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Diagnostic Accuracy of Pleural Fluid Cholesterol Levels in Differentiating Between Exudative and Transudative Pleural Effusions

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ABSTRACT

Objective: To determine the utility of pleural fluid cholesterol levels in differentiating between exudative and transudative pleural effusions.

Study Design: Cross-sectional analytical study.

Place and Duration of Study: Department of Pulmonology, Combined Military Hospital, Peshawar Pakistan, from Sep to Dec 2021.

Methodology: All patients aged less than 18 years, with pleural effusion confirmed on chest ultrasound, were included in our study. Patients with International Normalized Ratio >1.5, patients who were already under treatment for pleural effusion, patients on diuretics for more than 48 hours and patients not willing to participate in the study, were excluded. Light's Criteria was used to label effusions as either exudates or transudates. Pleural fluid cholesterol ≥1.2mmol/L was considered as exudate.

Results: Our study included a total of 78 patients, aged 52±21.27 years. Majority 63(80.7%) were males and most 51(65.4%) patients had exudative pleural effusion, while 27(34.6%) had transudative pleural effusion, as per Light's Criteria. Out of 51 patients with exudative pleural effusion by Light's Criteria, 41 had exudative pleural effusion on the basis of fluid cholesterol levels where mean pleural fluid cholesterol levels were 2.0±0.93 mmol/L and 1.04±2.32 mmol/L in exudative and transudative pleural effusions, respectively (p=0.01). Pleural fluid cholesterol levels of more than 1.2mmol/L had a diagnostic accuracy of 82%, sensitivity of 80% and specificity of 93% while the Positive Predictive Value was 95% and the Negative Predictive Value was 71%.

Conclusion: Pleural fluid cholesterol levels of more than 1.2mmol/L can reliably differentiate between exudative and transudative pleural effusions.

Keywords: Exudative Pleural Effusion, Light's Criteria, Pleural Fluid Cholesterol.

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INTRODUCTION

Pleural fluid is physiologically present in a small amount in the pleural cavity for mechanical lubrication[1] and any abnormal accumulation of fluid in the pleural cavity is labelled a Pleural Effusion (PE), which has a 1-year mortality reaching up to 57% in patients with heart failure.[2] PE can be categorized as transudative, which is secondary to systemic failure, or exudative, which is secondary to an inflammatory response in the body. The common causes of PE have been reported in literature as being heart failure, pneumonia, and pulmonary embolism.[3] A definite diagnosis often requires a more invasive approach rather than a simple thoracentesis, such as, histopathological examination of pleural tissue by doing a thoracoscopy. Fortunately, the cause of most pleural effusions is generally evident clinically or can be made by a simple fluid analysis, however, almost one-third of patients can have more than one underlying cause, which can be challenging for physicians on the bedside.[4] Light's Criteria has generally been the most reliable method to differentiate transudative (tPE) and exudative pleural effusions (ePE), with sensitivity and specificity of 97.5% and 80% respectively.[5] However, Light's Criteria also misclassifies 25% of transudates as exudates.[6] In literature, multiple markers have been studied in pleural fluid to assess diagnostic values.[7-10] Pleural fluid cholesterol (pCh) is a cost-effective and easily studied marker[6,11-13] with 98.18% sensitivity and 95.65% specificity in diagnosing exudates with a cutoff at 1.16mmol/L.[6] We searched keywords with 'pleural

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fluid cholesterol' on Pakmedinet and could not find any study from Pakistan on pCh for exudates, thus, we aimed to assess the diagnostic accuracy of pCh in different causes of pleural effusion as a cost-effective diagnostic marker with no extra intervention.

METHODOLOGY

This was a cross-sectional analytical study, conducted at the Department of Pulmonology, Combined Military Hospital (CMH), Peshawar Pakistan, from September to December 2021. Ethical approval was taken from the hospital Ethical Review Committee via letter no. 40/21.

Inclusion Criteria: All patients, in whom pleural effusion was confirmed on chest ultrasound and who were more than 18 years of age, were included in the study.

Exclusion Criteria: Patients with INR>1.5, patients who were already under treatment for pleural effusion, who were on diuretics for more than 48 hours and who were unwilling to participate in the study were excluded.

Sample size was calculated using Epitools sample size calculator. Patients satisfying the above-mentioned criteria were selected using non-probability convenience sampling. The mean value of pleural fluid cholesterol in exudates and transudates was taken from the study published by Hamal *et al*.[12] We set the confidence interval at 95%, power at 80% and ratio of sample size 1:1 in both groups using two-tailed test. Ultrasound-guided pleural fluid samples of 15-50ml were taken and Heparinized syringes were used to collect fluid for pH measurement. All samples were analyzed for cholesterol, protein, and lactate dehydrogenase (LDH) in Department of Pathology, CMH Peshawar, along with blood samples, to measure LDH and protein levels. LDH was measured by ultraviolet spectrophotometry with 340nm wavelength while protein was measured by Biuret Complex method and cholesterol with CHOD PAP (cholesterol oxidase peroxidase). Pleural effusions were classified as either transudate or exudate on the basis of Light's Criteria. pCh cut-off value was set at ≥1.2mmol/L for exudates. Statistical package for the Social Sciences (SPSS), version 25.0, was used for analysis. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of pCh to diagnose exudative pleural effusion was determined and an independent samples t-test was used for comparative means where a *p*-value ≤0.05 was considered significant.

RESULTS

A total of 78 patients were included in our study, among which, males were 63(80.7%) while females were 15(19.3%). The mean age was found to be 52±21.27 years. Tuberculous pleuritis was the most common cause of exudative PE 25(49%) followed by parapneumonic effusions 9(17.6%) and malignant pleural effusion 8(15.6%), as illustrated in Fig-1. There were 51 patients with exudates and 27 with transudates, according to Light's Criteria, among which mean cholesterol was 2.0±0.93 mmol/L and 1.04±2.32 mmol/L respectively with the difference between the two being significant (p=0.01), as shown in Table-I. Out of 51 patients with exudative pleural effusion as per Light's Criteria, 41(80.4%) had exudative pleural effusion on the basis of fluid cholesterol levels, while, out of 27 patients with transudative pleural effusion as per Light's Criteria, 25(92.6%) had transudative pleural effusion on the basis of fluid cholesterol levels. Different measures of diagnostic accuracy thus obtained for pleural fluid cholesterol levels ≥1.2mmol/L are shown in Table-II.

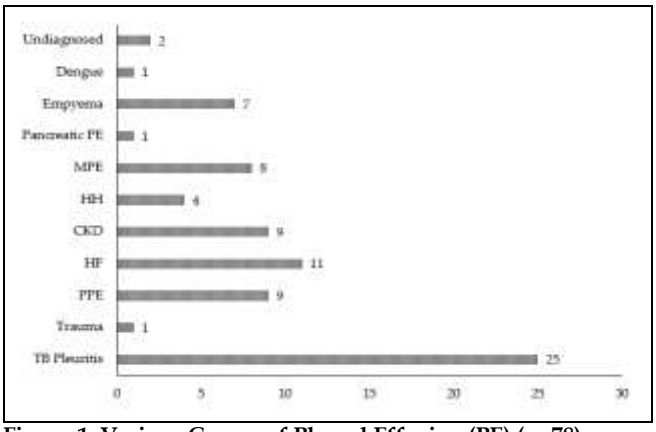

Figure-1: Various Causes of Pleural Effusion (PE) (n=78)

Table-I: Mean Pleural Fluid Cholesterol Values in Exudates and Transudates (n=78)

	Exudates	Transudates	*p*-value (≤0.05)
pCh mmol/L (mean±SD)	2.0±0.93	1.04±2.32	0.01

Table-II: 2x2 Table for Light's and pCh Criteria (n=78)

		Light's Criteria	
		Exudates	Transudates
pCh Criteria	Exudates	41	2
	Transudates	10	25

Table-III: Diagnostic Accuracy Measures for Pleural Fluid Cholesterol Levels (n=78)

Statistic	Value	95% CI
Sensitivity	80.39%	66.68% - 90.18%
Specificity	92.59%	75.71% - 99.09%
Positive likelihood ratio	10.85	2.84 - 41.47
Negative likelihood ratio	0.21	0.12 - 0.37
Disease prevalence	65.38%	53.76% - 75.80
Positive predictive value	95.35%	84.29% - 98.74%
Negative predictive value	71.43%	58.67% - 81.49%
Accuracy	84.62%	74.67 - 91.79

MPE=Malignant Pleural Effusion, HH= Hepatic Hydrothorax, CKD=Chronic Kidney Disease, HF= Heart Failure, PPE= Parapneumonic Pleural Effusion.

DISCUSSION

One study reported 99% sensitivity of pCh >1.21 mmol/L in cases of malignant pleural effusions[14] with the possible mechanism involved to be secondary to destruction of red and white blood cells in pleural effusion and increased pleural capillary permeability, leading to raised pCh levels.[15,16] The findings of our study indicate that pCh can be used confidently to differentiate among both types of effusions. In our study, tuberculous pleuritis was the most common etiology of ePE, followed by parapneumonic effusion and malignant pleural effusion, respectively. The mean cholesterol in ePE in our study was 2.0±0.93 while another study, observed mean cholesterol levels of 1.92±0.75mmol/L in exudative pleural effusions,[12] similar to another author,[11] with our findings being consistent with both, further confirming the diagnostic accuracy of pCh in ePE. Highest sensitivity and specificity were achieved when pCh cutoff value was set at 1.2mmol/L in our study. A bivariate metanalysis of 20 studies reported 88% sensitivity and 96% specificity of pCh in the diagnosis of ePE[17] with another author also reporting 99% sensitivity with the same cutoff levels of pCh in malignant pleural effusions, with 69.4% specificity[14] while other authors found sensitivity of 97.7% and specificity of 100% in their results.[12] In a similar study, 98.18% and 95.65% sensitivity and specificity, respectively, were reported.[6] While these findings are higher than our results, which were 80% and 93%, respectively, however, specificity in our study was comparable to the results published by another author with 94.44% results.[18] The possible reason for lower diagnostic values in our results may be due to total reliance on Light's Criteria in diagnosing ePE in our study. Despite these higher values, pCh criterion had 6 false-positive exudates in our results and this finding was also observed in other studies having small sample size.[12,19] Authors from other studies have reported wrong categorization of few transudates by Light's Criteria, which explains the presence of false exudates and lower sensitivity in our results.[11] Diagnostic accuracy of pCh for exudates was 84.62% in our analysis which was lower than previously published (90.83% and 98.3%).[20,21] Positive Predictive Value (PPV) in our study was 95% which was comparable to the PPV reported by other authors of 97.67% and 100%, However, the Negative Predictive Value (NPV) of our study was quite low at 71.43%, compared to 95%, 93.3% and 100% respectively in literature.[18,12,21] Thus, pCh is an easy to determine marker with higher reported specificity to diagnose ePE. With all of these diagnostic values, pCh levels can be used in diagnosing ePE as a reliable marker.

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LIMITATIONS OF STUDY

A notable limitation of our study was its small sample size which limits its generalizability to the rest of the population of Pakistan, along with another limitation which was that pCh is not useful in further differentiating exudates into two major causes of ePE, these being tuberculous, and malignant PE.

CONCLUSION

Pleural fluid cholesterol levels of more than 1.2mmol/L can reliably differentiate between exudative and transudative pleural effusions.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

NS & MA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

ARA & SG: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

JW & ZA: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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