# Study of the Bilirubin content of Pleural Fluid in Exudative Pleural Effusion

**Pankaj Magar[1], Anandkumar B. Luniya[2], Swapnil Thorat[3] , Vipin Agrawal[4], Himanshu Pophale[5], Archana Kanwade[6]**

[1] Asssociate Professsor, Smt. Kashibai Navale Medical College and General Hospital, Pune, Maharashtra, India
[2] Associate Professor, Krishna Hospital and Medical Research Center, Karad, Maharashtra, India
[3,4] Senior Resident, Smt. Kashibai Navale Medical College and General Hospital, Pune, Maharashtra, India
[5] Professsor, Smt. Kashibai Navale Medical College and General Hospital, Pune, Maharashtra, India
[6] Associate Professor, Marathawada Mitra Mandal College of Engineering, Pune, Maharashtra, India

**Abstract:**

Pleural effusion is the term used to describe a collection of fluid in the pleural space. The fact that in many series, the percentage of pleural effusions with an unknown aetiology is close to 15% illustrates how challenging it is to identify the source. The current study looks for bilirubin levels to identify different exudative pleural effusion causes. For the trial, a total of 207 patients with exudative pleural effusion were enrolled. Along with regular tests, the bilirubin levels in the pleural fluids were studied, and the results were statistically compared. Pleural fluid bilirubin levels cannot be utilised as a marker for determining the causes of exudative pleural effusions, according to the current study, which was able to identify 148 exudates with a sensitivity of 71%.

**Keywords:** Plural fluid; Bilirubin; exudative effusion

**Introduction**

The etiological distribution of pleural effusions in different series depends on the geographical area, patient's age, advances in the diagnostic methods, and treatment of underlying causes. Exudative pleural effusions are a common diagnostic problem in clinical practise because the list of causes is fairly exhaustive [1]. Sometimes they can be inferred from the clinical picture[2]. In several series, infections and cancer are the most frequent causes.

The most frequent causes in the West are malignancy and parapneumonic effusions. In India, the most common pleural effusion is caused by tuberculosis, followed by malignant effusion and a very small number by parapneumonic effusions[3].

India has the highest incidence of tuberculosis, with two thirds of all cases occurring there [4]. India has a higher prevalence of tuberculosis than the west, where parapneumonic and malignant effusions are more common. After tubercular lymphadenitis, pleural TB is the second most common cause of extrapulmonary tuberculosis. Malignancy shares the clinical,

biochemical, and cytological characteristics of the pleural effusion. Exudates and effusions that are primarily lymphocytic can make it difficult to diagnose one another.

The distinction between TB and non-TB has been made using the adenosine deaminase enzyme activity[5], gamma interferon, polymerase chain reaction, lysozyme measurement of pleural fluid tubercular protein antibodies, and numerous cancer markers including CA-125, squamous cell carcinoma antigen, etc. To distinguish between benign and malignant effusions, further diagnostic procedures such flow cytometry, chromosomal analysis of cancer cells, LDH isoenzyme assays and tumour marker assays, immunohistochemistry testing, and carcinoembryonic antigen are used.

Despite the availability of all tests, a more intrusive diagnostic tool, such as a pleural biopsy or thoracoscope, may be required to establish a diagnosis[6,7]. Therefore, it is necessary to establish the best diagnostic and economical strategy for making a prompt diagnosis of exudative pleural effusion.

Pleural fluid to serum bilirubin ratio was employed by Meisel et al. [8] in their study of 51 individuals to discriminate between tranudates and exudes. They reported that the sensitivity, specificity, and positive predictive accuracy of the pleural fluid bilirubin levels are 0.96, 0.83, and 0.85 respectively.

Lesley J Burgers et al. [9] studied 500 patients, out of which 270 were exudates and 123 were tranudates and rest were dropouts. They found pleural to serum bilirubin ratio identified exudates with accuracy 75%, sensitivity 81%, and specificity of 61%

Raman Prabhakaran, Karthik Balan, Subbian Karthikeyan [10] used Pleural fluid bilirubin levels of 0.48 and pleural to serum bilirubin ratio cut off of 0.62 and studied 50 patients from India. They found a sensitivity of 96.42%, specificity of 90.9% and positive predictive value of 93.1%

Rao S [11]studied 55 patients and used the pleural to serum bilirubin ratio cut off of 1.1 and was able to differentiate tuberculosis versus malignant effusions.

We aim to carry forward this idea and look for bilirubin levels to distinguish various etiologies of exudative pleural effusions.

AIM

To study pleural fluid Bilirubin levels in exudative pleural effusion of various etiologies.

**Material and methods**

Analytic cross-sectional study was done on a total of 207 patients diagnosed with exudative pleural effusion admitted to respiratory medicine ward of our hospital. All diagnosed cases of exudative pleural effusion as per Lights criteria above the age group of 14 years were enrolled for the study. Patients who are suspected to be having pleural effusion on the basis of detailed history, clinical findings, were admitted in respiratory medicine ward of our hospital and a thorough work up including the routine blood counts, sputum examination ,X-rays, USG , Gene expert were done in the hospital. Patient was explained the requirement procedural steps, risk and complication in the language he or she best understood. Written informed consent was taken for the same from the patient. Thoracocentesis was performed as per the BTS guidelines.

Pleural fluid examinations were done.

Statistical analysis

For quantitative variables with non-normal distribution, the results were presented as mean +/- standard deviation (SD), and for categorical variables, as frequencies with percentages. The data are provided as medians with interquartile ranges for non-Gaussian distribution. The Chi-square, Fisher exact, and Krushal-Wallis tests were used appropriately, and the one-way Analysis of Variance (ANOVA) for continuous variables was employed to compare the groups. In the presence of confounding factors, the analysis of covariance was employed as a multivariate analysis to compare the hematochemical parameters across the three groups. Repeated measures ANOVA was utilised to compare differences between variables that were evaluated repeatedly. Statistics were considered significant with P values under 0.05. SPSS statistics was used for all data analysis.

**Results**

The study was conducted on 207 patients having exudative pleural effusion. Among these, majority were in the young age group. **Males** constituted around 73% of study group.

Total of seven diseases were found to be causing pleural effusion in these population. However due to less number of patients and for the ease of statistical analysis and these were grouped into 4 depending on the aetiology. They are tuberculosis malignant para mnemonic and miscellaneous.

Etiology wise distribution

|  | Total patients | Percentage |
|---|---|---|
| Tuberculosis | 115 | 55.55 |
| Malignancy | 39 | 18.84 |
| Parapneumonic | 33 | 15.94 |
| Miscellaneous | 20 |  |
| Total | 207 | 100 |

Pleural fluid levels

|  | Tuberculosis | Malignancy | Synpneumonic | Miscellaneous | P value |
|---|---|---|---|---|---|
| Bilirubin |  |  |  |  |  |
| Total | 0.48+/-0.27 | 0.56+/-0.26 | 0.47+/-0.17 | 0.93+/-1.41 | 0.002 |
| Direct | 0.22+/-0.13 | 0.26+/-0.09 | 0.26+/-0.10 | 0.31+/-0.20 | 0.024 |
| Indirect | 0.26+/-0.16 | 0.31+/-0.21 | 0.21+/-0.21 | 0.62+/-1.31 | 0.004 |
| Protein | 4.76+/-0.93 | 4.21+/-1.0 | 4.39+/-0.91 | 4.33+/-0.96 | 0.006 |
| Albumin | 2.67+/-0.48 | 2.61+/-0.59 | 2.60+/-0.54 | 2.48+/-0.42 | 0.452 |

Pleural fluid to serum bilirubin ratio wise distribution

|  | Tuberculosis | Malignancy | Synpneumonic | Miscellaneous | P value |
|---|---|---|---|---|---|
| Bilirubin |  |  |  |  |  |
| Total | 0.87+/-0.45 | 0.86+/-0.52 | 0.76+/-0.30 | 0.71+/-0.51 | 0.354 |
| Direct | 0.98+/-0.66 | 0.95+/-0.72 | 0.91+/-0.44 | 0.79+/-0.67 | 0.660 |
| Indirect | 0.90+/-0.63 | 0.90+/-0.55 | 0.71+/-0.44 | 0.78+/-0.68 | 0.370 |

Sensitivity and specificity of pleural fluid bilirubin levels at 0.48 cut off

| Total Bilirubin | Tuberculosis | Malignancy | Synpneumonic | Miscellaneous | Total |
|---|---|---|---|---|---|
| >0.48 | 84 | 21 | 24 | 8 | 137 (66%) |
| <0.48 | 31 | 18 | 9 | 12 | 70 (33%) |
| Sensitivity | 73.04% | 53.85% | 72.73% | 40% | |
| Specificity | 42.86% | 30.95% | 35.06% | 31.02% | |
| PPV | 61.76% | 15.33% | 17.52% | 5.84% | |
| P value | 0.028 | 0.1052 | 0.5054 | 0.018 | |

Sensitivity and specificity of pleural fluid bilirubin to serum bilirubin ratio

| Total Bilirubin/serum bilirubin ratio | Tuberculosis | Malignancy | Synpneumonic | Miscellaneous | Total |
|---|---|---|---|---|---|
| >0.6 | 90 | 26 | 23 | 9 | 148 |
| <0.6 | 25 | 13 | 10 | 11 | 59 |
| Sensitivity | 78.26% | 66.67% | 69.70% | 45% | |
| Specificity | 36.96% | 27.81% | 28.16% | 25.67% | |
| PDV | 60.81% | 17.33% | 15.54% | 6.08% | |
| NPV | 57.63% | 78.33% | 83.05% | 81.36% | |
| P value | 0.0241 | 0.548 | 0.926 | 0.0124 | |

**Discussion**

The first effort to differentiate pleural effusion on the basis of pleural fluid bilirubin levels was made by We shall at all in the year 1990. Since then, pleural fluid bilirubin levels have been used as an aid to lights criteria for differentiation of transudative and exudative pleural effusion, but even exudative pleural effusions have a long list of etiologies. On the basis of routine microscopy and biochemistry reports of pleural fluid, it is exceedingly difficult to distinguish between the different etiologies.

The goal of the current investigation was to distinguish between these causes using the ratios and amounts of bilirubin in pleural fluid. Pleural fluid to serum bilirubin ratio was only able to identify 148 exudative pleural effusions out of 207 in the current investigation, giving it a sensitivity of 71%. As a result, it is less sensitive than Lights criterion for identifying exudates.

It is clear from this study that a pleural fluid to serum bilirubin ratio of 0.6 provides the most sensitivity for aetiology classification, while a ratio of 1.1 provides the highest specificity. Since the highest level of sensitivity is attained at the expense of specificity, the highest level of sensitivity cannot be acquired from a single pleural fluid to serum bilirubin ratio. The ratio of serum bilirubin to pleural fluid cannot be utilised to categorise the causes of exudative pleural effusion.

The mean pleural fluid bilirubin levels overlap across exudative pleural effusion etiologies. The bilirubin level in pleural fluid cannot be utilised as a diagnostic tool to rule out different causes of exudative pleural effusion. The ratio of bilirubin in pleural fluid to bilirubin in serum cannot be utilised as a marker to distinguish between distinct exudative pleural effusion etiologies.

**References:**

[1]Richard W. Light, MD, Pleural Diseases, Sixth Edition

[2] Light, Richard W., Pleural Effusion, New England Journal of Medicine June 20, 2002 346(25):1971.

[3] Maldhure, B.R. & Bedarkar, S.P. & Kulkarnl, H.R. & Paplnwar, S.P.. (1994). Pleural biopsy and adenosine deaminase in pleural fluid for the diagnosis of tubercular pleural effusion. Ind J Tub. 41. 161-165.

[4] Park, K. (2007) Parks Textbook of Preventive and Social Medicine. 19th Edition, M/S Banarsidas Bhanot Publishers, Jabalpur, 798-806.

[5] Light RW. Establishing the diagnosis of tuberculous pleuritis. Arch Intern Med. 1998 Oct 12;158(18):1967-8.

[6] Aoki, Y., et al. "A comparison study of IFN-γ, ADA, and CA125 as the diagnostic parameters in tuberculous pleuritis." Respiratory medicine 88.2 (1994): 139-143.

[7] McKenna, James M., Arcot J. Chandrasekhar, and Robert E. Henkin. "Diagnostic value of carcinoembryonic antigen in exudative pleural effusions." Chest 78.4 (1980): 587-590.

[8] Meisel, Simcha, et al. "Pleural fluid to serum bilirubin concentration ratio for the separation of transudates from exudates." *Chest* 98.1 (1990): 141-144.

[9] Burgess, Lesley J., Frans J. Maritz, and JJ Frans Taljaard. "Comparative analysis of the biochemical parameters used to distinguish between pleural transudates and exudates." Chest 107.6 (1995): 1604-1609.

[10] Prabhakaran, Raman, Karthik Balan, and Subbian Karthikeyan. "Efficacy of Total Pleural Fluid Bilirubin And Ratio to Serum Levels, Pleural Fluid Cholesterol And Total Protein Level in Diagnosing Pleural Effusion Exudates And Transudates And Its Correlation with light's Criteria." IOSR Journal of Dental and Medical Sciences 16.4 (2017): 67-70.

[11] Rao, S. "Pleural Fluid To Serum Bilirubin Ratio As A Diagnostic Aid In Tuberculous And Malignant Pleural Effusions." Lung India 13.1 (1995): 20-21.