

# Diagnostic Value of Pleural Fluid Bilirubin/Serum Bilirubin Ratio versus Pleural Fluid Protein/Serum Protein Ratio to differentiate Exudative from Transudative Pleural Effusion.

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## ABSTRACT

**Background:** Pleural effusion is the abnormal and excess accumulation of serous fluid in the pleural space. A number of biochemical tests are required to differentiate transudative from exudative pleural effusion. Pleural fluid to serum protein ratio, pleural fluid to serum lactate dehydrogenase ratio and pleural fluid to serum bilirubin ratio and serum cholesterol are commonly done to differentiate transudative from exudative pleural effusion. **Methods:** In this study on 25 patients with pleural effusion, by predefined criteria, these patients were divided into three groups as transudative, tubercular and non tubercular exudative group. All patients were investigated to differentiate transudative from exudative pleural effusion. Apart from routine investigations, biochemical tests of pleural fluid as well as blood were performed. Pleural fluid to serum protein ratio and pleural fluid to serum bilirubin were done in all patients. **Results:** Pleural fluid to serum protein ratio to differentiate exudative pleural effusion showed sensitivity, specificity, positive predictive value and negative predictive value of 86.66%, 100%, 100% and 83.33% respectively. Pleural fluid to serum protein ratio to differentiate transudative pleural effusion showed sensitivity, specificity, positive predictive value and negative predictive value of 100%, 86.66%, 83.33% and 100%. Pleural fluid to serum bilirubin ratio to differentiate exudative pleural effusion showed sensitivity, specificity, positive predictive value and negative predictive value of 100%, 85.71%, 84.62% and 100% respectively. Pleural fluid to serum bilirubin ratio to differentiate transudative pleural effusion showed sensitivity, specificity, positive predictive value and negative predictive value of 85.71%, 100%, 84.62% and 84.62% respectively. **Conclusion:** It is concluded that pleural fluid bilirubin to serum bilirubin is a simple, easy, cost effective and highly useful parameter to distinguish transudative from exudative pleural effusion but it does not tell the etiology of pleural effusion.

**Keywords:** Lactate dehydrogenase, Lactate dehydrogenase in Pleural Fluid, Lactate dehydrogenase Ratio, Pleural to Serum Bilirubin ratio, Pleural to Serum Protein Ratio.

## INTRODUCTION

Pleural effusion is defined as the accumulation of serous fluid in the pleural space. Normally the pleural space contains less than 15 ml of pleural fluid. It may develop when there is excess pleural fluid formation or decreased fluid removal by the lymphatics. Numerous criteria have been tried to differentiate transudative pleural effusion from exudative pleural effusion.

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A transudative pleural effusion occurs when systemic factors that influence the formation and absorption of pleural fluid are altered (Richard W. Light).<sup>[1]</sup> The exudative pleural effusion results from a disease of pleural surfaces, by increased permeability of the pleural capillaries for protein and lymphatic obstruction. Light et al<sup>[2]</sup> concluded that transudative and exudative pleural effusions can be distinguished by measuring protein and lactate dehydrogenase in the serum and in the pleural fluid. The pleural effusion is diagnosed as exudative pleural effusion on the basis of following criteria:-

1. Pleural fluid protein/ serum protein >0.5
2. Pleural fluid LDH/serum LDH >0.6
3. Pleural fluid LDH more than two thirds normal upper limit for serum

The exudative pleural fluid contains more than 3 gm of proteins per 100 ml of pleural fluid while transudative pleural effusions contain less than 3 gm per 100 ml of pleural fluid. LDH levels are >200 IU/L in exudative pleural effusions while <200 IU/L in transudative pleural effusions. LDH is raised in exudative pleural effusions above the serum level, but is otherwise a non specific finding (Light RW et al)<sup>[2]</sup>. Glucose levels are usually less than 60 mg/dl in transudative pleural effusions. Pleural fluid bilirubin is usually less than 55 mg/dl and the fluid-blood ratio is 0.3 or below in transudative pleural effusions (Valdes L et al)<sup>[3]</sup> Pleural fluid to serum bilirubin concentration ratio: Bilirubin is the end product of metabolism of haem moiety of haemoglobin, 80% of circulating bilirubin is derived from senescent RBC's. Bilirubin is present in body fluids (joint effusions, ascites, pleural effusion, CSF etc.) (Kaplan and Isselbacher)<sup>[4]</sup>. Meisel et al<sup>[5]</sup> discovered that pleural fluid to serum total bilirubin concentration ratio could serve as an alternative criteria to separate exudates from transudates. The various statistical tests for evaluating the bilirubin criteria according to etiology (a bilirubin ratio >0.6 for an exudative etiology and bilirubin ratio <0.6 for transudative one) yielded values in order of 90% and higher, therefore the bilirubin criteria is equivalent to the well accepted LDH and Protein criteria and it may serve as another criteria to distinguish exudates from transudates. Lakhotia et al<sup>[6]</sup> also compared the various biochemical markers to differentiate pleural exudates from transudates in 84 patients of pleural effusion, they concluded that measurement of bilirubin did not hold good in classifying the effusions.

#### Aims and Objectives

1. To estimate pleural fluid bilirubin, serum bilirubin and pleural fluid bilirubin/serum bilirubin ratio.
2. To estimate pleural fluid protein, serum protein and pleural fluid protein/serum protein ratio.
3. To compare pleural fluid bilirubin/serum bilirubin ratio with pleural fluid protein/serum protein ratio with regard to usefulness of pleural fluid bilirubin /serum bilirubin ratio in distinguishing between exudative and transudative pleural effusion.

#### MATERIALS AND METHODS

This study was conducted in the departments of Medicine and Biochemistry, Govt Medical College, Amritsar. Twenty five patients with pleural effusion admitted in various wards of Guru Nanak Dev Hospital, Amritsar were included. Informed consent

was obtained from all these patients for this study. The diagnosis of pleural effusion was established by history, physical examination, x-ray chest and ultrasonography. Routine investigations like haemoglobin, total leucocyte counts, differential leucocyte count, Erythrocyte sedimentation rate, random blood sugar, blood urea, serum creatinine, urine complete examination and 12 lead ECG were carried out in all patients. Biochemical examination of pleural fluid was carried out with estimation of pleural fluid protein, estimation of total serum protein, estimation of pleural fluid bilirubin level, estimation of total serum bilirubin level, Cytological examination of pleural fluid and pleural fluid culture for gram +ve and gram -ve organisms was also done. Pleural fluid protein and serum proteins were measured by Biuret method of Reinhold<sup>[15]</sup>, pleural fluid bilirubin and serum bilirubin were measured by Malloy and Evelyn<sup>[16]</sup>. All cases of pleural effusion were divided into three groups as transudative type, tuberculous and non-tuberculous exudative type. Collection of samples were obtained by thoracentesis and venous blood from antecubital vein were obtained within 30 minutes of one another. Both samples were immediately centrifuged and analysed for bilirubin and protein levels. Pleural fluids were also examined for red blood cells, white blood cells, gram staining, Ziehl-Neelsen staining for acid fast bacilli, malignant cells and culture/sensitivity for bacterial growth. Statistical analysis: the statistical differences between means of different parameters studied were estimated by student's unpaired "t" test and the results were compared on the basis of p value. 'P' value less than 0.05 was taken as significant; 'P' value less than 0.01 was taken as highly significant; 'P' value less than 0.01 was taken as very highly significant. The usefulness of each of the biochemical parameters for identifying exudates were evaluated by a Bayesian method in terms of sensitivity, specificity, positive predictive value, negative predictive value where TP is true positive diagnosis, TN the number of true negative diagnosis, FP is the number of false positive and FN is the the number of false negative diagnosis made using criteria based on parameter being studied.

#### RESULTS

Twenty five patients with pleural effusion were studied to distinguish between transudative and exudative pleural effusion with the following parameters: 1. Pleural fluid protein to serum protein ratio 2. Pleural fluid bilirubin to serum bilirubin ratio.

#### Causes of Pleural Effusion

**Table 1: showing the classification of 25 pleural effusions studied by the predefined criteria. 12 cases were classified as transudates and 13 were classified as exudates ( of which 8 tubercular, 2 malignant and 3 parapneumonic).**

Group 1	Transudative pleural effusion	No. of cases
1	Congestive cardiac failure	5
2	Nephrotic syndrome	5
3	Cirrhosis of liver	2
	Total	12
Group 2	Tubercular pleural effusion	8
Group 3	Non tubercular exudative pleural effusion	
1.	Malignant pleural effusion	2
2.	Parapneumonic pleural effusion	3
	Total	5

**Table 2: showing Pleural Fluid Protein/Serum Protein.**

Transudative pleural effusion		Exudative pleural effusion	
Pleural fluid protein/serum protein ratio	Number of cases	Pleural fluid protein/ serum protein ratio	Number of cases
0.20-0.30	3 ( 25%)	0.50-0.75	6( 46.15%)
0.31-0.40	4 ( 33.33%)	0.76-1.00	5( 38.46%)
0.41-0.50	3 ( 25%)	1.01-1.25	1( 7.69%)
0.51-0.60	2( 16.66%)	1.26-1.50	1(7.69%)
Total	12 ( 100%)	Total	13 (100%)

The above table shows that the maximum cases of transudative pleural effusion had pleural protein/serum protein ratio in the range of 0.31 to 0.4 (

33.33%) and maximum cases of exudative pleural effusion had pleural fluid protein/serum protein ratio in the range of 0.5 to 0.75 ( 46.15%).

**Table 3: showing Pleural fluid Bilirubin/Serum Bilirubin ratio in Transudative and Exudative pleural effusions.**

Transudative pleural effusions		Exudative pleural effusions	
Pleural fluid bilirubin / serum bilirubin ratio	Number of cases	Pleural fluid bilirubin / serum bilirubin ratio	Number of cases
0.20 -0. 30	4{ 33.33% }	0.50 -0.80	5 {38.46% }
0.31- 0.40	6{50.00% }	0.81 -1.10	3{23.07% }
0.41 -0.50	1 {8.33% }	1.11-1.40	3{23.07% }
0.51- 0.60	1 {8.33% }	1.41-1.70	2{15. 38% }
Total	12 {100% }	Total	13 {100% }

The above table shows that maximum cases of transudative pleural effusions had pleural/serum bilirubin ratio in the range of 0.31 to 0.4 (50%) and

maximum cases of exudative pleural effusion had pleural/serum bilirubin ratio 0.5 to 0.8 (38.46%).

**Table 4: showing Sensitivity, specificity, positive predictive value and negative predictive value of the three parameters used in transudative pleural effusions.**

	Pleural fluid protein	Pleural to serum protein ratio	Pleural to serum bilirubin ratio
Sensitivity	100%	100%	85.71%
Specificity	86.66%	86.66%	100%
Positive predictive value	83.33%	83.33%	84.62%
Negative predictive value	100%	100%	84.62%

**Table 5: showing Sensitivity, specificity, positive predictive value and negative predictive value of the three parameters used in exudative pleural effusions.**

	Pleural fluid protein	Pleural to serum protein ratio	Pleural to serum bilirubin ratio
Sensitivity	86.66%	86.66%	100%
Specificity	100%	100%	85.71%
Positive predictive value	100%	100%	84.62%
Negative predictive value	83.33%	83.33%	100%

## DISCUSSION

Pleural effusion is a common entity in hospitalised patients and it indicates the presence of disease which may be pulmonary, pleural or extra-

pulmonary. A number of tests are needed to know the cause of exudative pleural effusion. On the other hand if the fluid is clearly a transudate, one need not to worry about the therapeutic maneuvers directed at the pleura and treat only congestive cardiac

failure, nephrosis, cirrhosis or hypoproteinemia (Light).<sup>[1]</sup> The present study was done to compare the diagnostic value of pleural fluid to serum protein ratio with pleural fluid to serum bilirubin ratio to differentiate transudative pleural effusion from an exudative pleural effusion. In the present study, it was found that there was statistically no significance of age distribution in male and female patients with pleural effusion. Burgess et al<sup>[7]</sup> carried out study to compare various parameters to identify exudative pleural effusions. The parameters used were total protein, albumin, cholesterol, LDH and total bilirubin. A total of 500 pleural effusions and serum samples were analysed and a reliable diagnosis could be made in 393 cases. Using Light's criteria 93% of effusions were correctly classified yielding a sensitivity and specificity of 98% and 83% respectively. In 318 patients, pleural to serum bilirubin ratio was calculated which showed best results when cut off value of 0.6 was used. Of all those 216 exudates, 175 were correctly classified and 62 of 102 transudates were correctly classified. Accuracy, sensitivity and specificity for detection of exudates were 75%, 81% and 61% respectively. The positive predictive value was 81% and negative value was 61%. Diagnostic value of pleural fluid protein and pleural fluid to serum protein ratio in differentiating pleural transudate from exudates: Light et al<sup>[1]</sup> using a cut off value of 3 gm% found erroneous classification in 8% of transudates and 11% of exudates and using a dividing line of 0.5 based on pleural fluid protein and serum protein ratio yielded better classification with sensitivity, specificity, positive predictive value and negative predictive value of 90%, 98%, 99% and 98% respectively. Vives et al<sup>[8]</sup> in their study concluded that pleural fluid protein when used as a parameter to distinguish pleural exudate from a transudate had a sensitivity, specificity, positive predictive value and negative predictive value of 84%, 82.1%, 94.9% and 56.1% respectively and when pleural fluid protein to serum protein ratio was used as parameter, it had sensitivity, specificity, positive predictive value and negative predictive value of 85.5%, 86.5%, 91.1% and 60.4% respectively. Heffner et al<sup>[9]</sup> concluded in their study that pleural fluid protein had sensitivity, specificity, positive predictive value and negative predictive value of 91.5%, 83.0%, 94.6% and 75% respectively. For pleural fluid to serum protein ratio, the sensitivity, specificity, positive predictive value and negative predictive value were 89.5%, 90.9%, 96.9% and 73.3 % respectively. Romero et al<sup>[10]</sup> concluded that pleural fluid to serum protein ratio had a sensitivity and accuracy of 91% and 92% respectively. Anne C.Tarn and Luth Lapworth<sup>[11]</sup> used various biochemical parameters to differentiate pleural transudates from exudates and concluded that Light criteria and pleural protein to serum protein ratio are equally useful parameters. Light criteria had a sensitivity, specificity, positive predictive value

and negative predictive value of 99%, 98%,99% and 98% respectively whereas pleural protein to serum protein ratio had sensitivity, specificity, positive predictive value and negative predictive value of 90%, 98%, 99% and 82% respectively. Kale AB et al<sup>[12]</sup> in their study analysed various biochemical parameters in a total of 50 cases of pleural effusion and observed that pleural fluid protein, its ratio to serum proteins and pleural fluid lactate dehydrogenase had excellent diagnostic accuracy in differentiating exudative from transudative pleural effusion. Patel A.K., Choudhary S.<sup>[13]</sup> in their study concluded that pleural fluid cholesterol and total serum proteins are simple, cost affective and useful parameters to differentiate transudative from exudative pleural effusion. The present study using classifying threshold of pleural fluid protein 3 gm%, the sensitivity, specificity, positive predictive value and negative predictive value for diagnosis of transudates was 100%, 86.66%, 83.33%, and 100% respectively and for exudates was 86.66%, 100%, 100%, and 83.33% respectively. So it is clear that results of our study are in agreement to the previous studies. Diagnostic significance of pleural fluid to serum bilirubin ratio in differentiating pleural transudate from an exudate. Meisel et al<sup>[5]</sup> concluded in their study that using a cut off value of 0.6, pleural fluid to serum bilirubin ratio yielded a sensitivity, specificity and positive predictive value of 96%, 83% and 85% respectively. Burgess et al<sup>[7]</sup> also used a cut off value of 0.6 in classifying 318 patients and correctly classified 81% of exudates and 60% of transudates with a sensitivity, specificity, positive predictive value and negative predictive value and accuracy of 81%, 61%, 81%, 60% and 75% respectively. Heffner et al<sup>[9]</sup> performed a meta analysis to examine the diagnostic significance of 8 biochemical parameters in classifying pleural effusion as transudate and an exudate and concluded that pleural to serum bilirubin ratio yielded a sensitivity, specificity, positive predictive value and negative predictive value of 84.3%, 61.1%, 82.3% and 64.4% respectively. Anne C. Tarn and Luth Lapworth<sup>[11]</sup> used various biochemical parameters to differentiate pleural transudates from exudates and concluded that Light criteria and pleural protein to serum protein ratio are equally useful parameters. Light criteria had a sensitivity, specificity, positive predictive value and negative predictive value of 99%, 98%, 99% and 98% respectively whereas pleural protein to serum protein ratio had sensitivity, specificity, positive predictive value and negative predictive value of 90%, 98%, 99% and 82% respectively. A pleural fluid: serum bilirubin ratio of 0.6 was suggested as an alternative to Light's criteria for distinguishing exudates. In a study of 51 pleural fluids the diagnostic sensitivity was 96% and 83% as compared to Light's criteria in which sensitivity was 90% and specificity was 82%. Hence it was confirmed that the best results were obtained using a

cut-off of 0.6, but in a group of 318 patients both the sensitivity and specificity for detection of an exudate were found to be much lower (81% and 61%, respectively). Rehman et al<sup>[14]</sup> studied 66 patients of pleural effusion and found that Light's criteria proposed by Light et al in 1972 are standard for differentiating transudative from exudative pleural effusions. All other parameters including pleural bilirubin to serum bilirubin ratio falsely classified some pleural effusions. Kale AB et al<sup>[12]</sup> in their study analysed various biochemical parameters in a total of 50 cases of pleural effusion and observed that pleural fluid protein, its ratio to serum proteins and pleural fluid lactate dehydrogenase had excellent diagnostic accuracy in differentiating exudative from transudative pleural effusion. Patel A.K., Choudhary S.<sup>[13]</sup> in their study concluded that pleural fluid cholesterol and total serum proteins are simple, cost effective and useful parameters to differentiate transudative from exudative pleural effusion.

## CONCLUSION

It was concluded that 12 cases were of transudative pleural effusion and 13 cases were of exudative pleural effusion in the present study, pleural to serum bilirubin ratio with a cut off value of 0.6, correctly classified all the 12 transudative pleural effusions but misclassified 2 of 13 exudative pleural effusions included in the study. The correlation of the levels of pleural to serum bilirubin ratio with aetiology was not consistent and varies so it was finally established that pleural to serum bilirubin ratio cannot establish the etiology of the pleural effusion. In the present study, pleural to serum bilirubin ratio had a sensitivity, specificity, positive predictive value and negative predictive value of 85.71%, 100%, 84.62% and 84.62% respectively for diagnosis of a transudate and sensitivity, specificity, positive predictive value and negative predictive value of 100%, 85.71%, 84.62% and 100% respectively for diagnosing an exudative pleural effusion which were better than those observed in previous studies. Therefore in the present study, it is concluded that pleural to serum bilirubin ratio is a simple, easy, cost effective and highly effective parameter to distinguish transudative from an exudative pleural effusion.

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