

To Study the Pleural Fluid Bilirubin and Serum Bilirubin RatioRonak Jain¹, Pawan Kumar Shukla^{2*}, Satish Motiwale³, Ravi Dosi⁴¹Postgraduate Student, Department of Respiratory Medicine, Sri Aurobindo Medical College & PGI, Indore, India²Postgraduate Student, Department of Respiratory Medicine, Sri Aurobindo Medical College & PGI, Indore, India³Professor & Head, Department of Respiratory Medicine, Sri Aurobindo Medical College & PGI, Indore, India⁴Asso. Professor, Department of Respiratory Medicine, Sri Aurobindo Medical College & PGI, Indore, India**Original Research Article*****Corresponding author**

Pawan Kumar Shukla

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Abstract: Many different conditions result in the accumulation of pleural fluid it may develop as a complication of many local & systemic diseases. Whether fluid accumulating in the pleural space is a transudate or an exudates, is determined by the widely used criteria proposed by Light et al i.e, ³ the pleural fluid to serum LDH & protein concentration ratio. Protein level of 3.0gm% and LDH level of 200 IU are used as dividing lines to separate transudation from exudate.⁵ This study has been conducted in the Department of Respiratory Medicine, Sri Aurobindo Medical College & PG Institute Indore (M.P.) From November 2016 to 30 April 2017. Total protein concentration (gram/dl) was measured by the "BIURET METHOD". Total bilirubin concentration (mg/dl) measurement is based on "JENDRASSIK" & GROF METHOD" using diazotized acid with DMSO Sulphanilic acid as an activator for total bilirubin. Transudates, Exudates, Neoplastic Exudate, Non-Neoplastic Exudate Using a dividing line of 0.5 to separate transudates from exudates, 2 of 19 (10.5%) are falsely classified as having exudates while 17 of 19 (89.5%) are correctly classified as transudates. 2 of 14 (14.2%) Neoplastic exudates are incorrectly classified as a transudates and 12 (85.7 %) were correctly classified as exudates. In non neoplastic exudates are group 28 cases (87.5 %) out of 32 were correctly classified as exudates while 4 cases (12.5 %) were incorrectly classified as transudates. In this study 65 cases of pleural effusion were included, detail history and physical examination done and all cases were investigated including skia gram chest and routine biochemical and histopathological examination. Thoracocentesis was done and pleural fluid taken for biochemical and microscopic examination. According to criteria defined by Light et al, a pleural fluid is classified as exudates or transudates, pleural fluid is classified as exudates which match any one of the following criteria.

Keywords: Pleural fluid, Billirubin, Serum.**INTRODUCTION**

Many different conditions result in the accumulation of pleural fluid it may develop as a complication of many local & systemic diseases. Effusion due to pleural disease is the local cause is the & effusion due to hemodynamic alteration or oncotic change is the systemic cause. It is important to diagnose the possible cause for appropriate management.

When a patient is found to have a pleural Effusion, the first step is to determine whether the effusion is a transudation or an exudates; a transudate pleural effusion occurs when systemic factors elevate the hydrostatic pressure in systemic or pulmonary circulation or disease decrease plasma colloid osmotic pressure [1]. Whether fluid accumulating in the pleural space is a transudation or an exudates, is determined by the widely used criteria proposed by Light *et al.* i.e,³ the pleural fluid to serum LDH & protein concentration

ratio. Protein level of 3.0gm% and LDH level of 200 IU are used as dividing lines to separate transudate from exudate [5].

A few recent studies, using pleural fluid Bilirubin value for distinguishing transudation from exudate, found that a pleural fluid to serum total bilirubin Concentration ratio of 0.6 or more occurs in the presence of exudates & below this ratio in the case of transudate [2]. As the bilirubin behaves like high molecular weight protein, in the presence of increased permeability of pleural capillaries, plasma bilirubin enters the pleural space. The object of this study is to the utility of the pleural fluid bilirubin level in separating exudate from transudation and to compare this parameter with criteria established by Light *et al* [6].

Aim and objectives

- To study the clinical profile of pleural Effusion Causes.
- Comparative analysis of pleural fluid to distinguish transudate & exudate by Biochemecal parameter.
- To study the pleural fluid Bilirubin and Serum Bilirubin ratio.
- To eweluate statistical significacance & accuracy of pleural fluid bilirubin level and ratio of Pleural fluid bilirubin & serum bilirubin for the separation of Transudate and Exudate.

REVIEW OF LITERATURE

The pleural space and the fluid within it are not under static condition. During each respiratory cycle the pleral pressure and the geometry of the pleural space fluctuate widely.

Anatomy of Pleura

Embryologically, the pleura are formed during the 4th to 6th weeks of intra-uterine life. Lungs project into the pleuroperitoneal canal which forms the visceral and parietal layers of the pleura.

A layer of compressed connective tissue which may be up to 100 micrometer thick separates it from the adipose tissue of the chest wall and from alveoli [7].

Physiology of Pleura

The net hydrostatics pressure that forces the fluid from the parietal pleura into the space is the systemic capillary pressure (30 H₂O) minus the negative pleural pressure (5cm H₂O) or 35 cm H₂O minus that in the pleural fluid (8cm H₂O) or 26cm H₂O.

Protein Exchange: - Normallly there is small amount of fluid with a protein content of approximately 1.5gm / 100ml present in the pleural space. This protein has come.

CAUSES OF PLEURAL EFFUSION

Transudative pleural effusion

- Congestive heart failure
- Pericardial Disease
- Cirrhosis of liver
- Neophrtic syndrome
- Peritoneal dialysis.
- Superior Venacaval obstruction.
- Myxedema
- Puimmonary Embolism.
- Urinothorax.

Exudative pleural effusion

- Neoplastic Diseases
- Innfacious diseases
- Pulmonary Embolization.
- Gatrointestinal diseases.
- Collagen Variceal sclerotherapy

Causes & mechanism of pleural effusion

A numbers of diseases have been found to be associated with pleural effusion.

Diagnosis of pleural effusion

A pleural effusion is suspected on grounds of clinical features & its presence is finally confirmed by physical examination, Radiological features, Sonography & CT chest.

Cilinal features

Small effusion is often symptom-less and even very large effusion, if they accumulate slowly may causes little or no discomfort to the patient. If the effusion is due to inflammatory disease, it often starts with pleuritic chest pain which may be relieved as the fluid accumulates [1]. The usual symptoms of a large effusion are shortness of breath, often accompanied by a dull ache the affected side. This is especially likely if the effusion is due to malignant disease of the pleura.

MATERIAL AND METHODS

This study has been conducted in the Department of Medicine, Sri Aurobindo Medical College & PG Institute (MRTB Hospital & Cancer Hospital) Indore (M.P.) from November 2016.

Selection criteria

Cases of pleural effusion undergoing first thoracocenteries were included in the study. Detail clinical history was taken and specification about past history of chest or extra thoracic diseases, family history of pulmonary tuberculosis, addiction particularly uses of tobacco & smoking was inquired. Subsequently all the patients were subjected for laboratory investigation which included:

- Hb, Estimation, T & D, ESR
- Urine – R/M
- Blood urea / Sugar / Estimation.
- Sputum routine microscopy & culture
- sputum for AFB
- X- ray chest PA view
- USG Abdomen
- ECG
- CT – Chest
- Pleural fluid – R/M
- Peural fluid estimation – Total protein / LDH / Bilirubin
- Blood estimation of total protein / LDH / Bilirubin
- Blood samples were taken at the time of pleural fluid aspiration, all biochemical parameters were determined with fully authomated / auto-analyzer.

Methods

Total protein concentration (gram/dl) was measured by the “BIURET METHOD”.

The lactate Dehydrogenase (LDH) actively by the “KINETIC METHOD”, according to the

recommendation of the Scandinavian Committee on enzyme

Total bilirubin concentration (mg/dl) measurement is based on "JENDVASSIK & GROF METHOD" using diazotized acid with DMSO as an activater for total bilirubin is a reagent.

Pleural fluid was classified with the help of clinical history, physical examination, finding of other systems & pre-established criteria of light et al into transudates & exudaete.

Criteria suggested by light et al characterized Exudative pleural fluid as having any one of the following: -

- A pleural fluid protein / serum protein ratio > 0.5.
- A pleural fluid LDH / Serum LDH ratio > 0.6
- A pleural fluid LDH > 200 IU

Values of pleural fluid bilirubin and serum rario was evaluated and compared with the above mentioned criteria to determine its specificity, sensitively and accuracy in classifying a pleural a fluid as exudates & transudate.

Transudates

This included congestive heart failure which was determine by an enlarged heart on X- ray chest, elevated JVP, pitting oedema or ventricular gallop & response to diurectice therapy.

Liver cirrhosis was diagnosed by clear evidence of liver cirrhosis in the absence of heart failure, malignancy or pulmonary infiltrates. Other causes of pleural transude -tes were nephorotic syndrome, hypoalbuminemia.

Exudates

Were again divided into two groups to see the difference of levels of different biochemical parameters into these groups.

Neoplastic Exudate

Required biopsy, cyto-pathological finding as proof of malignant tissue, CT-demonstration of a process involving to the pleura

Non-Neoplastic Exudate

Which included exudative peural fluid caused by tuberculosis confirmed by clinical examination, examination of peural fluid, presence of simultaneous tubercular parenchymal involment and following the pataint for response to anti-tuberclar therapy. Other causes of inflammatory non neoplastic exudates included – pleural effusion associated with pneumonia required that there be an acute febrile illness with purulent sputum and pulmonary infiltrates or consolidation with a unilateral effusion unaccompanied by clinical sings of congestive heart failure.

RESULTS

Table-1: Pleural fluid protein /serum protein ration in various groups

Ratio of Pleural Fluid and Serum Protein (Gms%)	Transudate	Exudate			Total
		Neoplastic	Non-neo plastic	Total	
0.00 – 0.10	–	–	–	–	–
0.11 – 0.20	2	2	–	–	2
0.21 – 0.30	10	10	–	–	10
3.1 – 4.0	5	5	–	–	5
4.1 – 5.0	–	–	4	6	6
5.1 –6.0	1	1	13	21	23
6.1 –7.0	1	1	9	11	12
7.1 – 8.0	–	–	4	5	5
8.1 >	–	–	2	2	2
Total	19	14	32	46	65

In transudate group mean ratio of pleural fluid protein / serum protein is 0.33 ± 0.11 (range 0.1 – 0.63) which is lower than in patients suffering from

malignant effusion – mean + SD 0.58 ± 0.07 (range 0.5 – 0.80) or other non-neoplastic exudates – mean + CD 0.63 ± 0.1 (range 0.45 – 0.90).

Table-2: Statistical Analysis

	Transudate	Exudate		Total
		Neoplastic	Non -neo plastic	
n	19	14	32	46
Mean	0.3405	0.5893	0.65	0.6315
S.D.	0.1143	0.0716	0.11	0.1051
t	10.1475			
P	<<0.001			
Inference	Highly significant increase			

Using a dividing line of 0.5 to separate transudates from exudates, 2 of 19 (10.5%) are falsely classified as having exudates while 17 of 19 (89.5%) are correctly classified as transudates. 2 of 14 (14.2%) Neoplastic exudates are incorrectly classified as a transudates and 12 (85.7 %) were correctly classified as exudates.

In non-neoplastic exudates are group 28 cases (87.5 %) out of 32 were correctly classified as exudates

while 4 cases (12.5 %) were incorrectly classified as transudates.

Using a dividing line of 0.5 pleural fluid protein/serum protein ratio has a sensitivity of 96 %, specificity of 74 %, positive predictive value of 87 %, negative predictive value of 89 %. (P value << 0.0001 highly significant).

Table-3: Nature of pleural effusion

Nature of effusion	No. of cases	%
Transudates	19	29
Exudate	46	71
Total	65	100

Out of 65 cases under study applying standard criteria led by Light *et al.* 19 (29 %) cases were classified as transudates and 46 (71 %) cases were classified as exudates.

DISCUSSION

Pleural fluid accumulating in the pleural space is a transudate or an exudative is determined by the widely used criteria of the pleural fluid to serum LDH and protein concentration ratio. Such a distinction is important for limiting the extent of the differential diagnosis of possible causes for this condition.

Recently, pleural fluid to serum of pleural effusion is included.

On analysis of sex prevalence – male predominance is seen. Male / female ratio is 1.9:1.

On studying prevalence of disease in various age groups, in this study it has been found to be maximum in age group between 21 – 30 years, and it is lowest in age group 11–20 years (8%) with etiological distribution; the commonest cause of pleural effusion is tuberculosis which is more common in our country [4]. In this study out of 65 cases 31 cases (47 %) has tuberculosis which confirm on the basis of history, clinical examination, by sputum examination for AFB, examination of pleural flues, excluding other causes. Presence of simultaneous tubercular parenchymal involvement and the response to antitubercular drugs.

Frequency of different symptoms presented by patients in which fever was the commonest symptom 68 % and it is one of the common presenting features of pleural effusion. Next common presenting complaints are cough and dyspnoea – 49 % and 45 % respectively. Pleuritic chest pain in 26 %, which is initial feature of inflammation of pleural which disappears with the appearance of fluid.

Pleural Fluid Protein / Serum Protein Ratio As A Parameter

In this study pleural fluid protein / serum protein ratio in transudate group had a mean ratio \pm SD

of 0.33 ± 0.11 (range 0.1 – 0.63), in neoplastic effusion mean ratio \pm SD 0.58 ± 0.07 (range 0.5 – 0.80) and in non-neoplastic exudative group mean ratio \pm SD 0.63 ± 0.1 (range 0.45 – 0.9). Light *et al* by using a dividing line of ratio >0.5 in their study found that only 1 out of 47 transudate and 10 % of exudates were misclassified, while in this study with this parameter 10.5 % of transudates and 13 % of exudates were falsely misclassified. Light *et al* in their study found that pleural fluid / serum protein ratio as a parameter had a sensitivity of 90 % and specificity of 98%. While in this study we found have a sensitivity of 96 % and specificity of 74 %.

Ldh level as a parameter to differentiate exudate from transudate

Since time of Wroblewski *et al.* who first observed that Malignant neoplastic cells in tissue culture contribute increasing amount of LDH to the medium and the other important finding that Pleural fluid LDH from effusions containing malignant cells was higher than was simultaneous serum LDH—Interest has been continuing till date that LDH has an important role in differentiating transudate from exudative pleural effusion.

Light *et al.* in their study with a cutoff point of > 200 LDH pleural fluid level found that parameter had a sensitivity of 67 % and specificity of 95 %, in our study found to have a sensitivity of 97 % and specificity of 64 %. Light *et al.* found a positive predictive value of 100 % and negative predictive value of 50 % while in this study positive predictive value was 78 % and negative predictive value 77 % (P value $<.0005$ highly significant).

CONCLUSION

The study was conducted in the Department of Medicine, Sri Eurobond Medical College and PG Institute, Indore (M.P.)

In these study 65 cases of pleural effusion were included, detail history and physical examination

done and all cases were investigated including skiagram chest and routine biochemical and histopathological examination. Thoracentesis was done and pleural fluid taken for biochemical and microscope examination.

According to criteria defined by Light et al, a pleural fluid is classified as exudates or transudates, pleural fluid is classified as exudates which match any one of the following criteria:

- Pleural fluid protein / serum protein ratio >0.5
- Pleural fluid LDH > 200 IU
- Pleural fluid LDH / Serum LDH ratio > 0.6

Pleural fluid bilirubin/serum bilirubin ratio was estimated to evaluate their efficiency as a parameter to separate transudates from exudates, and serve as alternative criteria for the same.

Conclusion of the study is as follows:

- The proportion the pleural effusion was highest in age group 21 – 30 years,
- Male predominance is seen, male / female ratio of 1.9 : 1.
- Common site of effusion in this study is Right Site 38 %, were left and bilateral are 34 % and 28 % respectively.

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