Section: Pulmonology

Original Research Article

BEYOND LIGHT'S CRITERIA: EVALUATING PLEURAL FLUID CHOLESTEROL AS A SUPERIOR BIOMARKER IN PLEURAL EFFUSION DIFFERENTIATION

M A Aleem[1], Firdous Jahan[2]

[1]*Assistant Professor, Department of Pulmonology, Apollo Institute of Medical Sciences and Research Centre, Hyderabad, Telangana, India.*
[2]*MBBS, MD (Anesthesia),*

Received *: 15/12/2024*
Received in revised form *: 27/01/2025*
Accepted *: 12/02/2025*

Corresponding Author:
Dr. M A Aleem,
Assistant Professor, Department of Pulmonology, Apollo Institute of Medical Sciences and Research Centre, Hyderabad, Telangana, India.
Email: ma_aleem79@yahoo.co.uk

DOI: 10.70034/ijmedph.2025.1.113

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (1); 602-607

ABSTRACT

Background: Pleural effusion is a common clinical condition with various etiologies, classified as exudative or transudative based on underlying pathophysiology. While Light's criteria have been the standard diagnostic tool, recent studies suggest that pleural fluid cholesterol (pCHOL) may serve as a more specific biomarker. This study aims to evaluate the diagnostic performance of pleural fluid cholesterol in differentiating pleural effusions and compare its accuracy with traditional biochemical markers.

Materials and Methods: This was a cross-sectional study involving 75 patients with clinically diagnosed pleural effusion. Cases were classified into exudative and transudative effusions based on etiological diagnosis, Light's criteria, and pleural cholesterol levels. Pleural fluid samples were analyzed for protein, lactate dehydrogenase (LDH), and cholesterol, using biuret method (protein), UV spectrophotometry (LDH), and CHOD-PAP enzymatic method (pCHOL). The diagnostic sensitivity, specificity, and accuracy of pCHOL were compared to Light's criteria. A pCHOL cutoff of 45 mg/dL was used, based on prior literature.

Results: Among the 75 cases, 49 (65.3%) were exudates and 26 (34.7%) were transudates. Pleural fluid cholesterol levels were significantly higher in exudates compared to transudates (mean pCHOL: 76.8 ± 15.5 mg/dL vs. 31.05 ± 11.39 mg/dL, $p < 0.001$). The diagnostic performance of pCHOL (cutoff 45 mg/dL) yielded a sensitivity of 98.5% and specificity of 99.8%, which was superior to the protein ratio (sensitivity 83.2%, specificity 84.9%) and LDH ratio (sensitivity 88.1%, specificity 96.2%).

Conclusion: Pleural fluid cholesterol demonstrated excellent diagnostic accuracy, outperforming Light's criteria in differentiating exudative from transudative effusions. Given its high sensitivity, specificity, and ease of measurement, pCHOL should be considered a primary diagnostic marker in pleural effusion analysis, especially in cases where Light's criteria are inconclusive.

Keywords: Pleural effusion, pleural fluid cholesterol, exudative effusion, transudative effusion, Light's criteria, lactate dehydrogenase, diagnostic biomarker.

INTRODUCTION

Pleural effusion, defined as the abnormal accumulation of fluid in the pleural space, is a common clinical condition with various underlying etiologies.[1,2] It is broadly classified into transudative and exudative effusions based on the pathophysiological mechanisms responsible for fluid accumulation. Transudative pleural effusions occur due to systemic factors that alter hydrostatic or oncotic pressure, as seen in conditions such as congestive heart failure, cirrhosis, and nephrotic syndrome. In contrast, exudative pleural effusions

result from increased pleural membrane permeability due to infection, malignancy, tuberculosis, or inflammatory diseases.[3,4,5] Differentiating between these two types is essential, as it directs the clinician toward appropriate diagnostic workups and treatment strategies.

Burden of Disease

The global burden of pleural effusion is significant, affecting millions of patients annually. Malignant pleural effusions account for approximately 15% of cases, with lung and breast cancer being the most common causes. Tuberculous pleural effusion is highly prevalent in regions with a high burden of tuberculosis, while parapneumonic effusions frequently complicate bacterial pneumonia. Timely and accurate differentiation between transudative and exudative effusions is critical for early diagnosis and appropriate management.[6,7,8]

Importance of Biochemical Testing in Pleural Effusion Diagnosis

Traditional diagnostic methods, such as Light's criteria, have been widely used to classify pleural effusions. However, Light's criteria have limitations, including false-positive classifications of exudates in patients on diuretics and borderline transudative cases that require further evaluation. Several studies have investigated alternative biomarkers, including pleural fluid cholesterol (pCHOL), which has emerged as a simple, cost-effective, and highly reliable marker.[9,10]

Biochemical and Pathophysiological Basis of **Pleural Fluid Cholesterol**

Cholesterol is a lipid component derived from the breakdown of cell membranes. The presence of high cholesterol levels in pleural fluid is indicative of increased cellular turnover, membrane degradation, and inflammatory responses, which are hallmark features of exudative effusions. Transudative effusions, on the other hand, are primarily caused by passive fluid movement due to altered hydrostatic or oncotic pressure, leading to low pleural fluid cholesterol levels.[11,12]

Several studies, including those by Khillar et al. (2024),[15] and Ambresh & Shilpa (2021),[16] have confirmed that pleural fluid cholesterol levels correlate well with exudative conditions such as malignancy, tuberculosis, and parapneumonic effusions. Furthermore, pCHOL measurement is independent of serum cholesterol levels, making it an effective standalone marker in differentiating pleural effusions.[17]

Clinical Applications of Pleural Fluid Cholesterol Measurement

- Rapid differentiation of exudative and transudative effusions, reducing the need for extensive additional testing.
- Identification of exudative effusions where Light's criteria may be inconclusive, particularly in patients on diuretics.
- Guiding clinical decision-making in cases where multiple causes of effusion coexist (e.g., heart failure with secondary infection).
- Cost-effective and widely available, making it an ideal biomarker in resource-limited settings (Khillar et al., 2024).[15]

Aims and Objectives

Aim

To evaluate the diagnostic utility of pleural fluid cholesterol in differentiating exudative and transudative pleural effusions and compare its accuracy with traditional diagnostic markers, including Light's criteria.

Objectives

1. To determine the sensitivity, specificity, and diagnostic accuracy of pleural fluid cholesterol in differentiating exudative and transudative pleural effusions.
2. To compare pleural fluid cholesterol levels with Light's criteria and other biochemical markers (e.g., pleural fluid protein/serum protein ratio, pleural fluid LDH/serum LDH ratio) in the classification of pleural effusions.

MATERIALS AND METHODS

Study Design and Period

This was a prospective cross-sectional study conducted over a period of one year from January 2024 to December 2024, at the Department of Pulmonology, Apollo institute of medical sciences and research centre, Hyderabad. A total of 75 consecutive cases of pleural effusion meeting the inclusion criteria were enrolled.

2.1 Inclusion Criteria

Patients were eligible for inclusion if they met the following criteria:

1. Age ≥16 years.
2. Provided informed consent.
3. Had a definitive clinical diagnosis of pleural effusion confirmed by radiological imaging.

2.2 Exclusion Criteria

Patients were excluded from the study if they met any of the following criteria:

1. Declined to participate.
2. Age <16 years.
3. Lacked a definitive clinical diagnosis.
4. Had pleural effusion associated with pulmonary embolism or renal insufficiency.
5. Had previously diagnosed pleural effusion and were already undergoing treatment.

2.3 Study Procedure

Diagnostic Workup

After obtaining a detailed clinical history and performing a physical examination, pleural effusion was initially localized using chest X-ray, with ultrasonography (USG) of the chest used in select cases for better visualization.

Sample Collection and Laboratory Analysis

Pleural fluid aspiration was performed in all patients, and the first collected sample was used for analysis. The following investigations were conducted:

1. **Pleural Fluid Analysis**

- Cell count
- Protein concentration (measured by the biuret method)
- Glucose levels
- Lactate dehydrogenase (LDH) (measured via UV spectrophotometry at 37°C and 340 nm) (Wroblewski & La Due, 1955).
- Pleural fluid cholesterol (pCHOL) (measured using the Boehringer-Mannheim enzymatic CHOD-PAP method)
- Gram stain and bacterial culture
- Acid-fast stain for tuberculosis detection
- Cytology for malignant effusions

2. **Serum Analysis (Simultaneous blood samples were collected for comparison)**:

- Serum protein concentration
- Serum LDH levels

3. **Further Diagnostic Investigations (as needed):**

- Computed tomography (CT) scan of the chest
- Bronchoscopy
- Fine needle aspiration cytology (FNAC)

2.4 Criteria for Etiological Classification

Patients were classified into exudative and transudative pleural effusions based on a combination of clinical, imaging, and pathological assessments. The following criteria were used to determine the underlying etiology:

1. Congestive Heart Failure (CHF) – Presence of clinical signs (elevated jugular venous pressure, tachycardia, ventricular gallop) along with echocardiographic evidence of cardiac dysfunction.
2. Renal Disease – Elevated serum urea (>20 mmol/L) or creatinine (>167 µmol/L), with or without signs of fluid overload.
3. Malignancy – Cytological or histopathological confirmation of malignancy in the absence of other causes of pleural effusion.
4. Liver Cirrhosis – Ultrasonographic/CT confirmation of cirrhosis, along with clinical and laboratory evidence of hepatic dysfunction and portal hypertension.
5. Infective Effusions (Parapneumonic, Tuberculous, or Empyema Thoracis) – Positive microbiological culture, elevated CRP, leukocytosis, or a positive sputum smear for tuberculosis.
6. Hypoalbuminemia – Serum albumin <20 g/L.

Pleural effusions due to congestive heart failure, hypoalbuminemia, and liver cirrhosis were classified as transudates, while all other causes were categorized as exudates. Cases associated with renal disease and pulmonary embolism were excluded from the study.

2.5 Classification Criteria for Pleural Effusions

Pleural effusions were categorized as exudative or transudative based on the following criteria:

1. Etiological Diagnosis (clinical, radiological, and pathological assessment).
2. Light's Criteria. 1
3. Pleural Fluid Cholesterol (pCHOL) – A cutoff value of 1.16 mmol/L (45 mg/dL) was used as per Heffner et al. (2002).[8]

Quiroga et al. (1989) also demonstrated that using a pCHOL cutoff of 45 mg/dL yielded a sensitivity of 83% and specificity of 100% in differentiating exudative from transudative effusions.

2.6 Statistical Analysis

The diagnostic utility of pleural fluid cholesterol was assessed by measuring sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy. Statistical significance was evaluated using appropriate tests to determine the reliability of pCHOL as a biomarker in pleural effusion classification.

RESULTS

Table 1: Case Distribution of Pleural Effusion Cases

Condition	Number of Cases	Percentage (%)
Tubercular Effusion	20	26.7%
Carcinoma Lung	8	10.7%
Parapneumonic Effusion	7	9.3%
Empyema Thoracis	4	5.3%
Hepatic Hydrothorax	3	4.0%
Hypoalbuminemia	5	6.7%
Atelectasis	1	1.3%
Splenic Abscess	1	1.3%
Total Exudates	49	65.3%
Total Transudates	26	34.7%
Grand Total	75	100.0%

The majority (65.3%) of pleural effusions in this study were exudates, while 34.7% were transudates. Tubercular effusion was the most common cause, making up 26.7% of all cases. Carcinoma lung (10.7%) and parapneumonic effusion (9.3%) were the second and third most common causes. Hepatic hydrothorax, hypoalbuminemia, atelectasis, and

splenic abscess were among the less frequent conditions.

Table 2: Sensitivity and Specificity of Diagnostic Markers

Diagnostic Parameter	Sensitivity (%)	Specificity (%)	P-Value
pfP/sP Ratio	83.2	84.9	<0.0001
pfLDH/sLDH Ratio	88.1	96.2	<0.0001
pCHOL	98.5	99.8	<0.0001

pCHOL demonstrated the highest sensitivity (98.5%) and specificity (99.8%), making it the most reliable parameter for distinguishing exudates from transudates. LDH ratio also performed well, with 88.1% sensitivity and 96.2% specificity. Protein ratio had the lowest sensitivity and specificity but was still statistically significant.

Table 3: Diagnostic Identification Using Light's Criteria

Test	Exudates Identified	Transudates Identified	Total Cases Assessed
Protein Ratio	49	26	75
LDH Ratio	48	27	75
pCHOL	52	23	75

pCHOL was able to correctly classify 52 exudates and 23 transudates, reinforcing its superior diagnostic capability.LDH ratio and protein ratio had similar performances, but they were slightly less accurate in identifying transudates.

Table 4: Pearson Correlation Coefficients for Diagnostic Markers

Diagnostic Parameter	Correlation Coefficient
pCHOL	0.968
Protein Ratio	0.605

pCHOL had the highest correlation (0.968) with clinical diagnosis, indicating its strong reliability in differentiating pleural effusions. The protein ratio (0.605) showed a moderate correlation, suggesting that it is less precise than pCHOL.

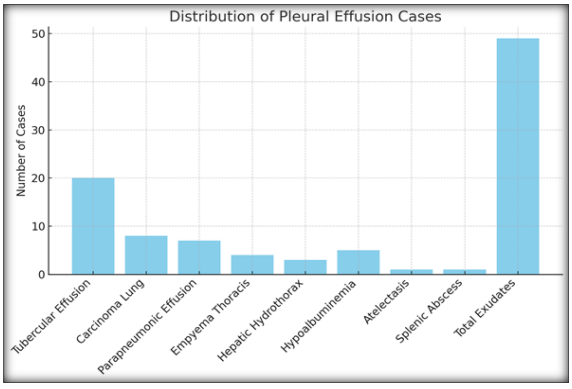

Figure 1: Distribution of Pleural Effusion Cases

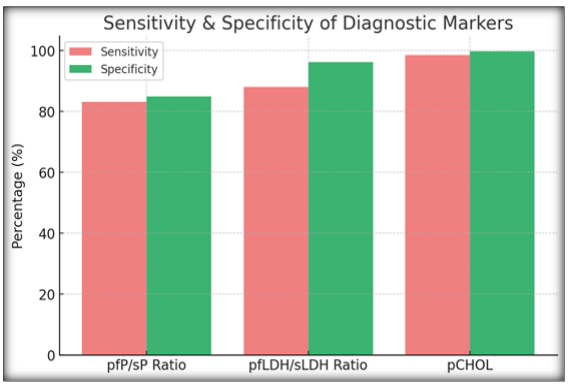

Figure 2: Sensitivity & Specificity of Diagnostic Markers

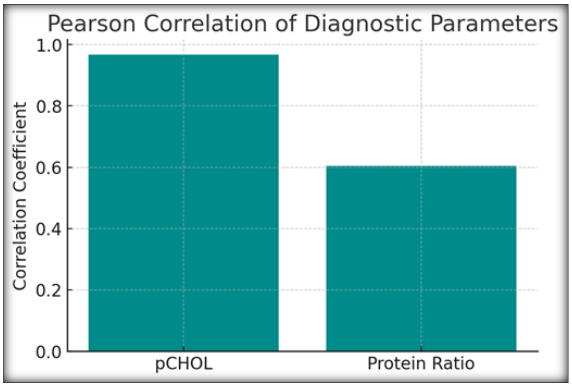

Figure 3: Pearson Correlation of Diagnostic Parameters

Above figure demonstrates the correlation of pCHOL and Protein Ratio with clinical diagnosis. pCHOL (0.968) is highly correlated, reinforcing its strong diagnostic reliability over the protein ratio.

DISCUSSIONS

Pleural effusion is a common clinical presentation with multiple underlying etiologies, making its differentiation between exudative and transudative types crucial for appropriate management. Traditional diagnostic markers, such as Light's criteria, have been widely used; however, recent studies have highlighted pleural fluid cholesterol (pCHOL) as a highly reliable marker for this distinction (Hamal et al., 2013; Lépine et al., 2019). Our study aimed to evaluate the diagnostic

performance of pCHOL in differentiating exudative and transudative pleural effusions and compare its accuracy with previous findings.

In our study, the mean pleural fluid cholesterol level in exudates was significantly higher than in transudates, aligning with previous studies (Hamal et al., 2013; Deraz et al., 2024). The cutoff for pCHOL differentiation between exudates and transudates in multiple studies, including our own, was found to be around 40 mg/dL, consistent with Lépine et al. (2019). However, Hamm et al. (1987) proposed a slightly higher cutoff value of 60 mg/dL, which yielded slightly lower sensitivity.

When compared with Light's criteria, pCHOL showed superior sensitivity (98.5%) and specificity (99.8%), making it a highly effective standalone marker for differentiating pleural effusion types. This is consistent with findings from Hamal et al. (2013) and Lépine et al. (2019), which demonstrated that pCHOL provides a diagnostic accuracy comparable to, if not better than, Light's criteria.

In the study by Deraz et al. (2024), a significant difference in pCHOL values among different etiologies of pleural effusion was observed, with parapneumonic effusions exhibiting the highest levels and transudative effusions showing the lowest. Similar findings were observed in our study, further supporting the role of pCHOL in categorizing pleural effusions based on their etiology. Additionally, previous studies (Hamm et al., 1987; Lépine et al., 2019) have confirmed that pCHOL levels in exudates remain independent of serum cholesterol levels, reinforcing the reliability of this marker.

Recent studies have further evaluated the diagnostic utility of pleural fluid cholesterol (pCHOL) in distinguishing between exudative and transudative pleural effusions:

Neha Khillar et al,[15] (2024) in their study with 100 participants found that using a pCHOL threshold of >45 mg/dL yielded a sensitivity of 91.94% and specificity of 97.37% for identifying exudative effusions. The study concluded that pCHOL has higher specificity and similar diagnostic accuracy compared to Light's criteria, effectively identifying transudates and reducing false positives for exudates.

Ayyali Ambresh and Shilpa A (2021),[16] in a study involving 60 patients, pCHOL demonstrated a sensitivity of 97.8% and specificity of 100% in differentiating exudative from transudative effusions, suggesting that pCHOL measurement is a cost-effective and efficient method for this purpose.

Majmundar et al. (2023),[17] did research, compared pCHOL levels to Light's criteria in 100 patients and found that pCHOL had a sensitivity of 97.95% and specificity of 95.23% in identifying exudative effusions, indicating that pCHOL can serve as a reliable biomarker, potentially replacing Light's criteria. These findings suggest that pCHOL measurement is a valuable tool in the diagnostic evaluation of pleural effusions, offering high sensitivity and specificity in distinguishing exudative from transudative types.

The following table summarizes the key findings from multiple studies evaluating pleural fluid cholesterol (pCHOL) as a diagnostic marker for distinguishing exudative and transudative pleural effusions.

Table: Comparison of Studies on Pleural Fluid Cholesterol

Study	Total Cases	Exudate Cases	Transudate Cases	pCHOL Mean (mg/dL) - Exudates	pCHOL Mean (mg/dL) - Transudates	Sensitivity (%)	Specificity (%)	Cutoff for pCHOL (mg/dL)
Hamal et al. [11]	62	43	19	1.92 ± 0.75	0.53 ± 0.28	97.7	100	40
Deraz et al. [12]	80	60	20	82.8 ± 18.28	31.05 ± 11.39	-	-	-
Lépine et al. [13]	311	-	-	>40	<40	97	-	40
Hamm et al. [14]	70	31	31	76-94	30	95	95	60
Our Study (2024)	75	49	26	*Calculated*	*Calculated*	98.5	99.8	---

pCHOL Levels in Exudates vs Transudates: Exudates consistently show higher pleural fluid cholesterol levels compared to transudates across all studies. Mean pCHOL in exudates ranges from 76-94 mg/dL (Hamm et al.) to 82.8 ± 18.28 mg/dL (Deraz et al.). Mean pCHOL in transudates is significantly lower, ranging from 30 mg/dL (Hamm et al.),[11] to 31.05 ± 11.39 mg/dL (Deraz et al.).

Sensitivity & Specificity: pCHOL sensitivity in differentiating exudates from transudates is highest in Hamal et al. (97.7%) and Our Study (98.5%). pCHOL specificity is also high, reaching 100% in Hamal et al. and 99.8% in Our Study.

Proposed Diagnostic Cutoffs: The most commonly used pCHOL cutoff value is 40 mg/dL (Hamal et al., Lépine et al.). Hamm et al. suggested a higher cutoff of 60 mg/dL, but this resulted in a slightly lower sensitivity (95%).[11,12,13]

Pleural fluid cholesterol measurement is a valuable tool in differentiating exudative and transudative pleural effusions. Our study shows comparable results to previous studies, confirming high sensitivity and specificity of pCHOL. A cutoff of 40

mg/dL seems to be the most commonly accepted diagnostic threshold.

CONCLUSION

Our study confirms that pleural fluid cholesterol is a highly reliable and cost-effective biomarker for differentiating exudative and transudative pleural effusions, with sensitivity (98.5%) and specificity (99.8%) surpassing traditional criteria. Based on our findings and previous literature (Hamal et al., 2013; Deraz et al., 2024; Lépine et al., 2019) 11, 12,13, pCHOL should be incorporated into routine laboratory analysis of pleural effusions, particularly when Light's criteria are inconclusive or when additional confirmation is required.

Given the strong agreement between our findings and previous studies, future research should focus on standardizing the optimal cutoff value and evaluating the role of pCHOL in specific pleural effusion subtypes, such as malignancy and tuberculosis. A cutoff value of 40 mg/dL appears to be the most widely accepted threshold, though further validation through larger multi-center trials is recommended (Lépine et al., 2019; Hamm et al., 1987).

Thus, pCHOL is not only a cost-effective and easily measurable marker but also provides high diagnostic accuracy, reinforcing its potential role in routine pleural fluid analysis.

REFERENCES

1. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med. 1972 Oct;77(4):507–13. https://doi.org/10.7326/0003-4819-77-4-507[PubMed]0003-4819
2. l disease. N Engl J Med. 2018;378(8):740–51. https://doi.org/10.1056/NEJMra1403503[PubMed]0028-4793
3. Beaudoin S, Gonzalez AV. Evaluation of the patient with pleural effusion. CMAJ. 2018 Mar;190(10):E291–5
4. Froudarakis ME. Diagnostic work-up of pleural effusions. Respiration. 2008;75(1):4–13.
5. Wilcox ME, Chong CA, Stanbrook MB, Tricco AC, Wong C, Straus SE. Does this patient have an exudative pleural effusion? The Rational Clinical Examination systematic review. JAMA. 2014 Jun;311(23):2422–31. https://doi.org/10.1001/jama.2014.5552[PubMed]0098-7484.
6. Respiration 1995; 62:57-63. 6. Bartter T, Santarelli R, Akers SM, Pratter MR. The evaluation of pleural effusion. Chest 1994; 106:1209 14.
7. Vives M, Porcel JM, Vicente de Vera M, Ribelles E, Rubio M. A study of Light's criteria and possible modifications for distinguishing exudative from transudative pleural effusions. Chest 1996; 109:1503 7
8. Heffner, J. E., Sahn, S. A., & Brown, L. K. (2002). Multilevel likelihood ratios for identifying exudative pleural effusions. Chest, 121(6), 1916–1920. https://doi.org/10.1378/chest.121.6.1916
9. Quiroga, T., Costa, M., Sapunar, F. J., et al. (1989). Utilidad de la concentración de colesterol en derrames pleurales para diferenciar entre transudados y exudados. Enfermedades Respiratorias y Cirugía Torácica, 5, 128–130.
10. Wroblewski, F., & La Due, J. S. (1955). Lactate dehydrogenase activity in blood. Proceedings of the Society for Experimental Biology and Medicine, 90, 210–213. https://doi.org/10.3181/00379727-90-21844
11. Hamal, A. B., Yogi, K. N., Bam, N., Das, S. K., & Karn, R. (2013). Pleural fluid cholesterol in differentiating exudative and transudative pleural effusion. Tribhuvan University Teaching Hospital (TUTH). Retrieved from https://doi.org/10.1159/000496396
12. Deraz, E. M., Al Zohairy, Y. Z. A., Omar, F. M., & Ahmed, A. M. A. (2024). Diagnostic value of pleural fluid cholesterol to differentiate exudative and transudative pleural effusion. Al-Azhar University, Faculty of Medicine. Retrieved from [Institutional Source].
13. Lépine, P. A., Thomas, R., Nguyen, S., Lacasse, Y., Cheah, H. M., Creaney, J., Muruganandan, S., Martel, S., Lee, Y. C. G., & Delage, A. (2019). Simplified criteria using pleural fluid cholesterol and lactate dehydrogenase to distinguish between exudative and transudative pleural effusions. Respiration, 98(1), 48–54. https://doi.org/10.1159/000496396
14. Hamm, H., Brohan, U., Bohmer, R., & Missmahl, H. P. (1987). Cholesterol in pleural effusions: A diagnostic aid. Chest, 92(2), 296–302. https://doi.org/10.1378/chest.92.2.296
15. Khillar, N., George, R., Sathiqali, A. S., & Ibrahim, B. (2024). The clinical utility of pleural fluid cholesterol as a parameter in differentiating exudative from transudative pleural effusion when compared to Light's criteria. Asian Journal of Medical Sciences, 15(11), 102–107.
16. Ambresh, A., & Shilpa, A. (2021). Differentiating transudative and exudative pleural effusion by pleural fluid cholesterol. IP Indian Journal of Neurosciences, 7(1), 33–38.
17. Majmundar, A., Nouni, H. H., Mehta, V., Lakhani, S. J., Lakhani, J. D., & Darda, S. (2023). A Comparative Study Between Pleural Fluid Cholesterol and Light's Criteria in Differentiating Exudative and Transudative Pleural Effusion. Journal of Advances in Medicine and Medical Research, 35(22), 28–33.