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Original Article

Biochemistry Section

Diagnostic Accuracy of Light's Criteria, Alkaline Phosphatase, Total Cholesterol, and D-dimer in Differentiating Transudative and Exudative Pleural Effusion: A Cross-sectional Study

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ABSTRACT

Introduction: Pleural Effusion (PE) results from an imbalance between pleural fluid production and absorption. It may occur due to multiple aetiologies, including heart failure, infections, malignancies, and liver disease. While Light's criteria remain the gold standard for classification, they misclassify up to 25% of transudates. Additional biochemical markers such as pleural fluid cholesterol, Alkaline Phosphatase (ALP), and D-dimer have shown promise in enhancing diagnostic accuracy.

Aim: To compare the diagnostic efficacy of pleural fluid total cholesterol, pleural ALP, and D-dimer levels with Light's criteria in differentiating exudative from transudative PEs.

Materials and Methods: The present hospital-based cross-sectional study was conducted jointly in the Departments of Respiratory Medicine and Biochemistry at Adesh Medical College and Hospital, Shahabad (M), Kurukshetra, Haryana, India, from November 2022 to October 2023. A total of 100 adult patients presenting with PE were recruited. Each patient underwent detailed clinical history, physical examination, chest radiography or Computed Tomography (CT) when indicated, and routine laboratory investigations. Pleural fluid samples were analysed for protein, Lactate Dehydrogenase (LDH), cholesterol, ALP, and D-dimer, while corresponding serum levels were also measured. Effusions were classified as transudative or exudative using Light's criteria. Data were statistically analysed using independent t-test, Chi-square or Fisher's exact test, binary logistic regression, and Receiver Operating Characteristic (ROC) curve analysis. A p-value <0.05 was considered statistically significant.

Results: In the present study, 71% of participants were male, and the mean age was comparable between the exudative and transudative groups. Pleural fluid cholesterol, pleural ALP, pleural/serum ALP ratio, pleural D-dimer, and pleural/serum D-dimer ratio were significantly higher in exudates than in transudates (p <0.001). ROC analysis demonstrated that all parameters had an Area Under the Curve (AUC) of 1.0, with 100% sensitivity and specificity at the identified cut-off values. Logistic regression analysis identified serum ALP as a protective factor and the pleural/serum LDH ratio as an independent predictor of exudative effusion.

Conclusion: Pleural fluid cholesterol, ALP, and D-dimer, along with their respective ratios, are highly reliable in differentiating exudative from transudative PEs and may serve as valuable adjuncts to Light's criteria. These findings warrant validation in larger multicentric studies.

Keywords: Fluid accumulation, Interstitial space, Lactate dehydrogenase, Pleural fluid biomarkers, Transudative fluid

INTRODUCTION

Pleural Effusion (PE) results from the accumulation of fluid in the pleural space, which normally contains 7-16 mL of fluid. It may arise due to increased fluid entry from capillaries, the interstitial lung space, or lymphatics, or due to impaired absorption via parietal pleural lymphatics. Common causes include heart failure, pneumonia, tuberculosis, malignancy, and pulmonary embolism. The underlying mechanisms include elevated hydrostatic pressure (as in heart failure), reduced oncotic pressure (hypoalbuminaemia), increased capillary permeability (infections), impaired lymphatic drainage (malignancy), and diaphragmatic defects (hepatic hydrothorax) [1].

Symptoms commonly include dyspnoea, cough, and pleuritic chest pain. Clinical signs include dullness to percussion and reduced breath sounds. Imaging modalities such as chest X-ray, ultrasonography, and CT, along with thoracocentesis, are key to diagnosis. Pleural fluid analysis is essential to differentiate transudative from exudative effusions [2].

Light's criteria, based on protein and LDH ratios, remain widely used, identifying nearly 98% of exudates but misclassifying approximately 25% of transudates, particularly in patients receiving diuretics or those with cirrhosis. The serum-pleural albumin gradient (>1.2 g/dL) may help reduce misclassification [3-5].

Approximately 30-40% of PE cases remain idiopathic. Several pleural fluid tests, including Adenosine Deaminase (ADA), amylase, bilirubin, and cholesterol, aid in identifying the underlying aetiology [6]. ALP levels above 75 IU/L have shown high sensitivity for exudates, although they poorly differentiate tuberculosis from malignancy [7]. Pleural fluid cholesterol, independent of serum levels, has been reported to distinguish exudates at cut-off values of 47-60 mg/dL with over 80% specificity [8]. Fibrin degradation products such as D-dimer have also demonstrated diagnostic potential, particularly in tuberculous and emphysematous effusions, though results vary across disease groups [9].

Thus, while Light's criteria remain the standard for classifying PEs, they frequently misclassify transudates and have limited accuracy in certain clinical scenarios [1,8]. Although individual biomarkers such as cholesterol, ALP, and D-dimer have been investigated, evidence remains scattered and inconsistent, and direct comparisons with Light's criteria within the same cohort are scarce. Moreover, pleural-to-serum ratios of ALP and D-dimer are poorly explored [1,8,9].

The present study was therefore undertaken to evaluate these biomarkers alongside Light's criteria, addressing the clinical need for reliable adjunctive markers when conventional criteria are inconclusive. Accordingly, the current study aimed to compare the diagnostic efficacy of pleural fluid total cholesterol, pleural ALP, and

D-dimer levels with Light's criteria in differentiating exudative from transudative PEs.

In addition, for comparative analysis, the study assessed age, pleural fluid/serum protein ratio, pleural fluid/serum LDH ratio, serum LDH, pleural fluid total cholesterol, pleural fluid ALP, serum ALP, pleural fluid/serum ALP ratio, pleural fluid D-dimer, serum D-dimer, and pleural fluid/serum D-dimer ratio between transudative and exudative effusions.

MATERIALS AND METHODS

The present hospital-based cross-sectional study was undertaken in the Departments of Respiratory Medicine and Biochemistry at Adesh Medical College and Hospital, Shahabad (M), Kurukshetra, over a one-year period from November 2022 to October 2023. The study was initiated after obtaining approval from the Institutional Ethics Committee (IEC) (vide No. AMCH/IEC-BHR/2022/09/04 dated 10.09.2022). A total of 100 patients who met the eligibility criteria were enrolled from the outpatient departments and wards of the Department of Respiratory Medicine.

Inclusion criteria: Patients of either sex, aged above 18 years, with clinical, radiological, and biochemical evidence of PE, irrespective of aetiology, and who provided informed consent were included in the study.

Exclusion criteria: Patients who were unwilling to participate, had a prior diagnosis of PE and were already receiving treatment, were pregnant, had obvious haemothorax due to trauma, or had conditions such as jaundice, dyslipidaemia, hypoproteinaemia, or pulmonary embolism were excluded.

Sample size calculation: Based on previous departmental records, an approximately equal proportion of patients with transudative and exudative PEs were admitted. Assuming a Cohen's d effect size {mean difference/pooled Standard Deviation (SD)} of 0.6 (range 0.5-0.79), with a two-sided 95% Confidence Interval (CI) and 80% study power, the minimum required sample size was 45 patients in each group.

The selected effect size was based on departmental data suggesting medium to large differences in biochemical markers between the two groups. Therefore, this effect size represented a realistic and conservative estimate. Accordingly, a total of 100 patients were included in the study. Sample size was calculated using Power Analysis & Sample Size (PASS) version 16 (NCSS LLC, Kaysville, UT, USA).

Study Procedure

A total of 100 patients presenting with clinical, radiological, and biochemical evidence of PE were recruited from the Outpatient Departments and wards after obtaining written informed consent in both English and the vernacular language.

Each patient underwent a comprehensive evaluation, including detailed history, general and local chest examination, and imaging studies such as digital chest X-ray (posteroanterior and lateral views) using an Allengers 800 mA X-ray machine. Chest CT using a Siemens 128-slice CT scanner was performed when indicated. Routine laboratory investigations and Electrocardiography (ECG) using a Philips 12-channel machine were carried out.

Sputum examination for Acid-Fast Bacilli (AFB) using Ziehl Neelsen staining was performed when required. Pleural fluid cytology was conducted in cases suspicious for malignancy. Biochemical analysis included measurement of serum and pleural fluid protein and LDH levels, Ziehl-Neelsen staining of pleural fluid for AFB, and estimation of pleural fluid ADA.

All patients were classified as having exudative or transudative PE based on Light's criteria [4]. According to these criteria, an effusion was considered exudative if any one of the following was present:

- Pleural fluid protein/serum protein ratio>0.5
- Pleural fluid LDH/serum LDH ratio>0.6
- Pleural fluid LDH level >two-thirds of the upper limit of normal serum LDH

Additionally, levels of D-dimer and ALP in both serum and pleural fluid, and cholesterol in pleural fluid, were measured in all patients. ALP and cholesterol were analysed using a fully automated chemistry analyser (Transasia EM-360), while D-dimer was estimated using a Tosoh Automated Immunoassay Analyzer-360 (TOSOH AIA-360). Serum ALP levels between 44-147 IU/L and pleural fluid ALP levels below 40 IU/L were considered normal [7]. Serum total cholesterol below 200 mg/dL was considered normal.

In pleural fluid, cholesterol levels below 45-60 mg/dL were typical of transudates, whereas levels exceeding 60 mg/dL indicated exudative effusions [8,10]. Serum D-dimer levels were normally below 500 ng/mL, while pleural fluid D-dimer levels were usually very low (<100 ng/mL) but markedly increased in exudative effusions [9]. These reference ranges were applied to interpret biochemical patterns in the present study.

STATISTICAL ANALYSIS

Continuous variables with normal distribution were summarised as mean and SD. Differences between transudative and exudative groups were analysed using the independent samples t-test. Categorical variables were compared using Pearson's Chi-square test or Fisher's exact test where appropriate. The ROC curve analysis was used to evaluate diagnostic performance and determine optimal cut-off values, along with sensitivity and specificity. A p-value <0.05 was considered statistically significant. All analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) and STATA (Statistics and Data Analysis) version 19 (Stata Corp LLC, College Station, TX, USA).

RESULTS

In the present study, independent samples t-tests were used to compare biochemical parameters between transudative and exudative PE groups. Pleural fluid total cholesterol, pleural ALP, the pleural fluid/serum ALP ratio, pleural D-dimer, and the pleural fluid/serum D-dimer ratio were all significantly higher in the exudative group compared with the transudative group (p <0.001) [Table/Fig-1].

Parameters	Exudative Pleural Effusion (PE) (N=50)	Transudative Pleural Effusion (PE) (N=50)	T-value	p-value
Age (years)	45.12±16.16	43.88±15.64	0.39	0.697
Pleural fluid/serum protein ratio	0.88±0.37	0.25±0.17	10.88	0.001
Pleural fluid/serum LDH	0.92±0.34	0.24±0.16	12.83	0.001
Serum LDH (U/L)	273.98±73.02	172.22±52.44	8.0	0.001
Pleural fluid total cholesterol (mg/dL)	70.36±16.14	18.74±6.4	21.02	0.001
Pleural fluid ALP (IU/L)	98.5±13.12	31.62±11.39	27.22	0.001
Serum ALP (IU/L)	236.77±75.02	378.49±212.56	-4.45	0.001
Pleural fluid/serum ALP ratio	0.45±0.1	0.1±0.03	23.18	0.001
Pleural fluid D-Dimer (ng/mL)	3967.22±470.4	24.1±8.27	59.26	0.001
Serum D-Dimer (ng/mL)	0.48±0.12	0.5±0.12	-0.91	0.362
Pleural fluid/Serum D-Dimer ratio	8895.34±2568.2	51.47±21.26	24.35	0.001

[Table/Fig-1]: Statistical comparison of age and biochemical markers in exudative and transudative Pleural Effusion (PE) (N=100).
Data are presented in Mean±Standard deviation, compared by independent samples t-test; p-value <0.05 significant

Categorical variables such as sex distribution were comparable between the two groups. Similarly, no statistically significant differences were observed between exudative and transudative PEs with respect to alcohol consumption, smoking status, history of tuberculosis contact, or prior trauma [Table/Fig-2].

Variables	Exudative (n=50) N (%)	Transudative (n=50) N (%)	Test statistic	p-value
Sex				
Male	35 (70)	36 (72)	0.049	0.826
Female	15 (30)	14 (28)		
Alcohol abuse				
Yes	18 (36)	17 (34)	0.044	0.834
No	32 (64)	33 (66)		
Smoking				
Yes	16 (32)	17 (34)	0.045	0.832
No	34 (68)	33 (66)		
Chest trauma				
Yes	7 (14)	3 (6)	1.78	0.182
No	43 (86)	47 (94)		
Contact with TB patient#				
Yes	5 (10)	2 (4)	-	0.436
No	45 (90)	48 (96)		

[Table/Fig-2]: Association of categorical variables with exudative and transudative Pleural Effusions (PE) (N=100).
Data are presented in Number (%); Compared by Chi-square test/#Fisher-exact test; p-value <0.05 significant

The ROC curve analysis for diagnosing exudative PE showed statistically significant results (p <0.001) for all evaluated parameters. As all variables- pleural fluid total cholesterol, pleural fluid ALP, pleural fluid D-dimer, pleural fluid/serum ALP ratio, and pleural fluid/serum D-dimer ratio were markedly higher in the exudative group, the area under the ROC curve (AUC) was 1.0 for each parameter, with 100% sensitivity and 100% specificity at the identified cut-off values [Table/Fig-3,4].

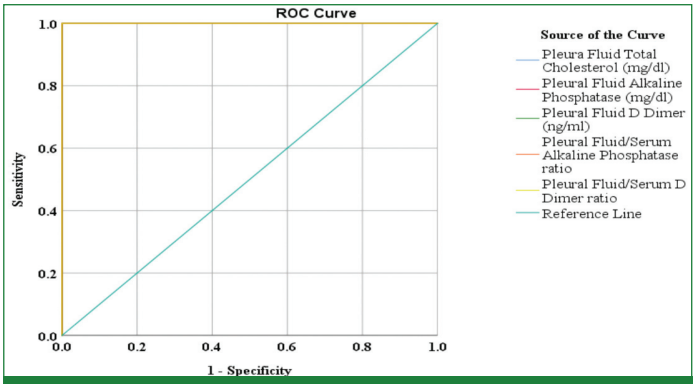
Parameters	AUROC (95% CI)	Cut-off value	Sensitivity (%)	Specificity (%)
Pleural fluid total cholesterol (mg/dL)	100 (100-100)	≥37.5	100	100
Pleural fluid Alkaline Phosphatase (ALP) (IU/L)	100 (100-100)	≥63.0	100	100
Pleural fluid D-Dimer (ng/mL)	100 (100-100)	≥1567	100	100
Pleural fluid/serum Alkaline Phosphatase (ALP) ratio	100 (100-100)	≥0.207	100	100
Pleural fluid/Serum D-Dimer ratio	100 (100-100)	≥2435	100	100

[Table/Fig-3]: Diagnostic accuracy of various biochemical parameters in differentiating exudative from transudative Pleural Effusions (PE) (N=100).
AUROC: Area under the receiver operating characteristics curve

To identify predictors of exudative PE, multivariable binary logistic regression analysis was performed. Among the variables that were significant in univariate analysis, only serum ALP and the Pleural fluid/serum LDH ratio emerged as independent predictors of exudative PE. Of these, serum ALP was associated with a lower risk, whereas the pleural fluid/serum LDH ratio served as a risk factor for exudative PE [Table/Fig-5].

DISCUSSION

Although Light's criteria remain the reference standard for classifying PEs, their limited specificity-particularly in patients with heart failure, cirrhosis, or those receiving diuretics- has been well documented, with transudates frequently misclassified as exudates. Previous studies



[Table/Fig-4]: Showing ROC curve analyses for pleural fluid total cholesterol, pleural fluid Alkaline phosphatase (ALP), pleural fluid D-Dimer, pleural/serum ALP ratio and, pleural/ serum D-Dimer ratio, respectively.

Predictor	Odds ratio (95% CI)	p-value
Serum Alkaline Phosphatase (ALP) (IU/L)	0.991 (0.984-0.998)	<0.001
Pleural fluid/Serum LDH Ratio	1.049 (1.026-1.072)	<0.001

[Table/Fig-5]: Independent predictors of exudative Pleural Effusion (PE) (N=100).
Multivariable Binary Logistic Regression analysis; P <0.05 significant

evaluating alternative biomarkers such as pleural fluid cholesterol, ALP, and D-dimer have reported variable diagnostic performance and have largely assessed these markers in isolation, often without direct comparison with Light's criteria within the same cohort.

In contrast, the present study demonstrated that pleural fluid cholesterol, ALP, D-dimer, and their pleural-to-serum ratios achieved 100% sensitivity and specificity in identifying exudative effusions. These results surpass the diagnostic accuracies reported in earlier studies, where pleural cholesterol sensitivities ranged from 84% to 99%, and ALP or D-dimer based parameters showed inconsistent performance.

The biomarker levels in the exudative group were significantly higher than those in the transudative group, resulting in a clear separation between the two distributions. Due to the absence of overlap, the selected cut-off values achieved near-perfect sensitivity and specificity. These findings confirm the strong diagnostic accuracy of the evaluated markers, as they correctly identified all exudative cases while excluding all transudative cases without error.

By directly comparing multiple biomarkers with Light's criteria within a single cohort and incorporating pleural-to-serum ratio analyses, this study provides stronger evidence supporting their role as reliable adjuncts, particularly in clinically equivocal cases.

In the present study, pleural fluid cholesterol levels were markedly higher in exudative effusions than in transudative ones. Statistical comparison with Light's criteria showed strong concordance, and ROC analysis identified a cut-off value of ≥37.5 mg/dL (p <0.001) for diagnosing exudative PE with 100% sensitivity and 100% specificity.

Gazquez I et al., reported that a pleural cholesterol cut-off of 50 mg/dL provided a sensitivity and specificity of 84%, comparable to Light's criteria [10]. Costa M et al., found even higher diagnostic accuracy when cholesterol was combined with pleural LDH, achieving a sensitivity of 99% and specificity of 98% [11]. Similar findings by Guleria R et al., and Dhandapani S et al., further validated cholesterol as both a standalone and adjunctive diagnostic marker, particularly when blood sampling is limited [12,13].

The study also examined ALP levels in both pleural fluid and serum. In exudative effusions, pleural ALP levels were significantly higher than in transudative effusions. Similarly, the pleural fluid/serum ALP ratio was markedly elevated in exudates. ROC curve analysis identified pleural ALP levels ≥63 IU/L and a pleural fluid/serum ALP ratio ≥0.207 as highly significant indicators of exudative effusions (p <0.001), each demonstrating 100% sensitivity and specificity.

These findings are consistent with those of Gupta KB et al., who reported that these parameters could reclassify misdiagnosed cases, achieving sensitivity and specificity rates of 100% [14]. Shanmuganathan P and Raghavan KS further noted that the pleural fluid/serum ALP ratio exhibited the highest sensitivity (93.9%) among the parameters studied, highlighting its diagnostic utility [15].

In patients with exudative PEs, serum D-dimer levels did not differ significantly between groups, whereas pleural fluid D-dimer levels were significantly elevated compared with transudative effusions. The pleural fluid/serum D-dimer ratio provided a clear distinction between exudates and transudates. ROC analysis demonstrated that pleural fluid D-dimer levels ≥1567 ng/mL or a pleural fluid/serum D-dimer ratio ≥2435 strongly indicated exudative effusion ($p < 0.001$), with 100% sensitivity and specificity.

These results were supported by El-Habashy MM et al., who observed significantly elevated pleural D-dimer and ALP levels in exudative effusions, particularly those of tuberculous origin [16]. No significant differences in serum levels were noted across different aetiologies, further reinforcing the diagnostic importance of pleural fluid analysis.

The perfect sensitivity and specificity observed in the present study underscore the potential clinical reliability of these biochemical markers in routine practice; however, external validation is essential. Multivariable binary logistic regression revealed that higher serum ALP acted as an independent protective factor, whereas the pleural fluid/serum LDH ratio emerged as a significant independent risk factor for exudative effusion.

Only these two variables remained in the final model, as the others were excluded due to significant multicollinearity with the primary predictors. Therefore, the emphasis on these variables was driven by statistical considerations rather than subjective selection, ensuring a robust and non-redundant predictive model. This further supports the complementary role of serum and pleural biomarkers in refining PE classification beyond Light's criteria.

Limitation(s)

The present study was a single-centre study, which may limit the generalisability of the findings to other clinical settings. Light's criteria were used as the reference standard, which may occasionally misclassify cases. Additionally, the study did not include long-term follow-up, external validation in an independent cohort, or subgroup analysis across different causes of exudative effusions.

CONCLUSION(S)

The present study demonstrated that pleural fluid cholesterol, ALP, and D-dimer levels, along with their pleural-to-serum ratios, provide excellent accuracy in differentiating exudative from transudative effusions and serve as valuable adjuncts to Light's criteria, particularly in equivocal cases. Serum ALP emerged as a protective factor, while the pleural fluid/serum LDH ratio independently predicted exudative effusion. These biochemical markers show strong potential as complementary diagnostic tools. However, validation through larger multicentric studies with standardised cut-off values and cost-effectiveness analyses is recommended. Future research should focus on standardising these biomarkers through prospective trials and integrating them into established clinical decision-making frameworks alongside Light's criteria to improve PE management.

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