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A comparative analysis of biochemical parameters in exudative and transudative pleural fluids using different criterias: a study in a tertiary care centre

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Abstract

Background: Pleural effusion is a common clinical problem resulting from thoracic or systemic diseases. Several biochemical parameters, serological and cytological markers are used to classify the type of pleural effusion. The oldest classification is Light's criteria which categorizes exudates by meeting one of these criteria: Pleural to serum protein ratio> 0.5, pleural to serum LDH ratio> 0.6 and isolated LDH > two third of normal upper limit of serum LDH. Others criteria are protein gradient and Serum effusion albumin gradient. Combination of clinical findings along with biochemical findings along with cytology helps in determining the etiology of pleural effusion.

Materials and Methods: One hundred fifty samples of pleural fluid paired with serum were examined. Pleural fluids were also subjected to biochemical study to find out the level of protein, albumin, glucose, Adenosine deaminase levels, LDH, total and differential cell counts, Gram's stain and Modified Ziehl-Neelsen stain. Serum samples were evaluated for protein, albumin and LDH levels.

Results: Out of 250 samples, total of 71.2% samples were exudative and 28.8% were transudative. There were 184 males and 66 females. Tuberculosis (42.7%) followed by para-pneumonic effusion (22%) was commonest etiology seen in exudative pleural effusions. In transudates, chronic liver disease (10.8%) followed by chronic renal disease (8.4%) was the commonest etiologies encountered. Light's criteria was nearly successful in classifying all exudates. All the inflammatory effusions were 100% classified by pleural LDH levels. All transudates are correctly classified by Serum effusion albumin gradient.

Conclusions: Light's criteria was most sensitive in identifying exudates but not specific in cases of transudates specially heart failure patients. Light's criteria was 97.7% successful in classifying exudative pleural effusion. Combination of pleural LDH and pleural fluid to serum protein ratio was successful in classify all the exudates correctly.

Keywords: Pleural effusion, Light's criteria, Biochemical, Exudative, Transudative

Introduction

Pleural effusion is a common clinical problem resulting from thoracic or systemic diseases. Several biochemical, serological and cytological markers are used to classify the type of pleural effusion.(1) The oldest classification for categorizing the pleural effusion is by Light's criteria which includes pleural fluid to serum protein ratio> 0.5, pleural fluid to serum (Lactate dehydrogenase) LDH ratio >0.6 and isolated pleural fluid LDH more than two-thirds the normal upper limit for serum LDH. Exudative pleural effusions meet at least one of the criteria, whereas transudative pleural effusions meet none.(2) The etiological factors of transudative pleural effusion include congestive heart failure, liver cirrhosis, renal failure and hypoproteinemia while exudative effusion include neoplasia including primary and metastatic, infectious diseases including tuberculosis, pneumonia, other granulomatous diseases, parasitic and viral infections.(2,3) Mononuclear cells predominate in transudative effusions and chronic Exudative effusions like those associated with carcinoma, tuberculosis and rheumatoid disease.(1,2) Cytology helps in differentiating reactive mesothelial cells, inflammatory conditions and neoplastic or metastatic lesions in pleural fluid. Combination of clinical findings along with biochemical parameters and cytology helps in determining the etiology of pleural effusion.(4)

Aim & Objective

To study the biochemical parameters in Pleural fluid samples.

Material & Methods

This study was conducted in the Department of Pathology, Rohilkhand Medical College & Hospital, Bareilly from December 2014 to November 2015. A Total of 250 cases of pleural effusions along with serum samples were included in the study. The following tests were performed on pleural fluid samples – Adenosine deaminase (ADA), albumin, total protein, glucose, LDH. Total and differential cell count, Gram's stain, bacterial culture and Modified AFB stain. Serum samples were simultaneously obtained for the measurement of glucose, total protein, albumin and LDH levels. Light's criteria for classifying exudates- (a) Pleural fluid/serum total protein ratio > 0.5 (b) Pleural fluid/serum LDH ratio > 0.6 (c) Pleural fluid LDH > 200 IU/I was used . For misclassified pleural effusions, serum - effusion albumin gradient was used. Final diagnosis was confirmed by PCR, culture on

Lowenstein- Jensen Media (LJ media), Modified Ziehl-Neelsen stain, Biopsy and clinical response to therapy.

Statistical Analysis: We calculated following statistical measures were calculated: Sensitivity = TP/(TP+FN); Specificity = TN/(TN+FP); Positive predicted value = TP/(TP+FP) and Negative predictive value = TN/(TN+ FN); where TP is the number for true positive diagnosis, TN the number of true negative diagnosis, FP the number of false positive diagnosis and FN the number for false negative diagnosis. These statistics were used with reference to the clinical etiologies. Quantitative data are represented as mean±1SD. Student t-test was applied to obtain p value.

Observations & Results

Total 250 pleural fluid samples along with blood samples from the patients presenting with pleural effusion were studied. The distribution of the diagnosis in different age groups and both the sexes is mentioned below (Table 1).

Table 1: Showing age wise distribution of diseases of pleural effusions

Final Diagnosis	Age group in years and sex											
	< 20		21- 40		41- 60		> 61		Total		Total	
	M	F	M	F	M	F	M	F	M	F	n	%
Exudates									138	40	178	71.2
Tuberculosis	11	6	22	5	14	3	14	1	61	15	76	30.4
Para-pneumonic	7	1	12	1	5	2	7	4	31	8	39	15.6
Liver abscess	1	-	1	-	1	-	-	-	3	-	3	1.2
Parasitic	2	-	-	-	2	-	-	-	4	-	4	1.6
Malignancy	1	-	1	1	4	6	3	5	11	10	21	8.4
Pancreatitis	-	-	1	-	-	1	-	2	1	3	4	1.6
Nonspecific	1	3	14	1	9	-	3	-	27	4	31	12.4
Transudates									46	26	72	28.8
Chronic liver disease	-	1	7	-	12	2	3	2	22	5	27	10.8
Chronic renal disease	1	-	1	-	9	4	7	-	17	4	21	8.4
Congestive heart failure	-	-	1	-	3	2	1	2	5	4	9	3.6
Anemia with hypoproteinemia	-	1	-	3	-	2	6	3	2	13	15	6.0
Total	24	12	60	11	59	22	44	19	184	66	250	

Out of 250, 178(71.2%) cases were exudates and 72(28.8%) were transudates. Amongst 178 exudates, majority 76(42.7%) of effusion were due to tuberculosis, followed by 39(22%) cases of para-pneumonic effusion, 31(17.4%) cases of non-specific inflammation, 21(11.7%) cases of malignant pleural effusion, 3(1.7%) cases of liver abscess and 4(2.2%) cases of pancreatitis and 4(2.2%) cases were of parasitic(filarial & echinococcus) infestation (Table 1).

Amongst 72 (28.8%) transudates, majority 27(37.5%) of effusions were due to chronic liver diseases, followed by 21(29.1%) cases of chronic renal failure, 15(20.8%) cases of anemia with hypoproteinemia and 9(12.5%) cases of congestive heart failure (Table 1).

Of these 178 exudates, 138 were in male patients and 40 in female patients (Table 1). As regards the age and sex distribution of the patients, out of total 178 exudates, majority 76(42.7%) were tubercular effusions of which 61(80.2%) male preponderance was noticed and majority cases were in the age group of 21-40 years (Table 1). In para-pneumonic effusions 39(22%), there were 31 male patients and 8 females. Amongst these, maximum (13) were in the age group of 21-40 years which included 12 males and 1 female (Table 1). Amongst the malignant effusions, there were 11 male and 10 female patients; maximum (10) were in the age group 41-60 year with female preponderance. Only 1 case of acute lymphoblastic leukaemia who was male was observed in age group of <20 years. There was 31(17.4%) non-specific exudates effusions in which diagnosis was not established (Table 1).

Of the 72(28.8%) cases of transudates, there were 46(63.8%) males and 26(36.2%) females (Table 1). Among transudates, maximum cases were of chronic liver disease 27(10.8%) cases; males were more than females majority were in the age group of 41-60 year. All the pleural fluid samples were categorized into exudates and transudates by using Light's criteria, protein gradient and serum effusion albumin gradient (Table 2).

Table 2: Various criteria's to distinguish Exudate &Transudate in Pleural Fluids

Criteria	Exudates		Transudates	
	n	%	n	%
Light's criteria	216	86.4	34	13.6
Pleural fluid to serum protein ratio(>0.5)	191	76.4	59	23.6
Pleural fluid to serum LDH ratio(>0.6)	167	67	83	33
Isolated Pleural LDH>200 U/L	120	48	130	52
Protein gradient (≤3.1 g/dl)	197	78.8	53	21.2
Serum effusion albumin gradient(≤1.2g/dl)	151	60.4	99	39.6

If one of the three parameters according to Light's criteria was met, the fluid was classified as exudate. In the present study, according to Light's criteria 216(86.4%) samples were classified as exudates. Whereas according to pleural fluid to serum protein ratio>0.5, there were 191(76.4%) exudative samples. There were 167(67%) samples which were exudates according to pleural fluid to serum LDH ratio>0.6. whereas there were 120(48%) samples as exudates according to isolated LDH level>200 U/L. Based on protein gradient (≤3.1 g/dl), there were 197(78.8%) samples as exudates. While there were 151(60.4%) samples classified as exudates according to serum effusion albumin gradient (≤1.2 g/dl) (Table 2).

Among tubercular effusions, Modified Ziehl-Neelsen staining demonstrated acid fast bacilli in 12(18%) cases. The sensitivity of Ziehl- Neelsen staining in detecting acid fast bacilli in tubercular pleural effusion was 18% (Fig. 1).

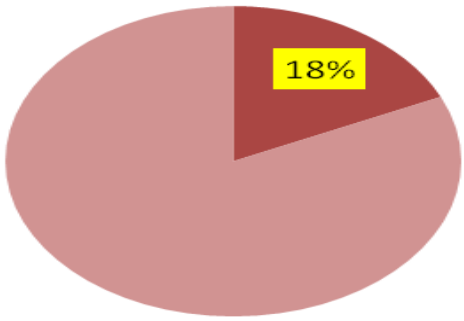

Fig. 1: Pie chart showing AFB positive cases in pleural fluids

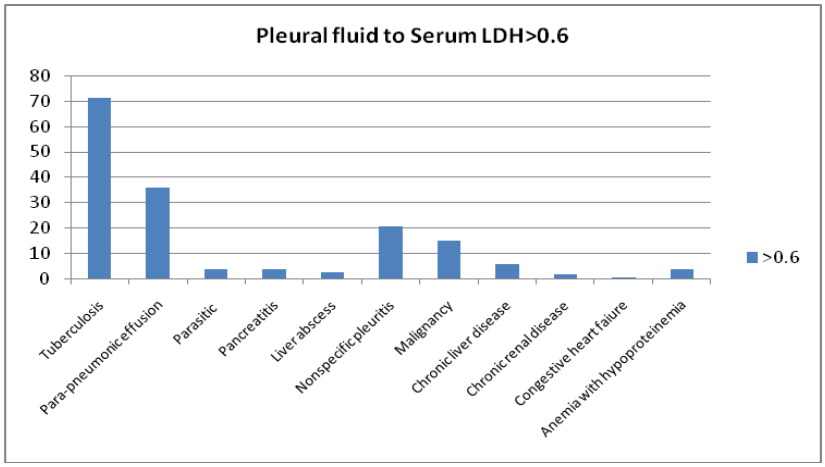

Fig. 2: Bar diagram showing pleural fluid LDH ratio>0.6 in different etiologies of pleural effusion

When applying different parameters to catergorise exudates and transudates, all the applied parameters showed significant p value in separating the exudates from transudates except Lymphocyte and neutrophil ratio, which was did not show significance(p value=0.1783).(Table 3).

Table 3: Comparison between Exudative and Transudative effusions

	Parameters	Exudates	Transudates	t- Test, p value	Significance
Pleural fluid parameters	Protein (gm/dl)	4.37±1.29	2.79±1.26	t = 8.278, p<0.0001	Highly Significant
	Sugar (mg/dl)	50.05±33.5	102.3±57.46	t= 8.9525, p<0.0001	Highly Significant
	Total Cell count (cells/ cu mm)	1796±2960	508.2±763.7	t = 3.693, p= 0.0003	Highly Significant
	Lymphocyte neutrophil ratio	19.79±25.7	24.5±23.09	t = 1.3500, p=0.1783	Not Significant
	Pleural LDH	612±1203.9	144±71.99	t =3.2922, p<0.0001	Highly Significant
	Protein ratio	0.71±0.20	0.49±0.23	t =7.537, p<0.0001	Highly Significant
Pleural fluid & Serum parameters	Protein gradient	1.89±1.34	2.98±1.56	t =5.5487, p<0.0001	Highly Significant
	LDH ratio	2.77±5.43	0.57±0.44	t =3.4292, p<0.0001	Highly Significant
	Albumin gradient	0.92±0.27	1.30±0.22	t =10.5997, p<0.0001	Highly Significant

Discussion

Out of the 250 pleural fluid samples, 178(71.2%) were exudates and 72(28.8%) were transudates, were studied according to the clinical diagnosis. The similar distribution was seen in a meta-analysis done by Heffner et al[5] and in another study conducted in by Hamal *et al*[6] (69.4% exudates and 30.6% transudates).

In present study, the most frequent cause of exudative pleural fluids was tuberculosis 76 (42.6%) followed by para-pneumonic effusion 39 (21.9%), non-specific inflammation 31(17.4%), malignancy 21(11.7%), parasitic 4(2.2%), pancreatic 4(2.2%) and liver abscess 3(1.7%) In developing countries like India tubercular effusion is the commonest cause of all exudative effusions.[2] This is similar to the observation in another study by Hamal et al[6], Lima et al[7], Alquarain et al[8] and Ferror *et al*[9] which supported our findings with the fact that India has a high prevalence of tuberculosis in the general population. This observation is different from that of the west where the incidence of para-pneumonic effusion and malignant effusion are much higher compared to that of tubercular effusion.[10]

In this study, there were 31(12.4%) cases of exudative effusions in which the diagnosis could not be established, thus they were labeled as nonspecific inflammation. This is consistent with the observation of Light *et al.*[11]

The most common cause of transudative pleural effusion observed was chronic liver disease (10.8%) followed by chronic renal disease (8.4%). Heart failure accounts for only 3.6% of the trasnsudative effusion. This is different from the observations seen in the West where heart failure is the most common cause of transudates.[10]

The basic step for the classification of exudates and transudates is to estimate the pleural protein value.[1] Pleural protein ≥3.0 g/dl are classified as exudates and less than 3.0 as transudates.[1,2,3] Light's criteria are nearly 100% sensitive at identifying exudates, but patients with pleural effusion caused by heart failure on diuretics may be misclassified by this criteria.[2] This may be attributed to the fact that fluid loos may result in false increase in protein content.[12] In this situation, protein gradient greater than 3.1g/dl and albumin gradient greater than 1.2 g/dl should be used.[1,2,12] Chakko et al showed that diuretic therapy in cases of heart failure with pleural effusion leads to a concentration of pleural fluid protein which can fall in the exudative range.[14] The microvascular endothelium remains intact in cases with transudative effusions, the pleural microvascular network is considered to be involved in the disease process in cases with exudative effusions. Based on the consequent increase in protein extravasation, it has been hypothesized that the albumin difference between serum and pleural effusions would be decreased in exudative effusions.[11,12]

The present study showed the results by pleural protein and protein ratio in distinguishing transudates from exudates was statistically highly significant (p<0.0001). The sensitivity and specificity of pleural protein was 87.6%, and 52.7% respectively. The misclassification rate was 34%. On the contrary, Das *et al.* estimated fluid protein in 40 samples and found the sensitivity of 80% and specificity of 70% with a misclassification rate of 25%.[13] Light *et al.* stated that this criteria alone leads to misclassification in 10%.[2]

Out of 34 transudates which were wrongly labeled as exudate, 6 samples were of patients with heart failure who were receiving diuretics. These samples were truly classified by protein gradient and albumin gradient. Out of 34 mislabeled transudates, 17 samples were of chronic liver disease. These cases presented in medicine department of our hospital with the symptoms and signs generalized anasarca. Their renal functions were within normal limit but liver functions were deranged. Trial of diuretics was given to them prior to thoracocentesis. This may be the reason of misdiagnosis of these cases by the criteria of pleural protein alone. All these cases were truly classified using pleural LDH levels and albumin gradient.

Eleven mislabeled transudates classified by pleural protein alone were observed in patients of chronic renal disease on dialysis therapy. The pleural fluid specimens in these cases were blood tinged. This may be the reason of false labeling of these samples as exudates. All the cases were classified as transudates using albumin gradient criteria.

Carr *et al.* found that 8% of their exudates and 15% of their transudates were misclassified by this criterion.[15] It was noticed that 72 pleural fluids with misclassification rate of 28.8% in which 65 fluids were misclassified as exudates and 7 fluids as transudates by fluid LDH alone, with a sensitivity of 63.4% and a specificity of 90.2%. Present study showed that fluid LDH correctly diagnosed 64% of exudates including inflammatory etiologies. All the inflammatory etiologies were correctly classified by this parameter alone. Our results are consistent with study done by Valdes et al who found the closer result with sensitivity of 65% and specificity of 95%.[16]

The LDH levels are elevated in inflammatory pathology. Activated, injured or dead mesothelial cells and other inflammatory cells that have migrated into the pleural space in inflammatory processes are an important source of pleural fluid LDH.[17,18]

Among these 24 misclassified transudates, the serum LDH were at lower side in comparison with fluid LDH. The findings are supported by Joseph *et al.* who explained that as the pleural fluid concentration of LDH is independent of the serum concentration, the LDH concentration in any fluid with a relatively low serum LDH concentration can result in a high LDH ratio causing false classification of a transudate as an exudates.[19] These cases were truly classified by serum effusion albumin gradient.

In present study, the Light' criteria is the most sensitive (97.7%) criteria to diagnose exudates. This finding is consistent with Light *et al*.[2], Burgess *et al*[20] and Roth *et al.*[12] But specificity (41.6%) of Light's criteria is less in this study. Light's criteria are able to classify 80.5% exudates and 88.2% transudates correctly. This result to separate transudate from exudates is statistically significant (p value=0.0001).

In this study albumin gradient correctly diagnosed 6 cases of heart failure as transudates that were wrongly classified as exudates by Light's criteria. These patients were receiving diuretics prior to thoracocentesis. These findings are supported by Roth *et al*[12] and Hamm *et al*[21]. Both the authors stated that Light's criteria may lose accuracy for transudates due to CHF after the patient has undergone diuresis.

Conclusion

Light's criteria was most sensitive in identifying exudates but not specific in cases of transudaes especially heart failure patients. Light's criteria was 100% successful in classifying tubercular and malignant effusions ascexudates. The most of the exudates were truly classified by pleural LDH. But few transudates like heart failure were not truly classified by this parameter. All the inflammatory pathologies were truly classified by pleural fluid LDH alone. Combination of pleural LDH and pleural fluid to serum protein ratio was successful in classifying exudates correctly in all the cases. Light's criteria was 97.7% sensitive in classifying exudates. Specificity of the Light's criteria was low (41.6%) in classifying transudates especially in heart failure cases. Heart failure cases were correctly classified by using Serum effusion albumin gradient.

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