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Diagnostic Accuracy of Pleural Fluid Cholesterol in Differentiating Between Exudative and Transudative Pleural Effusion in Pediatric Patients: A Simple Alternative to Conventional Criteria

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ABSTRACT

BACKGROUND & OBJECTIVE: Differentiation of exudative from transudative pleural effusions is crucial in determining the etiology and guiding appropriate management in pediatric patients. This study aims to determine diagnostic accuracy of pleural fluid cholesterol in differentiating exudative from transudative pleural effusion in pediatric patients.

METHODOLOGY: This cross-sectional study was conducted in the Pathology and Pediatric Medicine Department of Children Hospital and Institute of Child Health, Multan from July 2025 to January 2026. Patients aged 1-14 years with definite clinical and radiological evidence of pleural effusion were included in the study. Effusions were classified according to Light's criteria which served as gold standard. Pleural fluid cholesterol 45mg/dl was used as cut off to identify exudative pleural effusion. The diagnostic performance of pleural fluid cholesterol was analyzed using sensitivity, specificity, positive and negative predictive values, likelihood ratios, and overall accuracy.

RESULTS: Among 97 patients there were 58 (59.8%) males and 39 (40.2%) females. Median pleural fluid cholesterol was significantly higher in exudative effusions 71(63-83.5) as compared to transudative effusions 34(22.75-38) p < 0.0001. Pleural fluid cholesterol was found to have sensitivity of 95.1% and specificity of 88.9% in differentiating exudative from transudative pleural effusion with overall diagnostic accuracy of 92.8%.

CONCLUSION: Pleural fluid cholesterol is a simple, cost-effective, and reliable biomarker for differentiating exudative from transudative pleural effusions in children and it correlates well with Light's criteria.

KEY WORDS: Cholesterol, Exudates, Lactate dehydrogenase, Pleural effusion, Transudates

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INTRODUCTION

Pleural effusion (PE) is defined as the collection of excessive fluid in the pleural space, resulting from either overproduction of fluid or disruption of normal lymphatic drainage.[1] Pleural effusions are primarily categorized into exudates and transudates. Transudative effusions are caused by underlying systemic conditions resulting in altered hydrostatic or oncotic pressure, while exudative effusions are generally caused by inflammatory response in the body involving pleura. Pneumonia, tuberculosis, congestive cardiac failure and pulmonary embolism are among frequently reported etiologies of pleural effusion,[2] together accounting for nearly 75% of the cases.[3]

Pleural effusion is detected in roughly 1.5 million individuals annually across the United States. In contrast developing countries experience a substantially higher burden, primarily attributed to higher incidence of tuberculosis and inadequately treated infections.[3] Tuberculous pleural effusion (TPE) is among the most frequent manifestations of extrapulmonary tuberculosis in adults, continuing to pose a significant diagnostic challenge in endemic settings.[4] Establishing a definite diagnosis is often problematic, as conventional reference methods such as Ziehl–Neelsen (ZN) staining, pleural fluid (PF) culture for *Mycobacterium tuberculosis* (MTB), and pleural biopsy are invasive, time consuming and have limited diagnostic sensitivity.[5] Parapneumonic pleural effusion (PPE) is one of the frequent complications related to bacterial pneumonia, occurring in nearly 18% of patients diagnosed with community-acquired pneumonia (CAP).[6] While clinical assessment and routine analysis of pleural fluid are often sufficient to determine underlying cause, up to one-third of cases involve multiple co-existing etiologies, making accurate bedside diagnosis more complex and challenging for clinicians.[7]

Light's criteria remain traditional and extensively used diagnostic tool for distinguishing exudative and transudative pleural effusions. Light's criteria states that pleural fluid is exudative if any of the following criteria are met

1. Pleural fluid protein/serum protein ratio > 0.5

2. Pleural fluid LDH/serum LDH ratio > 0.6

3. Pleural fluid LDH > 2/3 of upper limit of normal serum LDH.

Although Light's criteria demonstrate high sensitivity and specificity however certain limitations persist. Despite thorough diagnostic evaluation, the etiology remains unclear in approximately 10–20% of

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cases,[8] with greater uncertainty observed in patients with PF protein levels between 2.5 and 3.5 g/dL.[9] Accurate identification of the underlying cause is essential for appropriate management of pleural effusion, highlighting the importance of timely and precise diagnosis.

Therefore, a comprehensive and structured diagnostic approach integrating clinical evaluation, imaging studies, detailed analysis of pleural fluid is pivotal for optimal patient management.[10] Given the limitations of Light's criteria several alternative diagnostic methods have been proposed. One such approach involves the combined assessment of PF cholesterol, PF protein, and PF lactate dehydrogenase (PF-LDH) to enhance diagnostic accuracy.[11] In addition, PF cholesterol has been suggested as a single marker for efficiently differentiating pleural effusions, with evidence suggesting lower misclassification rates than the individual components of Light's criteria.[12] Notably, when a cutoff value of 1.16(45mg/dL) mmol/L is used, PF cholesterol has demonstrated 98.18% sensitivity with 95.65% specificity for identifying exudative effusions.[13]

In Pakistan, particularly in South Punjab, common causes of pediatric pleural effusion include parapneumonic infections and tuberculosis, yet local evidence evaluating pleural fluid biochemical markers in children is limited, particularly data regarding diagnostic value of PF cholesterol in children is inadequate. Present study was conducted to assess role of PF cholesterol as single, cost-effective biomarker for differentiating PE as exudates and transudates in pediatric population for low-resource healthcare settings and to reduce mis-classifications caused by Light's criteria.

METHODOLOGY

This cross-sectional study was conducted in the Pathology department and Pediatric Medicine department, Children Hospital and Institute of Child Health, Multan from July 2025 to January 2026. Ethical approval was obtained from Institutional Ethical Review Committee (1504). Children aged 1–14 years with definite clinical and radiological findings consistent with pleural effusion and undergoing diagnostic thoracocentesis were included in the study using non-probability consecutive sampling technique. Informed consent was obtained from patient's parents/guardians. Patients with bleeding disorders, hemothorax, and not giving consent were excluded. By using sample-size.net calculator taking an expected sensitivity of 80% and specificity of 93%,[14] with a 95% confidence level and a precision of 10%, sample size of 95 patients was calculated.

Pleural fluid samples were collected at the time of thoracocentesis in sterile syringes and were subjected to gross examination (volume, turbidity, and presence of coagulum) and biochemical analysis including pleural fluid cholesterol, protein and LDH. 2 ml Venous blood specimen was also taken for serum protein and LDH. Biochemical tests were performed on Selectra Mach-5 fully automated chemistry analyzer. Cholesterol was performed using enzymatic cholesterol oxidase peroxidase method, protein using Biuret method and for LDH IFCC enzymatic method was used. Normal and pathological controls were successfully run for all analytes before performing patient samples. Patient's age, gender, causes of pleural effusion, appearance of pleural fluid, chemical analysis of fluid, serum protein and LDH were recorded on a predesigned proforma. Pleural effusion was categorized into exudate or transudate as per Light's criteria. Cut off value of 45mg/dl for PF-cholesterol was used to identify exudative pleural effusion.[13]

Results were entered and analyzed using SPSS 22. Data distribution was checked by Shapiro wilk test. As data showed skewed distribution quantitative variables were presented as median and Interquartile ranges, while qualitative variables were presented as frequency and percentage. Independent sample Mann whitney test was used for comparison of analytes (pleural fluid protein, cholesterol and LDH) between transudative and exudative effusions. A p-value <0.05 was considered statistically significant. No formal adjustment for confounders or effect modifiers was performed because the primary objective was to evaluate the diagnostic accuracy of pleural fluid cholesterol. 2x2 Table was drawn taking Light's criteria as established diagnostic standard for exudative PE identification. Diagnostic accuracy of pleural fluid cholesterol was evaluated by calculating sensitivity [TP/(TP+FN) x100], specificity [TN/(TN+FP) x100], positive predictive value (PPV) [TP/(TP+FP) x100], negative predictive value (NPV) [TN/(TN+FN) x100], Positive and negative likelihood ratios (LR) [Positive LR = Sensitivity / (1 − Specificity)], [Negative LR = (1 − Sensitivity) / Specificity], and accuracy [(TP+TN)/(TP+TN+FP+FN)x100] with 95% confidence intervals (CI).

RESULTS

This study included 58 (59.8%) boys and 39 (40.2%) girls among a total of 97 patients. Turbidity of pleural fluid was observed in 70 cases (72.2%) and coagulum in 43 samples (44.3%). Based on

Light's criteria there were 61 (62.9%) patients with exudative and 36 (37.1%) with transudative pleural effusion. Overall median age of patients was 7(4-10) years while median pleura fluid protein, cholesterol and LDH were 3.3(2.45-4.70) g/dL, 63(36-75) mg/dL, 354(75-5874) U/L respectively. Parapneumonic effusion was identified as the predominant cause of PE in our study (Figure 1). There was statistically significant difference of median PF cholesterol in exudative and transudative effusion (p = 0.000). PF cholesterol difference between transudates and exudates was comparable to traditional biochemical markers (Table I). Table II shows the 2×2 comparison between Light's criteria and PF cholesterol classification. PF cholesterol demonstrated high diagnostic performance in distinguishing PE as exudates and transudates with sensitivity of 95.1% and specificity 88.9% (Table III). The high sensitivity and low negative likelihood ratio suggest

that PF cholesterol is particularly useful to rule out exudative pleural effusion

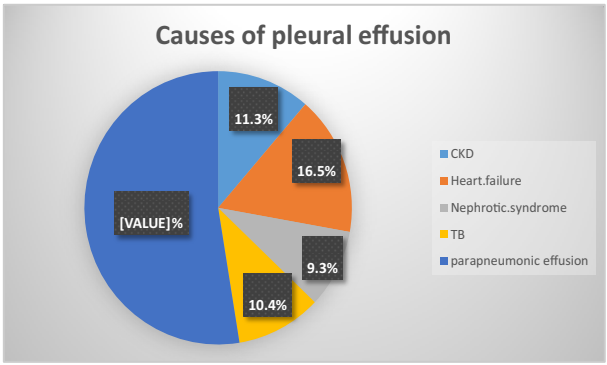

Figure 1: Distribution of underlying causes of pleural effusion in pediatric patients (n=97)

DISCUSSION

Our study reports that PF cholesterol is significantly higher in exudative PE. This high pleural fluid cholesterol is associated with the underlying pathophysiology of pleural inflammation, where cellular breakdown and lysis of erythrocytes and leukocytes within the pleural cavity contributes to increased pleural fluid cholesterol levels.[14] An additional mechanism contributing to the rise in pleural fluid cholesterol involves its transfer from plasma lipoproteins. In exudative effusions, enhanced capillary permeability of pleura facilitates the leakage of these cholesterol particles into the pleural space.[14] In addition, pleural mesothelial cells can synthesize cholesterol to fulfill local metabolic requirements. Notably, increased pleural fluid cholesterol levels seen in exudative effusions are largely independent of corresponding serum cholesterol concentrations, further supporting its significance as locally derived diagnostic marker.[15]

Table I: Comparison of median Pleural fluid cholesterol, protein & LDH in transudative and exudative pleural effusion (n=97)

Analyte	Transudate	Exudate	p
Pleural Fluid cholesterol (mg/dl)	34(22.75-38)	71(63-83.5)	0.000
Pleural Fluid protein(g/dL)	1.9(1.12-2.6)	4.4(3.3-5.1)	0.000
Pleural Fluid LDH(U/L)	76(71.5-1400.75)	1376(124-8000)	0.000

Table II: 2x2 contingency table comparing pleural fluid cholesterol classification with Light's criteria

		Light's criteria		
		Exudate	**Transudate**	**Total**
Pleural fluid cholesterol	Exudate	58	4	62
	Transudate	3	32	35
	Total	61	36	97

Table III: Diagnostic accuracy measures of pleural fluid cholesterol for differentiating exudative from transudative pleural effusions (n=97)

Statistics	**Value**	**95% CI**
Sensitivity	95.10%	89.6%-100%
Specificity	88.90%	78.6%-99.1%
PPV	93.50%	87.5%-99.7%
NPV	91.40%	82.1%-100%
Positive likelihood ratio	8.6	3.39-21.6
Negative likelihood ratio	0.06	0.02-0.17
Accuracy	92.80%	87.6%-97.9%

In our study PF cholesterol demonstrated high sensitivity and specificity. These diagnostic accuracy parameters indicate that PF cholesterol is highly effective in correctly identifying exudative effusions. The high negative predictive value (91.4%) observed in our study suggests that low pleural fluid cholesterol levels can reliably exclude an exudative effusion. This characteristic is particularly useful in pediatric practice, where minimizing invasive investigations and repeated procedures is a key clinical priority. Pleural fluid cholesterol was in accordance with Light's criteria as only a small proportion of cases were misclassified. This finding indicates that PF cholesterol performs comparable to Light's criteria in clinical practice. Positive likelihood ratio of 8.6 observed in this study suggests that children with elevated pleural fluid cholesterol are significantly more likely to have exudative pleural effusions. Conversely, the low negative likelihood ratio of 0.06 reinforces the utility of this biomarker in effectively ruling out exudative effusions. The overall diagnostic accuracy of 92.8% further supports the reliability of PF cholesterol as a robust biomarker in pediatric PE.

Our study also revealed that parapneumonic effusion is the leading cause of PE in pediatric patients, which is consistent with previous studies conducted in Karachi and Peshawar, Pakistan that also identified parapneumonic effusion as predominant cause of pleural effusion in pediatric population.[16,17]

Study from Peshawar found that mean PF cholesterol was significantly higher in exudates (2.0 ± 0.93 mmol/L) as compared to transudative effusions (1.04 ± 2.32 mmol/L) with p = 0.01. These researchers reported that PF cholesterol cutoff above 1.2 mmol/L provided 82% diagnostic accuracy, with 80% sensitivity and 93% specificity.[14] Likewise, a study conducted in India[18] demonstrated that PF cholesterol was significantly elevated in exudative effusions as compared to transudative effusions (p = 0.009). We also found that PF cholesterol was significantly higher in exudative effusions

(p = 0.000). An Indian study reported 86% sensitivity, 55% specificity, and 81% diagnostic accuracy of PF cholesterol when evaluated against Light's criteria.[19] Subedi and colleagues observed that PF cholesterol, when used independently, achieved 93.5% sensitivity, 100% specificity, PPV 100%, and NPV 87.5%, making it most reliable and specific parameter when compared to Light's criteria.[20] Rufino et al. observed 97.22% sensitivity, 85.71% specificity, 98.59% PPV and 75% NPV for PF cholesterol.[21] Likewise, Hamal et al. documented 97.7% sensitivity and 100% specificity for PF cholesterol in distinguishing exudative and transudative PE.[22] The observed variability among studies can be attributed to variations in cholesterol cutoff values, study design, population characteristics, disease prevalence and healthcare settings.

In context of tuberculous pleural effusion, Goyal and colleagues demonstrated that PF cholesterol is a highly effective diagnostic tool and may even outperform PF adenosine deaminase (ADA) in regions with a high prevalence of tuberculosis. Their study demonstrated 95.9% sensitivity and 100% specificity, and they recommended a cutoff of 50 mg/dL for pleural fluid cholesterol in diagnosing tuberculous pleural effusion.[23]

Notably, PF cholesterol provides several practical benefits in pediatric patients. It relies on a single pleural fluid sample and avoids the need for simultaneous blood collection, thereby minimizing discomfort, simplifying the procedure, and lowering overall healthcare costs. These advantages make it a valuable diagnostic biomarker, especially in resource-limited healthcare settings.

CONCLUSION

Pleural fluid cholesterol may serve as a useful biochemical marker for differentiating exudative from transudative pleural effusions in children. This is particularly advantageous in pediatric practice, where prompt decisions and minimally invasive approaches are essential.

This study focuses on pediatric patients, a population in which evidence regarding pleural fluid cholesterol remains limited. The study evaluated pleural fluid cholesterol against the established Light's criteria, allowing direct assessment of its diagnostic utility. It provides locally relevant data from a tertiary care pediatric setting and contributes to the limited literature on alternative biochemical markers for pleural effusion classification.

Limitation:

Single center study and small sample size may limit the generalizability of the findings. Large multicenter pediatric studies are required to validate these findings and establish standardized, age specific cutoff values.

Ethical approval:

Ethical approval was taken from institutional review board of The Children's Hospital and The Institute of Child Health, Multan with the IRB number 1504, Dated 28-07-2025.

Conflict of Interest:

Authors declare no conflict of interest.

Financial Disclosure:

None

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Authors' Contributions:

MS & AF: Conceptualization and study design

MSN, ZR & SR: Data Collection and manuscript drafting.

MSN, SL & MS: Data Analysis and critical review.

AF, ZR & SR: Supervision & Manuscript drafting & proof reading.

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