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"Comparative Analysis of Biochemical Parameters to Differentiate Transudative and Exudative Pleural Fluid"

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Abstract **:** ***Background:*** *Light's criteria is the gold standard to differentiate transudative pleural effusion (PE) from exudative PE, but it requires four biochemical estimations which, in developing countries such as India, may not be feasible in every patient due to economic constraints.* ***Aims & Objectives:*** *To evaluate the comparative usefulness of pleural fluid biochemical parameters with relative usefulness of pleural cholesterol to the traditional Light' criteria.* ***Methodology:*** *This observational nonrandomized multiple arm prospective study was carried out in a group of new PE cases, admitted between December 2015 to September 2017 in the Department of Medicine at Gajra Raja Medical College, Gwalior, India. A total of 100 adult patients of both gender were selected by adhering strictly to certain inclusion and exclusion criteria.****Statistical Analysis :*** *Sensitivity, specificity, positive predictive value and negative predictive value of different biochemical parameters single or in combination were analyzed by SPSS 19 software. Strict confidentiality of the study reports was maintained and all the queries and apprehensions of the patients and their families were addressed with utmost care. Prior to initiating the study, counselling of the patients and their families were done and an informed written consent was taken.* ***Results:*** *According to their etiology, 88 cases of effusion were exudates & 12 transudates. Using Pleural Cholesterol range of 45-60 mg/dl and values for pleural fluid protein & LDH (Light's criteria),the best diagnostic power corresponded to the combination of pleural cholesterol and LDH; cholesterol level between 45-60 mg/dL and/or LDH over 200 IU/L differentiate exudates from transudates with a sensitivity o and a specificity of >90%.* ***Conclusion :*** *The measurement of pleural cholesterol and LDH permits the separation of pleural exudates from transudates with accuracy similar to the original report of Light et al., with the advantage of requiring only two laboratory determinations and no simultaneous blood sample, especially in a country like India where financial and technical constraints are immense.*

Keyword's: *Pleural Effusion, Transudate, Exudate, Light's Criteria, Pleural Cholesterol , Pleural LDH.*

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I. Introduction

Pleural effusion (PE) is of two types depending on the underlying pathophysiology, that is, ''transudates'' and ''exudates.'' Transudates occur when the mechanical factors influence the formation or reabsorption of pleural fluid, like a decrease in plasma oncotic pressure or elevated systemic or pulmonary hydrostatic pressure. Exudate results from inflammation or irritation or other disease process involving the pleura, resulting in increased permeability.[1]

Transudate or Exudate

Traditionally, serous fluids are classified as transudates or exudates. Transudates derive from ultra filtration across a membrane and have a low protein content, whereas exudates are formed by active secretion or leakage and have a high protein content. The presence of a transudative effusion implies a non-inflammatory process caused by a disturbance of hydrostatic or colloid osmotic pressure with no pleural disease involvement. In contrast, an exudates implies involvement of the pleura by an inflammatory or malignant process causing increased capillary permeability.

When pleural fluid is sent for examination, the laboratory is often asked to determine whether it is a transudate or an exudate. In reality, the question being asked is what is the cause of this effusion?

The first step in determining the etiology of a PE should be to find out whether it is a transudate or an exudate. Light *et al*., used pleural fluid and serum levels of protein and LDH to establish criteria for differentiating transudates from exudates. This high diagnostic accuracy made the criteria of Light *et al.*, the 'gold standard' for initial categorization of PE.[2,3] However, Light's criteria require four biochemical estimations which, in developing countries such as India, may not be feasible in every patient due to economic constraints. Also, several prospective studies were unable to reproduce the results obtained by Light *et al*.[4,5,6]

Although a review of the causes of pleural effusion in seven of the largest and most frequently cited studies showed that nearly half were due to cancer, the most common, but least reported, cause of pleural effusion is congestive cardiac failure.[7] These effusions are often small, bilateral and expected to be seen as part of the illness, so the diagnosis is obvious.[7]

Thoracocentesis is usually technically uncomplicated, well tolerated and relatively safe. It can be performed on almost any pleural effusion. Pleural fluid taps are carried out for two main reasons: the procedure may be therapeutic in alleviating the pulmonary compromise created by a large effusion; where the cause of a pleural effusion is unclear, biochemical analysis may help to provide a diagnosis. However, a diagnosis may not be established in up to 20% of exudates even after intensive evaluation.[8]

The main purpose of this study is to evaluate a large number of PE patients to compare, prospectively, the relative usefulness of pleural concentrations of cholesterol to the traditional criteria of Light *et al.*,[3] and their different individual parameters' [pleural lactate dehydrogenase (LDH) concentration, pleural fluid to serum LDH ratio, and pleural fluid to serum protein ratio] for separating exudates from transudates and to determine whether a similar result could be obtained by combining cholesterol with only one or two of the individual indicators of Light *et al.*, thus simplifying the diagnostic procedure and lowering the cost.[7]

II. Materials And Methods

This observational non-randomized multiple arm prospective study was carried out in a group of new PE cases, admitted between December 2015 to September 2017 in the Department of Medicine at Gajra Raja Medical College, Gwalior, India. A total of 100 adult patients of both gender were selected by adhering strictly to certain inclusion and exclusion criteria.

AIMS & OBJECTIVES

1. To conduct a clinical and etiological study of pleural effusion by conventional methods.
2. To evaluate the reliability and diagnostic efficacy of pleural / plasma cholesterol ratio.
3. To compare its efficacy with Lights criteria.

INCLUSION CRITERIA

1. Age ≥14 years of both gender.
2. Patients with definite clinical diagnosis and PE evidenced by radiological imaging, where thoraocentesis yield a sufficient good quantity of pleural fluid for examination.
3. Patients of PE who have not received any therapy for his/her present disease.
4. Patients giving consent.

EXCLUSION CRITERIA

1. Age ≤14 years of both gender.
2. Patients with history of PE due to trauma (penetrating or non penetrating).
3. Patients not willing to participate in the study.

STUDY PROCEDURE

All the PE patients after admission in the emergency, detailed history taking and clinical examination were performed. Patient was assessed for the history of fever, productive or dry cough, night sweats, hemoptysis, chest pain, lower extremity edema, orthopnea, paroxysmal nocturnal dyspnea, decreased urine output, and other relevant symptoms. Clinical assessment including general survey and systemic examination was done. Patient was investigated for parameters (acc. to availability) like routine blood examination, serum cholesterol, serum LDH, chest x‑ray, electrocardiography, echocardiography, renal function tests, liver function tests, biochemical and cytological examination of pleural fluid (cell count, cell type, specific gravity, protein, sugar, LDH, adenosine deaminase (ADA), cholesterol, acid fast bacilli, malignant cells, mycobacterial culture), sputum for acid fast bacilli, ultrasonography of thorax, and computed tomography of thorax (in selected patients) for evaluation of PE.

The PEs were classified as exudative and transudative on the basis of etiological diagnosis, Light's criteria, and pleural fluid cholesterol (a pleural fluid value >45 mg/dL and ratio of pleural fluid and serum cholesterol of >0.3 taken to define exudates).[8,9] According to Light's criteria if any one of the following is present, then the fluid was classified as an exudate: (1) pleural fluid to serum total protein ratio greater than 0.5, (2) pleural fluid to serum LDH ratio greater than 0.6, and/or (3) pleural fluid LDH greater than 200 IU/L.[10]

STASTICAL ANALYSIS

Sensitivity, specificity, positive predictive value and negative predictive value of different biochemical parameters single or in combination were analyzed by SPSS 19 software. Strict confidentiality of the study reports was maintained and all the queries and apprehensions of the patients and their families were addressed with utmost care. Prior to initiating the study, counselling of the patients and their families were done and an informed written consent was taken.

III. Observations & Results

A total of 100 patients with PE were studied of which 53 (53%) were cases of tuberculous effusion and 47 (47%) were cases of nontuberculous effusion. The remaining 47 cases were of malignant effusion (two cases), transudative effusion (twelve cases), parapneumonic effusion (twenty six cases), and empyema (five cases). There were a greater number of male patients than female patients in this study with 58% males and 42% females. The present study comprised of patients aged from 18 years to 74 years (mean age: 44.01 years). In present study maximum cases (88%) presented with exudative type of pleural effusion. Of these 53 cases (53%) had Tuberculosis, 26 cases (26%) had Parapneumonic Effusion. 12% cases presented with transudative type of pleural effusion. Of these 7 cases (7%) had CCF. Type of fluid show a correlation with etiology of the effusion. Exudative pleural effusion is most common in tuberculosis 53/88(59.09%) with Parapneumonic Effusion 26/88 (30%) while Transudative pleural effusion is most common in Cardiac Failure. The p value is <0.0001 thus indicating infection as most common cause of Exudative Pleural Effusion.Maximum no. of cases of Exudative Pleural Effusion are found in age group between 21-60 years with a mean age of 44.40 years with a p-value of <0.05 suggesting a significant correlation of age group exposed to infectious disease and resulting Exudative Pleural Effusion. Maximum no. of cases of Transudative Pleural Effusion are found in age group between 21-60 years with a mean age of 47.00 years with a p-value of <0.05 suggesting a non-significant correlation.

The mean protein level in tuberculous effusion was 4.77 ± 1.03 g/dL, in malignant effusion was 4.8 ± 0.2 g/dL, in pneumonic effusion was 4.7 ± 0.4 g/dL, in empyema it was 4.7 ± 0.2, and in case of transudate it was 2 ± 0.7 g/dL. The pleural fluid and serum protein ratio was >0.5 g% in tubercular, malignant, synpneumonic, and empyema but <0.5 g% in transudative PE [Tables 1 and 2]. The glucose level in the pleural fluid ranged from 48 to 148 mg%. Low glucose levels were associated with Tuberculous effusions, synpneumonic, empyema and malignant effusion, and high glucose levels were seen in transudate.

Table :-1

TYPES OF EFFUSION	NO.OF CASES	PLEURAL FLUID		
		PROTEIN	LDH	CHO
TUBERCULAR	5 3	4.77 ± 1.03	240 ± 40	65 ± 18
PARAPNUEMONIC	2 6	4.7 ± 0.4	530 ± 80	75 ± 5
MALIGNANT	2	4.8 ± 0.2	340 ± 50	75 ± 10
EMPYEMA	5	4.7 ± 0.2	1250 ± 250	75 ± 4.5
TRANSUDATIVE	1 2	2 ± 0.7	95 ± 45	35 ± 5

Table :-2

TYPES OF EFFUSION	NO.OF CASES	SERUM		
		PROTEIN	LDH	CHO
TUBERCULAR	5 3	6.9 ± 1.8	350 ± 40	190 ± 40
PARAPNUEMONIC	2 6	6.9 ± 0.8	350 ± 50	200 ± 50
MALIGNANT	2	6.2 ± 0.6	370 ± 50	175 ± 35
EMPYEMA	5	7.3 ± 0.2	370 ± 45	210 ± 50
TRANSUDATIVE	1 2	6.0 ± 0.5	360 ± 30	200 ± 50

According to the above observations of Table 3 , p value of <0.05 for Pleural cholesterol 45-60 mg/dl with sensitivity and specificity more than 90% suggests a significant correlation in diagnosing pleural fluid as exudate if Pleural cholesterol is between 45-60 mg/dl.

Table 3,4&5, clearly shows a significant correlation in pleural biochemical parameters in diagnosing as exudates with levels of Protein, LDH, Cholesterol in pleural with above said cut off levels. There is no significant correlation in diagnosing pleural fluid as exudative or transudative by measuring serum levels of any of the biochemical parameters. Pleural/Serum Ratio of Biochemical Parameters of Protein, LDH , Cholesterol suggests highly significant correlation in distinguishing Transudate and Exudate. The Sensitivity of Pleural

Fluid cholesterol is less compared to light's criteria but when combined with LDH, sensitivity is more than Light's criteria. The Specificity of Pleural Fluid cholesterol is better compared to light's criteria and also when combined withLDH, specificity is more than Light's criteria. The PPV of Pleural Fluid cholesterol is more compared to light's criteria but when combined with LDH PPV is 100%. The NPV of Pleural Fluid cholesterol is more compared to light's criteria and also when combined with LDH NPV is more than Light's criteria.

Table :-3

TYPES OF EFFUSION	No.	P/S RATIO		
		PRO	LDH	CHO
TUBERCULAR	53	> 0.5	> 0.6	> 0.3
PARAPNUEMONIC	26	> 0.5	> 0.6	> 0.3
MALIGNANT	2	> 0.5	> 0.6	> 0.3
EMPYEMA	5	> 0.5	> 0.6	> 0.3
TRANSUDATIVE	12	< 0.5	< 0.6	< 0.3

Table :-4

Pleural Cholesterol	Exudate Accordingly	Sensitivity	Specificity
35	97	91%	25%
40	91	97%	50%
45	**86**	**98%**	**92%**
50	85	97%	92%
55	83	94%	92%
60	83	94%	92%
65	80	90%	92%
70	53	60%	92%

Table :-5

PARAMETERS	SENSITIVITY	SPECIFICITY	PPV	NPV
PL. FLUID PROTEIN	83%	75%	93%	53%
P/S PROTEIN	85%	66%	91%	53%
PL. FLUID LDH	79%	75%	93%	47%
P/S LDH	85%	75%	93%	56%
LIGHT'S CRITERIA	98%	82%	90%	83%
PL. FLUID CHOLESTEROL	90%	99%	93%	95%
CHOLESTEROL+LIGHT CRITERIA	99%	95%	91%	92%
CHOLESTEROL+LDH	**99%**	**98%**	**100%**	**98%**

IV. Discussion

According to the causal disease, 12 (12%) pleural fluid samples were labelled as transudates and 88 (88 %) were labelled as exudates. It may be observed that 3 of the 88 exudates were misclassified as transudates (sensitivity 97%) and 1 of the 12 transudates was erroneously labeled as exudates (specificity 92%). The three misclassified exudates corresponded to complicated parapneumonic effusions & Tubercular effusion, and of the erroneously classified transudates, one was secondary to congestive heart failure. When the concentration of cholesterol in pleural fluid, with a cutoff point of 45 mg/dL, was used for classification, 2 of the 88 exudates were misclassified with a sensitivity of 98%, while all the transudates were misclassified with a specificity of 92%, If the cutoff point of 60 mg/dL as proposed by Hamm *et al.*,[4] was used, sensitivity fell to 80% and specificity remained 92%.

All the transudates that were erroneously classified by the criteria of Light *et al*., were correctly identified through cholesterol level and, inversely, all exudates that were misclassified by cholesterol were correctly identified by the measurements of Light *et al.*[3]

Table 5 shows the sensitivity and specificity calculated for the criteria of Light *et al*., for cholesterol alone and for all the possible combinations of cholesterol and the individual components of the set of Light *et al*. It may be observed that cholesterol has a higher sensitivity ($P < 0.05$) but a lower specificity ($P < 0.01$) than the criteria of Light *et al*., and that their combined use improves sensitivity (99%) but not specificity (95%).

Of the six alternatives that combine cholesterol and one or two of the indicators of Light *et al.*, only that of cholesterol level greater than 45 mg/dL and LDH level greater than 200 U/L exhibit a better diagnostic yield than the triad of Light *et al.*, and this is due to a significantly higher specificity ($P < 0.02$). Our results show that the combination of an increased concentration of cholesterol level greater than 45 mg/dL and/or LDH level greater than 200 U/L in pleural fluid constitutes a useful tool for separating exudates from transudates.[11,12] The diagnostic yield of this combination is similar to that obtained by Light *et al.*[3,13] in their original investigation and superior to those reported by other authors.[14,15]

Our initial assumption, that the simultaneous use of the criteria of Light *et al*., and cholesterol would be complementary, was not confirmed, since the specificity of this combination was, in our patients, as low as that of the criteria of Light *et al.*,[3] alone. This could be interpreted as a lack of a contributory effect of cholesterol, but Table 14 shows that the combinations which include pleural‑serum protein ratio were the ones that exhibit the lowest specificity, while the combination of cholesterol and LDH shows the highest.[12] This misleading effect of protein ratio is present in all the studies that report low specificities. Most of the errors were observed in congestive heart failure and protein ratio was the deceiving index in most cases. This aspect has been recently addressed by Chakko *et al*.,[16] who demonstrated that the treatment of heart failure may change the chemistry of pleural fluid probably by withdrawing water and, thus, concentrating proteins. If this is so, the interpretation of protein ratio in heart failure would depend on previous treatment, which is a variable that is difficult to standardize. This would mean that this indicator is not suitable in patients with heart failure and, probably, in those with liver cirrhosis in whom diuretics have been used. As most transudates considered for differential diagnosis correspond to those etiologies, it seems reasonable to abandon this low‑specificity indicator. Roth *et al*.,[17] showed that this limitation of the criteria of Light *et al.*, could be overcome by measuring the serum‑effusion albumin gradient which, when over 1.2 mg/dL, indicated a transudate. Replacing the serum PE protein ratio by this other indicator undoubtedly increases the specificity of the criteria of Light *et al*., but a simultaneous blood sample is still required.

V. Conclusion

The measurement of pleural cholesterol and LDH permits the separation of pleural exudates from transudates with accuracy similar to the original report of Light *et al*., with the advantage of requiring only two laboratory determinations and no simultaneous blood sample, especially in a country like India where financial and technical constraints are immense.

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