate. The patient with the misclassified transudate had a malignant effusion secondary to lung carcinoma. The cause of transudate here was unclear; however, it is reported in the literature that about 5% of malignant effusions are misclassified as transudates using Light's criteria, especially in early stages where the effusion is predominantly thought to occur due to lymphatic obstruction rather than pleural seeding with malignant cells.[10] Among the six patients with misclassified exudate, five had heart failure, and one had CLD with suspected hepatic hydrothorax. Four of the heart failure patients were on diuretics at the time of pleural fluid analysis; one had a blood-stained effusion with more than 5000 red blood cell/mm^3. The probable reason for the misclassification was due to the use of diuretics and the traumatic nature of the pleural tap. The patient with CLD had a neutrophilic predominant effusion, which resolved with a course of antibiotics; the presence of infection could have altered the characteristics of the pleural fluid.

When pleural fluid cholesterol was used as a criterion, five exudates were classified as transudates, and one transudate was classified as exudate. Four cases were associated with pneumonia among the patients with misclassified transudate; one had tuberculosis, and the other three had non-tubercular bacterial pneumonia. One of the patients with non-tubercular pneumonia had chronic heart failure as a comorbid illness. The probable reason for the misclassification here was the presence of heart failure and the variable degree of pleural inflammation present in pneumonia, which can affect the permeability of the pleural membrane and could have potentially led to low pleural fluid cholesterol. The fifth case presented with acute pancreatitis and was also found to have associated CLD.

The heart failure cases and the malignant effusion, which were misclassified as exudates with Light's criteria, were correctly classified when pleural fluid cholesterol was used. The pneumonia and pancreatitis cases misclassified as transudate with pleural fluid cholesterol were correctly classified as exudates when Light's criteria were used. The patient with CLD and pleural fluid infection, misclassified as an exudate when Light's criteria were used, remained classified as an exudate when pleural fluid cholesterol was used.

Statistical analysis revealed that pleural fluid cholesterol significantly improved specificity ($P<0.05$) compared to Light's criteria, with only a marginal decrease in sensitivity. The specificity, sensitivity, and diagnostic accuracy reported were comparable to previous studies that were done.[4-7,11,13]

Limitations of the study

While the diagnostic comparison provided valuable insights into the performance of different biochemical parameters in assessing pleural effusion, there were limitations in the study. The sample size was relatively small, there was also potential for selection bias as samples were recruited from a single center. We could not assess the performance metrics at various pleural fluid cholesterol levels as the lab was equipped only to assess the level of cholesterol values below or above 45 mg/dL.

CONCLUSION

In our study, several misclassifications were observed with both diagnostic methods. Light's criteria misclassified six transudates as exudates, primarily in patients with heart failure, likely due to diuretic use or traumatic pleural taps.

In contrast, pleural fluid cholesterol correctly identified these cases but misclassified five exudates as transudates, particularly in patients with concurrent pneumonia and CHF or CLD. These findings highlight the complexities in pleural effusion diagnosis and suggest that a combination of criteria might offer the most accurate results, particularly in settings where false positives could lead to unnecessary interventions.

Despite these limitations, our study suggests that pleural fluid cholesterol offers a more specific alternative to Light's criteria for diagnosing transudates, particularly in complex cases. While both methods have limitations, pleural fluid cholesterol could serve as a valuable addition to diagnostic protocols, either as a standalone test or as part of a combined approach with other pleural fluid markers to distinguish between exudative and transudative fluids.

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Authors' Contributions:
NK- Design of the study, preparation of clinical protocol, data collection, prepared the first draft of the manuscript; **RG**- Definition of intellectual content, data analysis, statistical analysis and interpretation, manuscript preparation and submission; **SAS**- Concept, implementation of the study protocol, coordination, manuscript revision; **BI**- Literature survey and preparation of tables.

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