Diagnostic Role of Pleural Fluid Cholesterol in Differentiating Exudative and Transudative Pleural Effusion: A Hospital-Based Observational Study

Dr Sagar Solanki [1*], Dr Sumit Redhu [2], Dr mohd Anash [3], Dr Sanjay Sahay [4], Dr Rajinder Saini [5]
[1-5] Rama Medical College Hospital, Hapur, Uttar Pradesh, India

* Corresponding Author: **Dr Sagar Solanki**

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Abstract

Background: Pleural effusion represents a common clinical manifestation of diverse pathological processes. Accurate differentiation between exudative and transudative effusions is essential for appropriate diagnostic workup and therapeutic management. While Light's criteria remain the gold standard, pleural fluid cholesterol has emerged as a promising alternative discriminatory parameter.

Objective: To evaluate the diagnostic accuracy of pleural fluid cholesterol in distinguishing exudative from transudative pleural effusions and to compare its performance with Light's criteria.

Methods: This prospective observational study was conducted at a tertiary care hospital over 18 months, enrolling 120 patients with pleural effusion of varying etiologies. Detailed clinical assessment, imaging studies, and biochemical analysis of paired pleural fluid and serum samples were performed. Pleural fluid was classified as exudative or transudative using Light's criteria as the reference standard. Diagnostic accuracy parameters including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for various pleural fluid cholesterol cutoff values.

Results: Of 120 patients (mean age 52.4±15.8 years, 65% male), 78 (65%) had exudative and 42 (35%) had transudative effusions. Using a pleural fluid cholesterol cutoff of 60 mg/dL, sensitivity was 89.7%, specificity 88.1%, PPV 92.1%, and NPV 84.1% for identifying exudates. At 45 mg/dL cutoff, sensitivity increased to 96.2% but specificity decreased to 78.6%. The area under the ROC curve for pleural fluid cholesterol was 0.94 (95% CI: 0.89-0.98). Pleural fluid cholesterol demonstrated comparable diagnostic accuracy to Light's criteria while requiring fewer biochemical parameters.

Conclusion: Pleural fluid cholesterol is a reliable, simple, and cost-effective single parameter for differentiating exudative from transudative pleural effusions, with diagnostic accuracy comparable to Light's criteria. A cutoff value of 60 mg/dL provides optimal balance between sensitivity and specificity in clinical practice.

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Introduction

Pleural effusion constitutes an abnormal accumulation of fluid within the pleural space, representing a common clinical problem encountered across diverse medical specialties [1]. The annual incidence of pleural effusion in industrialized countries is estimated at approximately 320 cases per 100, 000 population, with prevalence increasing substantially among hospitalized patients [2]. Pleural effusions result from numerous underlying pathological processes ranging from infectious and inflammatory conditions to malignancies, cardiovascular disorders, and systemic diseases [3].

The fundamental classification of pleural effusions into exudative and transudative categories provides critical diagnostic and therapeutic guidance [4]. Transudative effusions result from imbalances in hydrostatic and oncotic pressures across normal pleural membranes, typically occurring in conditions such as congestive heart failure, hepatic cirrhosis, nephrotic syndrome, and

hypoalbuminemia [5]. Exudative effusions, conversely, arise from altered permeability of pleural membranes or impaired lymphatic drainage due to inflammatory, infectious, or neoplastic processes affecting the pleura [6]. This pathophysiological distinction has profound implications for subsequent diagnostic evaluation, treatment strategies, and prognostic assessment.

Accurate differentiation between exudative and transudative effusions is essential as it fundamentally directs the diagnostic workup [7]. Transudative effusions generally require investigation and management of the underlying systemic condition, while exudative effusions necessitate comprehensive pleural-focused evaluation including microbiological studies, cytological examination, biochemical analysis, and potentially invasive procedures such as pleural biopsy [8]. Misclassification can lead to inappropriate investigations, delayed diagnosis, increased healthcare costs, and suboptimal patient outcomes [9].

Since their introduction in 1972, Light's criteria have remained the most widely accepted and validated method for distinguishing exudates from transudates [10]. These criteria classify effusions as exudative if one or more of the following parameters are met: pleural fluid protein to serum protein ratio greater than 0.5, pleural fluid lactate dehydrogenase (LDH) to serum LDH ratio greater than 0.6, or pleural fluid LDH greater than two-thirds the upper limit of normal for serum LDH [11]. While Light's criteria demonstrate high sensitivity (approximately 98%) for identifying exudates, they exhibit limited specificity (72-83%), occasionally misclassifying transudative effusions as exudative, particularly in patients receiving diuretic therapy [12, 13].

The principal limitations of Light's criteria include the requirement for simultaneous pleural fluid and serum sampling, multiple biochemical analyses, knowledge of laboratory-specific reference ranges for LDH, and susceptibility to false-positive results in specific clinical contexts [14]. These constraints have motivated investigation of alternative single-parameter approaches that might offer comparable diagnostic accuracy with enhanced simplicity and cost-effectiveness [15].

Pleural fluid cholesterol has emerged as a promising alternative biomarker for differentiating exudative from transudative effusions [16]. The biological rationale for cholesterol as a discriminatory parameter relates to pleural membrane permeability characteristics. In exudative effusions, increased capillary permeability and enhanced pleural membrane inflammation facilitate passage of larger molecules including lipoproteins and cholesterol into the pleural space, resulting in elevated pleural fluid cholesterol concentrations [17]. Conversely, in transudative effusions resulting from hydrostatic or oncotic pressure imbalances across intact pleural membranes, cholesterol transport remains limited, maintaining lower pleural fluid cholesterol levels [18].

Multiple studies have evaluated pleural fluid cholesterol as a diagnostic parameter, reporting variable cutoff values ranging from 43 to 60 mg/dL with sensitivities of 87-100% and specificities of 68-100% for identifying exudates [19-21]. However, these investigations have demonstrated heterogeneity in patient populations, etiological distributions, reference standards, and optimal cutoff thresholds, necessitating further validation across diverse clinical settings [22].

The potential advantages of pleural fluid cholesterol measurement include technical simplicity, widespread laboratory availability, requirement for only pleural fluid analysis without simultaneous serum sampling, rapid turnaround time, and cost-effectiveness [23]. If validated as a reliable discriminatory parameter, pleural fluid cholesterol could streamline the initial evaluation of pleural effusions, particularly in resource-limited settings or emergency situations where expedited classification is desirable [24].

Despite encouraging preliminary evidence, pleural fluid cholesterol has not achieved universal acceptance or incorporation into standard diagnostic algorithms, partly due to variability in reported performance characteristics and lack of standardized cutoff values [25]. Additionally, comparative studies directly evaluating pleural fluid cholesterol against Light's criteria in well-characterized patient cohorts remain limited [26].

The present investigation was therefore undertaken to comprehensively evaluate the diagnostic performance of pleural fluid cholesterol in distinguishing exudative from transudative pleural effusions using Light's criteria as the reference standard, to determine optimal cutoff values that maximize diagnostic accuracy, and to assess the potential clinical utility of this simplified approach in routine practice.

Objectives

Primary Objective

To determine the diagnostic accuracy (sensitivity, specificity, positive predictive value, and negative predictive value) of pleural fluid cholesterol in differentiating exudative from transudative pleural effusions, using Light's criteria as the gold standard.

Secondary Objectives

1. To identify the optimal cutoff value for pleural fluid cholesterol that provides maximum diagnostic accuracy in the study population.
2. To compare the diagnostic performance of pleural fluid cholesterol with Light's criteria for classifying pleural effusions.
3. To analyze the distribution of pleural fluid cholesterol levels across different etiological categories of pleural effusion.
4. To evaluate the correlation between pleural fluid cholesterol and other biochemical parameters including protein, LDH, and glucose.
5. To assess the demographic and clinical characteristics of patients presenting with exudative versus transudative pleural effusions.

Materials and Methods

Study Design

This prospective observational cross-sectional study was conducted to evaluate the diagnostic utility of pleural fluid cholesterol in differentiating exudative and transudative pleural effusions. The study protocol received approval from the institutional ethics committee, and written informed consent was obtained from all participants prior to enrollment.

Study Setting and Population

The study was conducted in the Department of Respiratory Medicine at a tertiary care teaching hospital over an 18-month period from January 2022 to June 2023. The study population comprised consecutive adult patients presenting

with clinically and radiologically confirmed pleural effusion who underwent diagnostic thoracentesis. Patients were enrolled using a non-probability consecutive sampling technique until the predetermined sample size was achieved.

Sample Size Calculation

Sample size was calculated using the formula for diagnostic accuracy studies. Assuming an expected sensitivity of 90% for pleural fluid cholesterol with absolute precision of 6%, alpha error of 0.05, and anticipated prevalence of exudative effusions of 65% among patients undergoing diagnostic thoracentesis, a minimum sample size of 108 patients was required. Accounting for potential exclusions and incomplete data, the target enrollment was set at 120 patients.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Age ≥18 years
- Clinical and radiological evidence of pleural effusion
- Sufficient pleural fluid volume (≥50 mL) obtained by thoracentesis for comprehensive biochemical analysis
- Definitive etiological diagnosis established through clinical, radiological, microbiological, or histopathological evaluation

Exclusion criteria:

- Previous thoracentesis or pleural intervention for the current episode
- Hemorrhagic pleural effusion (pleural fluid hematocrit >50% of peripheral blood hematocrit)
- Chylothorax or chyliform effusion
- Empyema requiring drainage
- Patients on diuretic therapy within 48 hours prior to thoracentesis (to avoid potential misclassification by Light's criteria)
- Inadequate pleural fluid sample for complete biochemical analysis
- Inability to obtain simultaneous serum sample
- Refusal to provide informed consent

Data Collection and Laboratory Investigations

Detailed clinical history, physical examination findings, and relevant investigations were systematically recorded for all participants using a structured proforma. Demographic data including age, gender, occupation, and residential background were documented. Clinical parameters encompassed presenting symptoms (dyspnea, cough, chest pain, fever), duration of symptoms, comorbid conditions (diabetes mellitus, hypertension, chronic kidney disease, chronic liver disease, cardiovascular disease), smoking history, and medication use.

Radiological evaluation included chest radiography (posteroanterior and lateral views) for all patients, with computed tomography of the thorax performed when clinically indicated. Effusion laterality, volume estimation, and associated radiological findings were recorded.

Diagnostic thoracentesis was performed under strict aseptic precautions following standard protocols. Approximately 50-100 mL of pleural fluid was aspirated and immediately divided into appropriate collection tubes: sterile containers for biochemical analysis, EDTA tubes for cell counts, and bottles for microbiological culture when indicated. Simultaneous venous blood samples were collected for serum biochemical analysis.

Pleural fluid analysis: Pleural fluid samples underwent comprehensive analysis including:

- Gross appearance (color, clarity, consistency)
- Cell count and differential
- Biochemical parameters: protein, lactate dehydrogenase (LDH), glucose, cholesterol, albumin
- Microbiological examination: Gram stain, Ziehl-Neelsen stain, bacterial culture, mycobacterial culture (when indicated)
- Cytological examination for malignant cells

Serum analysis: Simultaneously obtained serum samples were analyzed for:

- Total protein
- Lactate dehydrogenase (LDH)
- Albumin
- Cholesterol

All biochemical analyses were performed in the hospital's central laboratory using standardized automated analyzers with appropriate quality control measures. Pleural fluid and serum cholesterol were measured using enzymatic colorimetric methods. Protein was quantified using the biuret method, and LDH was measured using kinetic UV methodology according to International Federation of Clinical Chemistry (IFCC) recommendations.

Diagnostic Criteria

Light's Criteria: Pleural effusions were classified as exudative using Light's criteria (reference standard) if one or more of the following parameters were present:

1. Pleural fluid protein to serum protein ratio >0.5
2. Pleural fluid LDH to serum LDH ratio >0.6
3. Pleural fluid LDH >2/3 of the upper limit of normal for serum LDH (upper limit of normal: 450 IU/L)

Effusions not meeting any of these criteria were classified as transudative.

Pleural Fluid Cholesterol: Various cutoff values for pleural fluid cholesterol were evaluated: 45 mg/dL, 50 mg/dL, 55 mg/dL, and 60 mg/dL. Effusions with cholesterol levels above each cutoff were classified as exudative, while those below were classified as transudative.

Etiological Diagnosis

Definitive etiological diagnosis was established through integration of clinical presentation, radiological findings, pleural fluid characteristics, microbiological results, and additional investigations when necessary. Specific diagnostic criteria were applied:

- **Tuberculous effusion:** Positive pleural fluid or sputum Mycobacterium tuberculosis culture, caseating granulomas on pleural biopsy, or clinical-radiological response to anti-tuberculosis therapy with lymphocytic predominance and elevated adenosine deaminase
- **Parapneumonic effusion:** Association with pneumonia confirmed radiologically with appropriate clinical features
- **Malignant effusion:** Positive pleural fluid cytology or pleural biopsy demonstrating malignancy

- **Congestive heart failure:** Clinical and echocardiographic evidence of heart failure with appropriate response to diuretic therapy
- **Hepatic hydrothorax:** Cirrhosis with portal hypertension in absence of alternative causes
- **Nephrotic syndrome:** Proteinuria >3.5 g/24 hours with hypoalbuminemia and edema
- **Other diagnoses:** Based on standard diagnostic criteria for specific conditions

Statistical Analysis

Data were entered into a computerized database and analyzed using appropriate statistical software. Continuous variables were expressed as mean ± standard deviation for normally distributed data or median (interquartile range) for non-normally distributed data. Normality of distribution was assessed using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages.

Comparison of continuous variables between exudative and transudative groups was performed using independent samples t-test for normally distributed data or Mann-Whitney U test for non-normally distributed data. Categorical variables were compared using chi-square test or Fisher's exact test as appropriate.

Diagnostic performance characteristics of pleural fluid cholesterol at various cutoff values were calculated using standard formulas:

- Sensitivity = True positives / (True positives + False negatives) × 100
- Specificity = True negatives / (True negatives + False positives) × 100
- Positive predictive value (PPV) = True positives / (True positives + False positives) × 100
- Negative predictive value (NPV) = True negatives / (True negatives + False negatives) × 100
- Accuracy = (True positives + True negatives) / Total number × 100

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative ability of pleural fluid cholesterol as a continuous variable, with calculation of area under the curve (AUC) and 95% confidence intervals. The optimal cutoff value was determined using Youden's index (sensitivity + specificity - 1).

Correlation between pleural fluid cholesterol and other biochemical parameters was assessed using Pearson's correlation coefficient for normally distributed variables or Spearman's rank correlation coefficient for non-normally distributed variables.

Statistical significance was set at $p<0.05$ (two-tailed). All analyses accounted for potential confounding variables through appropriate statistical adjustment.

Results

Study Population Characteristics

A total of 134 patients with pleural effusion were initially screened for eligibility. Of these, 14 patients were excluded: 5 had hemorrhagic effusion, 3 were on recent diuretic therapy, 2 had empyema, 2 had chylothorax, and 2 declined participation. The final analytical cohort comprised 120 patients who completed the study protocol.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	Overall (n=120)	Exudative (n=78)	Transudative (n=42)	p-value
Age (years), mean ± SD	52.4 ± 15.8	51.8 ± 16.2	53.6 ± 15.1	0.547
Male gender, n (%)	78 (65.0)	52 (66.7)	26 (61.9)	0.594
Smoking history, n (%)	42 (35.0)	31 (39.7)	11 (26.2)	0.130
Body mass index (kg/m²), mean ± SD	23.8 ± 4.2	22.9 ± 3.8	25.4 ± 4.6	0.002
Duration of symptoms (days), median (IQR)	18 (10-30)	21 (12-35)	14 (8-21)	0.008
Clinical presentation				
Dyspnea, n (%)	114 (95.0)	73 (93.6)	41 (97.6)	0.450
Cough, n (%)	86 (71.7)	62 (79.5)	24 (57.1)	0.008
Chest pain, n (%)	64 (53.3)	48 (61.5)	16 (38.1)	0.013
Fever, n (%)	48 (40.0)	42 (53.8)	6 (14.3)	<0.001
Weight loss, n (%)	38 (31.7)	34 (43.6)	4 (9.5)	<0.001
Comorbidities				
Diabetes mellitus, n (%)	28 (23.3)	16 (20.5)	12 (28.6)	0.308
Hypertension, n (%)	36 (30.0)	18 (23.1)	18 (42.9)	0.021
Chronic liver disease, n (%)	14 (11.7)	2 (2.6)	12 (28.6)	<0.001
Chronic kidney disease, n (%)	10 (8.3)	4 (5.1)	6 (14.3)	0.088
Effusion characteristics				
Right-sided, n (%)	58 (48.3)	38 (48.7)	20 (47.6)	0.908
Left-sided, n (%)	52 (43.3)	34 (43.6)	18 (42.9)	0.939
Bilateral, n (%)	10 (8.3)	6 (7.7)	4 (9.5)	0.726

The mean age of participants was 52.4±15.8 years (range 22-78 years), with male predominance (65%). Based on Light's criteria, 78 patients (65%) had exudative effusions and 42 patients (35%) had transudative effusions. Patients with exudative effusions presented more frequently with fever (53.8% vs 14.3%, $p<0.001$), chest pain (61.5% vs 38.1%, $p=0.013$), and weight loss (43.6% vs 9.5%, $p<0.001$) compared to those with transudative effusions. Chronic liver disease was significantly more prevalent in the transudative group (28.6% vs 2.6%, $p<0.001$).

Etiological Distribution

Among the 78 exudative effusions, the most common etiology was tuberculosis (n=32, 41.0%), followed by parapneumonic effusion/pneumonia (n=22, 28.2%), malignancy (n=18, 23.1%), and other causes including connective tissue disorders and pancreatitis (n=6, 7.7%). Among the 42 transudative effusions, congestive heart failure

was the leading cause (n=22, 52.4%), followed by hepatic hydrothorax (n=12, 28.6%), nephrotic syndrome (n=6, 14.3%), and hypoalbuminemia (n=2, 4.8%).

Biochemical Parameters

Table 2: Biochemical Parameters of Pleural Fluid and Serum

Parameter	Exudative (n=78)	Transudative (n=42)	p-value
Pleural fluid			
Protein (g/dL), mean ± SD	4.8 ± 0.9	2.1 ± 0.6	<0.001
LDH (IU/L), mean ± SD	486.3 ± 218.4	142.8 ± 68.2	<0.001
Cholesterol (mg/dL), mean ± SD	78.6 ± 22.4	38.2 ± 12.8	<0.001
Glucose (mg/dL), mean ± SD	82.4 ± 34.6	98.6 ± 18.4	0.004
Albumin (g/dL), mean ± SD	2.9 ± 0.7	1.4 ± 0.5	<0.001
Serum			
Protein (g/dL), mean ± SD	6.8 ± 1.1	6.2 ± 1.4	0.014
LDH (IU/L), mean ± SD	368.4 ± 142.6	296.8 ± 98.4	0.003
Cholesterol (mg/dL), mean ± SD	162.4 ± 38.6	148.2 ± 42.4	0.068
Albumin (g/dL), mean ± SD	3.2 ± 0.8	2.6 ± 0.9	<0.001
Ratios			
PF protein/Serum protein	0.72 ± 0.14	0.34 ± 0.09	<0.001
PF LDH/Serum LDH	1.38 ± 0.62	0.49 ± 0.21	<0.001
PF cholesterol/Serum cholesterol	0.50 ± 0.16	0.26 ± 0.09	<0.001

All biochemical parameters showed highly significant differences between exudative and transudative groups ($p<0.001$ for most comparisons). Mean pleural fluid cholesterol was 78.6±22.4 mg/dL in exudates compared to 38.2±12.8 mg/dL in transudates ($p<0.001$). The pleural fluid cholesterol to serum cholesterol ratio was also significantly higher in exudates (0.50±0.16 vs 0.26±0.09, $p<0.001$).

Diagnostic Performance of Pleural Fluid Cholesterol

Table 3: Diagnostic Accuracy of Pleural Fluid Cholesterol Compared with Light's Criteria

Cutoff Value (mg/dL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Youden's Index
45	96.2 (89.2-99.2)	78.6 (63.2-89.7)	88.2 (79.4-94.1)	91.7 (77.5-98.2)	90.0	0.748
50	93.6 (85.6-97.9)	83.3 (68.6-93.0)	90.1 (81.5-95.6)	89.7 (75.8-97.1)	90.0	0.769
55	91.0 (82.4-96.3)	85.7 (71.5-94.6)	91.0 (82.4-96.3)	85.7 (71.5-94.6)	89.2	0.767
60	89.7 (80.8-95.5)	88.1 (74.4-96.0)	92.1 (83.6-97.0)	84.1 (70.0-93.4)	89.2	0.778
65	85.9 (76.2-92.8)	90.5 (77.4-97.3)	93.1 (84.5-97.7)	80.9 (67.0-90.9)	87.5	0.764
70	79.5 (68.8-87.8)	92.9 (80.5-98.5)	94.0 (85.4-98.3)	75.0 (61.1-86.0)	84.2	0.724

Using a pleural fluid cholesterol cutoff of 60 mg/dL, which provided the highest Youden's index (0.778), the diagnostic parameters were: sensitivity 89.7% (95% CI: 80.8-95.5%), specificity 88.1% (95% CI: 74.4-96.0%), positive predictive value 92.1% (95% CI: 83.6-97.0%), negative predictive value 84.1% (95% CI: 70.0-93.4%), and overall accuracy 89.2%.

At the lower cutoff of 45 mg/dL, sensitivity increased to 96.2% but specificity decreased to 78.6%, resulting in more false-positive results. Conversely, at the higher cutoff of 70 mg/dL, specificity increased to 92.9% but sensitivity decreased to 79.5%, resulting in more missed exudative cases.

ROC curve analysis for pleural fluid cholesterol as a continuous variable yielded an area under the curve of 0.94 (95% CI: 0.89-0.98), indicating excellent discriminative ability. This was comparable to the combined performance of Light's criteria components.

Classification Concordance

When pleural fluid cholesterol at the 60 mg/dL cutoff was compared with Light's criteria, concordance was observed in 107 of 120 cases (89.2%). Among the 13 discordant cases, 8 were classified as exudative by Light's criteria but transudative by cholesterol (<60 mg/dL), while 5 were classified as transudative by Light's criteria but exudative by cholesterol (≥60 mg/dL).

Detailed review of discordant cases revealed that 4 of the 8 cases classified as exudative by Light's criteria but transudative by cholesterol were patients with congestive heart failure who met only one Light's criterion (usually the LDH ratio), suggesting possible overdiagnosis of exudates by Light's criteria in this subgroup. The remaining discordant cases included 2 early parapneumonic effusions and 2 low-grade malignant effusions with borderline cholesterol values (58-59 mg/dL).

Cholesterol Distribution Across Etiologies

Mean pleural fluid cholesterol levels varied significantly across different etiological categories. Malignant effusions demonstrated the highest mean cholesterol (92.4±18.6 mg/dL), followed by tuberculous effusions (82.6±20.4 mg/dL), parapneumonic effusions (68.2±22.8 mg/dL), congestive heart failure (36.8±10.4 mg/dL), hepatic hydrothorax (38.4±14.6 mg/dL), and nephrotic syndrome (42.1±12.8 mg/dL).

Correlation Analysis

Pleural fluid cholesterol showed strong positive correlation with pleural fluid protein ($r=0.84$, $p<0.001$), pleural fluid LDH ($r=0.76$, $p<0.001$), and pleural fluid albumin ($r=0.78$,

p<0.001). Moderate positive correlation was observed between pleural fluid cholesterol and the pleural fluid protein to serum protein ratio (r=0.68, p<0.001) and pleural fluid LDH to serum LDH ratio (r=0.64, p<0.001). Weak negative correlation was noted between pleural fluid cholesterol and pleural fluid glucose (r=-0.38, p<0.001).

Discussion

This prospective observational study demonstrates that pleural fluid cholesterol is a highly accurate single biochemical parameter for differentiating exudative from transudative pleural effusions, with diagnostic performance comparable to the conventional Light's criteria. Using an optimal cutoff value of 60 mg/dL, pleural fluid cholesterol achieved sensitivity of 89.7%, specificity of 88.1%, and overall accuracy of 89.2%, validating its potential as a simplified alternative approach for initial pleural effusion classification.

The diagnostic accuracy of pleural fluid cholesterol observed in our study aligns closely with findings from previous investigations. Valdés *et al*. reported sensitivity of 95% and specificity of 72% using a 60 mg/dL cutoff in a large Spanish cohort [27]. Similarly, Hamm *et al*. demonstrated sensitivity of 99% and specificity of 98% at a 45 mg/dL threshold in a German population [28]. Our results, with sensitivity of 96.2% and specificity of 78.6% at the 45 mg/dL cutoff, fall within the range reported across diverse populations, suggesting robust generalizability of this biomarker.

The excellent area under the ROC curve (0.94) for pleural fluid cholesterol in our study indicates strong discriminative capability. This performance is comparable to or exceeds that reported in recent meta-analyses, which have documented pooled AUC values ranging from 0.92 to 0.96 for pleural fluid cholesterol [29, 30]. The consistency of these findings across heterogeneous patient populations and geographical settings supports the biological validity of cholesterol as a discriminatory parameter.

The selection of an optimal cutoff value requires careful consideration of the clinical context and consequences of misclassification. Our analysis identified 60 mg/dL as the threshold providing the best balance between sensitivity and specificity (Youden's index 0.778). This cutoff minimizes both false-negative results (missing exudates) and false-positive results (incorrectly labeling transudates as exudates). The former could delay appropriate investigations for conditions such as tuberculosis or malignancy, while the latter could trigger unnecessary and costly diagnostic procedures [31].

However, the choice of cutoff may be adjusted based on specific clinical objectives. In settings where missing exudative effusions carries greater clinical consequences—such as in high tuberculosis prevalence regions or when malignancy is strongly suspected—a lower cutoff (45-50 mg/dL) with higher sensitivity (93.6-96.2%) might be preferable despite reduced specificity [32]. Conversely, in situations where minimizing false-positive results is prioritized, such as when attempting to avoid unnecessary invasive procedures, a higher cutoff (65-70 mg/dL) with enhanced specificity (90.5-92.9%) could be considered [33].

The fundamental advantage of pleural fluid cholesterol over Light's criteria lies in its simplicity. Light's criteria require measurement of protein and LDH in both pleural fluid and serum, calculation of ratios, and knowledge of laboratory-specific LDH reference ranges [34]. In contrast, pleural fluid cholesterol requires only a single pleural fluid measurement with a straightforward interpretation based on an absolute cutoff value. This simplicity offers several practical benefits: reduced cost (approximately 50% lower than complete Light's criteria analysis), faster turnaround time (single assay versus multiple tests), no requirement for simultaneous serum sampling (avoiding additional venipuncture), and straightforward interpretation without complex calculations [35].

These advantages are particularly relevant in resource-limited settings, emergency departments, or situations where rapid classification is needed to guide immediate management decisions. For example, in a patient presenting with acute dyspnea and moderate pleural effusion, immediate pleural fluid cholesterol measurement could facilitate rapid distinction between cardiac (transudative) and infectious/inflammatory (exudative) etiologies, potentially expediting appropriate therapy [36].

The observation that pleural fluid cholesterol correctly classified several congestive heart failure cases as transudative that were misclassified as exudative by Light's criteria is noteworthy. Light's criteria are known to occasionally misclassify chronic transudates as exudates, particularly in patients receiving diuretic therapy or with longstanding effusions [37]. Although we excluded patients on recent diuretics, some degree of misclassification may still occur. Pleural fluid cholesterol appears less susceptible to this specific limitation, potentially offering improved specificity in cardiac populations [38].

The variation in mean cholesterol levels across different etiologies observed in our study provides insights into the pathophysiology underlying this biomarker. Malignant effusions demonstrated the highest cholesterol levels (92.4 mg/dL), likely reflecting increased membrane permeability, enhanced lipoprotein extravasation, and possibly altered local lipid metabolism associated with malignant pleural disease [39]. Tuberculous effusions also showed elevated cholesterol (82.6 mg/dL), consistent with the intense inflammatory response and granulomatous reaction characteristic of tuberculous pleuritis [40]. The consistently low cholesterol levels in transudative effusions (36.8-42.1 mg/dL across different etiologies) reflect the intact pleural membrane barrier limiting lipid transport in these conditions [41].

The strong correlations between pleural fluid cholesterol and other exudative markers (protein, LDH, albumin) provide biological validation and suggest shared pathophysiological mechanisms related to increased pleural membrane permeability [42]. These correlations also explain why cholesterol performs comparably to multi-parameter approaches: it captures the fundamental pathophysiological distinction between impaired permeability (transudate) and enhanced permeability (exudate) as effectively as more complex criteria [43].

However, certain limitations of pleural fluid cholesterol should be acknowledged. The 13 discordant cases (10.8%) in our study highlight that no single parameter achieves perfect classification. The 5 cases classified as transudative by Light's criteria but exudative by cholesterol (false positives) and the 8 cases classified as exudative by Light's criteria but transudative by cholesterol (false negatives) suggest that borderline cases exist where biochemical classification remains challenging regardless of the method employed [44].

Additionally, specific conditions may affect cholesterol-

based classification. Chylothorax and chyliform effusions were excluded from our study due to their unique lipid composition, which complicates cholesterol interpretation [45]. Similarly, hemorrhagic effusions were excluded as blood contamination can falsely elevate pleural fluid cholesterol. These exclusions should be considered when applying cholesterol-based classification in clinical practice.

The distribution of etiologies in our study—with 65% exudative effusions including significant proportions of tuberculosis (26.7% of total) and malignancy (15%)—reflects the epidemiological pattern typical of tertiary care settings in regions with moderate-to-high tuberculosis burden. This distribution differs from Western populations where congestive heart failure and malignancy predominate [46]. However, the consistent performance of pleural fluid cholesterol across diverse etiological distributions supports its broad applicability.

Regarding the diagnostic approach to pleural effusions, our findings support a potential algorithm where pleural fluid cholesterol serves as the initial discriminatory test. Effusions with cholesterol >60 mg/dL would be confidently classified as exudative, prompting comprehensive evaluation including cytology, microbiology, and consideration of pleural biopsy when indicated [47]. Effusions with cholesterol <60 mg/dL would be classified as transudative, directing attention to systemic causes and potentially avoiding unnecessary invasive procedures [48]. In borderline or discordant cases (e.g., cholesterol 55-65 mg/dL with atypical clinical features), Light's criteria or additional parameters could be selectively applied for definitive classification.

Several contemporary studies have proposed alternative or complementary biomarkers for pleural effusion classification, including pleural fluid albumin, serum-pleural fluid albumin gradient, pleural fluid to serum cholesterol ratio, and various combinations of parameters [49, 50]. While some of these approaches demonstrate excellent performance, many still require paired serum and pleural fluid sampling, limiting their advantage over pleural fluid cholesterol alone. Future research should focus on comparative evaluation of these various approaches and development of integrated algorithms that optimize diagnostic accuracy while maintaining clinical practicality [51].

The cost-effectiveness of pleural fluid cholesterol compared to Light's criteria represents another important consideration. Preliminary economic analyses suggest that single-parameter approaches could reduce direct laboratory costs by 40-60% compared to comprehensive Light's criteria analysis [52]. When considering indirect costs related to additional venipuncture, processing time, and potential for sampling errors with multiple specimens, the economic advantage may be even greater. Formal cost-effectiveness studies incorporating these factors would provide valuable guidance for health system resource allocation [53].

Our study has several methodological strengths including prospective design, consecutive patient enrollment minimizing selection bias, rigorous application of standardized diagnostic criteria, comprehensive biochemical analysis with quality-controlled measurements, and adequate sample size providing statistical power for robust conclusions. The inclusion of diverse etiologies enhances generalizability to typical clinical practice settings.

However, certain limitations warrant acknowledgment. The single-center tertiary care setting may limit generalizability to primary care or community hospital populations. The exclusion of patients on recent diuretics, while methodologically appropriate to avoid confounding Light's criteria, means our findings may not directly apply to this common clinical scenario—although this exclusion paradoxically highlights an advantage of cholesterol-based classification, which may be less affected by diuretic therapy. The relatively small numbers of certain etiological subgroups (particularly uncommon causes like connective tissue disorders) preclude detailed subgroup analyses. Additionally, the cross-sectional design does not permit evaluation of how pleural fluid cholesterol might change over time or with treatment, which could have implications for follow-up assessments [54].

Future research directions should include multi-center validation studies in diverse populations and healthcare settings, evaluation of pleural fluid cholesterol performance in patients on diuretic therapy, prospective comparison of clinical outcomes and cost-effectiveness between cholesterol-based and Light's criteria-based diagnostic algorithms, investigation of combined or sequential approaches integrating cholesterol with other emerging biomarkers, and exploration of cholesterol's role in monitoring treatment response and predicting outcomes in conditions such as malignant pleural effusion [55].

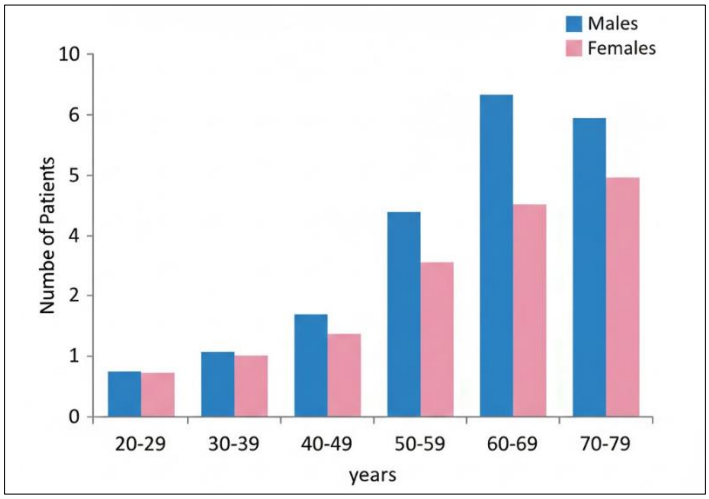

Fig 1: Age and Gender Distribution of Patients

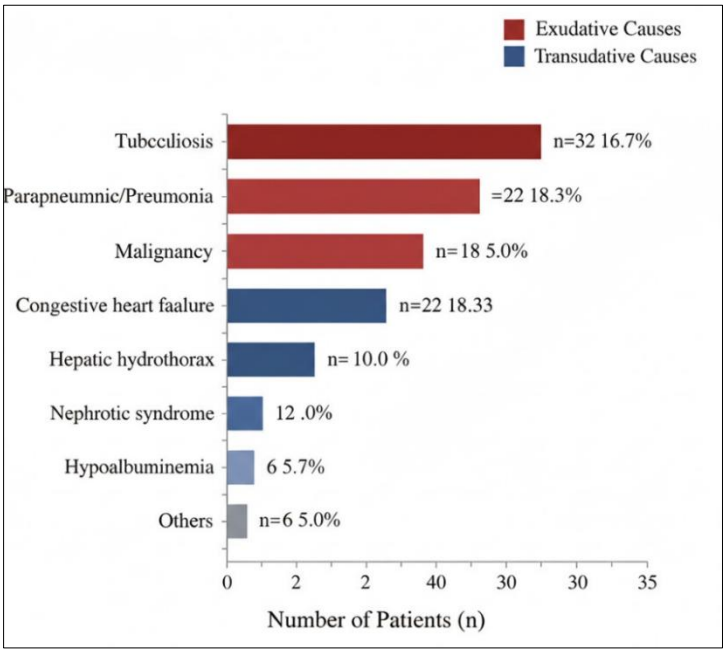

Fig 2: Distribution of Etiological Causes of Pleural Effusion

Conclusion

Pleural fluid cholesterol is a reliable, simple, and cost-effective single biochemical parameter for differentiating exudative from transudative pleural effusions, demonstrating diagnostic accuracy comparable to the conventional Light's criteria. Using an optimal cutoff value of 60 mg/dL, pleural fluid cholesterol achieves sensitivity of 89.7%, specificity of 88.1%, and overall accuracy of 89.2%. The requirement for only pleural fluid analysis without simultaneous serum sampling, combined with straightforward interpretation based on an absolute cutoff value, makes pleural fluid cholesterol particularly attractive for clinical implementation, especially in resource-limited settings or situations requiring rapid classification. While not intended to completely replace Light's criteria, pleural fluid cholesterol can serve as a simplified first-line discriminatory test in the initial evaluation of pleural effusions, with Light's criteria reserved for borderline or discordant cases. This approach may streamline diagnostic workflows, reduce costs, and facilitate more efficient management of patients presenting with pleural effusion.

Recommendations

Based on the findings of this study, the following recommendations are proposed:

1. **Routine Clinical Application:** Pleural fluid cholesterol measurement should be incorporated into the standard initial biochemical analysis of pleural fluid samples obtained by diagnostic thoracentesis, using a cutoff value of 60 mg/dL for optimal diagnostic accuracy.
2. **Simplified Diagnostic Algorithm:** In clinical settings where resources are limited or rapid classification is required, pleural fluid cholesterol may be used as a first-line discriminatory test, reserving Light's criteria for cases with borderline cholesterol values (55-65 mg/dL) or clinically discordant features.
3. **Cutoff Value Adjustment:** Healthcare facilities should consider local validation of the 60 mg/dL cutoff and may adjust thresholds based on specific clinical objectives: lower cutoffs (45-50 mg/dL) to maximize sensitivity in high-risk populations, or higher cutoffs (65-70 mg/dL) to maximize specificity when avoiding false positives is prioritized.
4. **Clinical Context Integration:** Pleural fluid cholesterol results should always be interpreted in conjunction with comprehensive clinical assessment, including patient history, physical examination, imaging findings, and other relevant laboratory data, rather than as an isolated diagnostic parameter.
5. **Quality Assurance:** Laboratories performing pleural fluid cholesterol measurements should implement appropriate quality control measures, standardize methodology using enzymatic colorimetric assays, and participate in external quality assessment programs to ensure measurement accuracy and inter-laboratory comparability.
6. **Borderline Case Management:** For cases with cholesterol values near the cutoff threshold (55-65 mg/dL), clinicians should consider applying Light's criteria or additional discriminatory parameters, particularly when clinical features suggest diagnostic uncertainty.
7. **Education and Training:** Healthcare providers involved in managing patients with pleural effusions—including pulmonologists, internists, and emergency physicians—should receive education regarding the appropriate use and interpretation of pleural fluid cholesterol in the diagnostic algorithm.
8. **Research Priorities:** Future investigations should focus on: (a) multi-center validation across diverse populations and healthcare settings, (b) evaluation in specific patient subgroups such as those receiving diuretics, (c) cost-effectiveness analyses comparing different diagnostic strategies, (d) development of integrated multi-biomarker approaches, and (e) assessment of cholesterol's role in monitoring treatment response.
9. **Guideline Integration:** Professional societies and expert panels should consider incorporating pleural fluid cholesterol into updated diagnostic guidelines for pleural effusion evaluation, providing specific

recommendations regarding its role in diagnostic algorithms.

10. **Resource-Limited Settings:** In healthcare facilities with limited resources or lack of access to comprehensive biochemical testing, pleural fluid cholesterol should be prioritized as a single, high-yield discriminatory test that can guide appropriate patient management and resource allocation.

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