A comparative study of serum effusion albumin gradient and Light’s criteria to differentiate exudative and transudative pleural effusion

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ABSTRACT

Context: The incidence of pleural effusion is approximately one million per year. For diagnosing and treatment plan, pleural effusions have to be classified into transudate and exudate. If the diagnosis is not appropriate, it may result in severe complications. The established criterion for differentiating exudates from transudates is Light’s criteria. But there were some false positive results in case of transudative effusions when Light’s criteria were used. Aims: This study was done to determine the accuracy of serum effusion albumin gradient (SEAG) when compared to Light’s criteria in differentiating transudates and exudates. Settings and Design: It is a prospective observational study. In the present study, the sample size is 66 patients, in whom the SEAG was used for the classification of pleural effusions with a cut-off value of 1.2 g/dl. Methods and Materials: All the blood samples were collected and biochemical parameters like total protein, albumin, and LDH were analyzed in both serum and pleural fluid using XL 640 fully automated random access analyzer. Statistical Analysis Used: Results were analyzed using SPSS software version 20. Results: 20 of 22 transudates and 41 of 44 exudates were classified correctly using SEAG. The diagnostic accuracy of SEAG (92.42%) is better than Light’s criteria (87.87%) in differentiating both transudative and exudative effusions. Conclusions: The SEAG is superior to Light’s criteria in identifying the transudative effusions. It is also observed that Light’s criteria identified exudative effusions better than SEAG.

Keywords: Exudates, Light’s criteria, SEAG, transudates

Introduction

The most commonly seen lung pathology is pleural effusion due to different causes which may be a manifestation or a complication of respiratory or nonrespiratory disorder.¹ The most common causes of transudative effusions are congestive cardiac failure, cirrhosis of liver, pulmonary embolism, etc., whereas causes for exudative effusions are TB, pneumonia, carcinoma, etc.

Transudates have been differentiated from exudates by using established Light’s criteria since long.² As there are some misclassifications with this criterion, several alternative measurements have been proposed.³-⁷ Much work has not yet been done on serum-effusion albumin gradient (SEAG) unlike serum ascitic fluid albumin gradient (SAAG).

Subjects and Methods

1. Design of the study: Prospective observational study.
2. Setting: Medical units and TB and Chest disease wards.
3. Inclusion Criteria: The patients >14 years old, from medical

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and TB unit wards who had a therapeutic or diagnostic thoracocentesis performed between 2013 and 2015. Etiology of effusion was determined by the following criteria.

- Patients with pedal edema, radiological evidence of cardiomegaly, congested lungs, and responded to treatment for congestive heart failure were categorized as having congestive heart failure.
- Patients with pedal edema, decreased urine output, raised blood urea, and serum creatinine levels were diagnosed with renal failure.
- Patients with proteinuria, edema, and hypoalbuminemia were diagnosed as nephrotic syndrome.
- Patients with ascites and based on histopathological evidence, cirrhosis of liver was diagnosed.
- Malignant pleural effusion was diagnosed with evidence of malignant cells either in cytological examination or in biopsy specimen.
- Acute fever with purulent expectoration, pulmonary infiltrate on X-ray, and a good response to antibiotic treatment, or identification of the organism in the pleural effusion is diagnostic of parapneumonic effusion.

### Investigations done in all patients

Patients were investigated by physician for an elaborate number of tests like hemoglobin, total and differential counts, ESR, blood urea, serum creatinine, chest X-ray, ECG, pleural fluid total and differential counts, pleural fluid Gram staining, Ziehl–Neelsen staining, and culture and sensitivity for diagnosing transudates and exudates. Echocardiogram, 24-hour urinary protein, lipid profile, pleural fluid cytology for malignant cells, ultrasound chest, CT scan chest, pleural biopsy, and liver biopsy were specifically done in selected patients whenever required.

In the Department of Biochemistry as a part of this study, serum total protein, albumin, globulin, serum LDH, pleural fluid protein, albumin, globulin, and pleural fluid LDH were done to simplify this differentiation.

The following biochemical parameters were estimated and calculated: (1) The criteria of Light et al. (namely, pleural fluid/serum protein ratio, pleural fluid/serum LDH ratio, pleural fluid LDH concentration); (2) Albumin gradient (serum albumin concentration minus pleural effusion albumin concentration). When separating transudates from exudates, cut off points recommended in the literature were used.

The clinical presumption of the nature of the effusion (transudate or exudate) was based on all available information obtained just before performing thoracocentesis and was compared with that obtained from biochemical criteria. Biochemical parameters were determined using a selective discrete multichannel analyzer (Transasia, Erba Mannheim, XL-640). Total protein concentration was estimated using the biuret method. Determination of albumin was done using BCG dye-binding method (modified method of Doumas et al.). LDH level was measured using a kinetic ultraviolet optimized standard method according to IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) and DGKC (German Society of Clinical Chemistry) in semi auto analyzer (Agappe, Mispa Excel Chemistry Analyzer).

### Exclusion criteria

Traumatic hemothorax, postoperative effusion, and multiple disease.

### 4. Statistics Analysis

For continuous variables, mean and range were calculated. The values obtained for each of Light's criteria and SEAG were analyzed using the unpaired t-test to assess the significance of the separation between exudates and transudates. Sensitivity and accuracy were calculated to compare the efficiency of the two criteria. A P value of <0.05 is taken as a measure of significance. A P value of <0.01 is taken as highly significant. Results were analyzed using SPSS software version 20.

### Results

In the present study, the sample size includes 66 patients. The SEAG was used for the classification of pleural effusions with a cut-off value of 1.2 g/dl.

Light’s criteria of pleural fluid/serum protein ratio >0.5, pleural fluid/serum LDH ratio >0.6, and absolute pleural fluid LDH >200 IU/L are useful in differentiating the exudates and transudates.

### Discussion

Pleural fluid accumulation occurs when the pathological processes cause an imbalance of hydrostatic pressure gradient, capillary membrane permeability, and lymphatic capacity resulting in protein poor transudates or inflammatory exudates. The initial assessment of the patient with pleural effusion should include an ultrasonography-guided thoracocentesis to categorize the effusion as transudate or an exudate. The preliminary step in the analysis of pleural effusion is differentiation between exudates and transudates as it often gives an idea of the differential diagnosis and the need for further investigations. For this purpose, different diagnostic techniques are required which are invasive. Such invasive procedures like pleural biopsy are required for pleural effusions secondary to pleural abnormalities which are usually exudative. If the effusion is found to be exudative, invasive techniques such as cytopathology, pleural biopsy, and thoracotomy may be required so that a definitive diagnosis can be established and treatment is planned accordingly. Otherwise if the effusion is transudative, further testing is not needed as per the algorithm proposed by a recent study done by Milevoj Kopcinovic et al. and underlying causes like congestive heart failure, nephrosis, cirrhosis, or hypoproteinemia can be treated without any invasive procedure involving pleura or lung.
Demographic characteristics of this study show that more of exudative cases were found in the age group of 30–49 [Table 1]. Similar findings are seen in a study done by Sahi and Dwivedi in which they found that transudative pleural effusion appears in advanced age group but exudative pleural effusion is seen in early age groups.[8] If we see the sex distribution from Table 2, it is seen that exudative effusion is more common among male (68%) than female (62.5%).

Currently, the standard method for distinguishing pleural effusions is criteria proposed by Light et al. in 1972 (Pleural fluid/serum protein ratio > 0.5, pleural fluid/serum LDH ratio > 0.6, and absolute pleural fluid LDH > 200 IU/L—denote an exudates).[9]

In this study, the mean protein ratio (P < 0.001), the mean LDH ratio (0.002), and the mean pleural fluid LDH (0.007) are found to be significantly higher in exudates when compared to transudates, which are according to Light's criteria [Table 3].

The mean albumin gradients were significantly raised in transudates (1.85 ± 0.82 g/dl) as compared to exudates (0.82 ± 0.44 g/dl) with a P value of < 0.001, which is highly significant.

If the absolute pleural fluid values alone are taken instead of serum values for comparison, they may give erroneous results because the pleural fluid levels are influenced by changes in the serum. Though the Light's criteria has been the well-established criteria for differentiating transudates from exudates for the past several decades, there are several problems with the misclassifications.[2]

However, in recent years, several other parameters such as the pleural fluid cholesterol level and the pleural fluid to serum cholesterol ratio,[6,7] the alkaline phosphatase value,[8] pleural fluid to serum cholinesterase ratio,[10] and the pleural fluid to serum bilirubin concentration ratio[11] have been proposed in distinguishing the transudates from exudates more reliably than those of Light's criteria. All these alternative parameters still misclassified some effusions, and their superiority with respect to the Light's criteria is therefore insignificant. These misclassifications are mainly seen in patients with congestive heart failure using diuretics. There is elevated protein content in these effusions called as “Pseudo exudates” which is falsely classified as exudate as confirmed by Romero-Candeira et al.[8] To avoid these misclassifications, a new proposal was made “SEAG.”[12-14]

If the pleural effusion is categorized as exudative under Light's criteria, but the patient clinically appears to be of transudative type, Light himself later proposed that SEAG could be used.[13]

The present study applied this principle of adopting the SEAG as a means of distinguishing exudates from transudates. This study also includes comparing and analyzing the better way among the two criteria of SEAG and Light's criteria in the differential diagnosis of pleural effusion.

### Table 1: Comparison of true nature of exudates and transudates in different age groups

| Age in years | Exudates | Transudates | Total | In percentage |
|--------------|----------|-------------|-------|---------------|
| 14-29        | 8        | 4           | 12    | 18.2%         |
| 30-49        | 22       | 10          | 32    | 48.5%         |
| ≥50          | 14       | 8           | 22    | 33.3%         |
| Total        | 44       | 22          | 66    | 100%          |

### Table 2: Sex-wise distribution of exudative and transudative pleural effusions

| No of cases | Exudates | % of exudates | Transudates | % of transudates |
|-------------|----------|---------------|-------------|-----------------|
| Males       | 50       | 34            | 16          | 32              |
| Females     | 16       | 10            | 62.5        | 6               |

### Table 3: Comparison of exudates and transudates with respect to different parameters

| Parameters | Nature of effusion | n  | Mean±SD | Sig (2-tailed) |
|------------|--------------------|----|---------|----------------|
| SEAG       | Exudate            | 44 | 0.82±0.44 | .000           |
|            | Transudate         | 22 | 1.85±0.81 | .000           |
| Protein    | Exudate            | 44 | 0.73±0.10 | .000           |
|            | Transudate         | 22 | 0.44±0.20 | .000           |
| LDH ratio  | Exudate            | 44 | 1.60±1.37 | .010           |
|            | Transudate         | 22 | 0.82±0.76 | .002           |
| Pleural fluid LDH | Exudate | 44 | 1.08±1.45 | .041           |
|            | Transudate         | 22 | 0.45±0.62 | .007           |

### Table 4: Distribution of different cases of exudative and transudative pleural effusions

| Exudates | Transudates |
|----------|-------------|
| Tuberculosis | CHF | 9 |
| Malignancy  | Cirrhosis of liver | 8 |
| Synpneumonic effusion | Anemia and hypoproteinemia | 4 |
| Empyema | Constrictive Pericarditis | 1 |
| Total  | 44 (66.6%)   | 22 (33.3%) |
be maintained.\[16,17\] Whatever the albumin or globulin entered into pleural space will be cleared through subpleural lymphatics. The basis of transudate effusion is the imbalance between the hydrostatic and osmotic gradient.\[18\]

Exudative effusions are associated with inflammation of pleural membrane. This leads to disruption of pleural and pulmonary microvasculature but it is intact in case of transudative effusions. This gives rise to leakage of protein and fluid, resulting in loss of gradient. The parameters which we are analyzing for differentiation of transudates from exudates like albumin and protein are leaked into pleural fluid from serum but LDH comes from pleural fluid leukocytes within the pleural space itself.\[19-23\] Therefore, in this study, SEAG is considered for discriminating exudates from transudates as it is based on measurement of effusion and serum albumin concentration alone.\[23,24\] SEAG is thought to directly reflect the colloid osmotic pressure.

From Table 4, it is seen that out of 44 exudative pleural effusions, SEAG could rightly classify 41 effusions, but misclassified 1 case of tuberculosis and 2 cases of malignancy as transudates. Light's criteria could rightly classify all the 44 cases as exudative effusions.

From Table 5, it is imperative that out of 22 transudative pleural effusions, SEAG could rightly classify 20 of them as transudates. Light's criteria could classify only 14 of them as transudates and it misclassified 5 cases of CHF on diuretics, 2 cases of cirrhosis, and one case of constrictive pericarditis as exudates.

Tables 6 and 7 give the data required for calculating sensitivity, PPV, and accuracy showing number of true positive, false negative, and false positive cases in each category according to SEAG and Light's criteria.

From Tables 7, 8 and 9, it is seen that sensitivity of Light's criteria (100%) appears to be superior over SEAG (93.18) for classifying exudates, whereas SEAG (90.90%) is more sensitive in classifying transudates when compared to Light's criteria (70%).

Table 5: Comparison of final diagnosis of exudative pleural effusions with SEAG diagnosis and Light's criteria diagnosis

| Clinical final diagnosis          | SEAG diagnosis | Light's criteria diagnosis |
|----------------------------------|----------------|---------------------------|
| Tuberculosis                     | 29             | Tuberculosis 29           |
| Malignancy                       | 08             | Malignancy 08             |
| Synpneumonic effusion            | 06             | Synpneumonic effusion 06  |
| Empyema                          | 01             | Empyema 01                |
| Total                            | 44             | Total 44                  |

Table 6: Comparison of final diagnosis of transudative pleural effusions with SEAG diagnosis and Light's criteria diagnosis

| Final diagnosis                  | SEAG Diagnosis | Light's criteria diagnosis |
|---------------------------------|----------------|---------------------------|
| CHF                             | 09             | CHF 07                    |
| Cirrhosis of liver              | 08             | Cirrhosis of liver 08     |
| Anemia and hypoproteinemia      | 04             | Anemia and hypoproteinemia 04 |
| Constrictive pericarditis       | 01             | Constrictive pericarditis 01 |
| Total                           | 22             | Total 20                  |

On the other hand, the number of false positive cases is minimum with Light's criteria (PPV-100%) in classifying transudates when compared to SEAG (PPV-90.90%), whereas PPV (100%) for SEAG is more for classifying exudates when compared to Light's. But if the overall accuracy is taken into consideration, SEAG (92.42%) appears to be superior to Light's (87.87%) in differentiating transudates from exudates.

A study by Roth et al. had shown that in a series of 59 patients, used the SEAG for the classification of pleural effusions with a cut-off value of 1.2 g/dl, all the transudates and 39 of the 41 exudates were classified correctly. In their study, the SEAG had a sensitivity and specificity of 87%, and 92%, respectively. There are several recent studies which are having similar implications using SEAG as criteria.\[25,26\]

Other studies like Das and Krishna revealed that with SEAG value of 1.2 g/dl, could correctly classify 96.15% of exudates and 93.6% of transudates with a total misclassification of only 5% with a sensitivity and specificity of 96.1% and 93%.\[27\] In the study of Burgess et al., the gradient had a sensitivity and specificity of 87% and 92%, respectively.\[28\] In the study of Dhari et al.,\[29\] sensitivity for identifying exudates was 100% with Light's criteria but for transudates it was 87% which is comparable to our study. The corresponding sensitivity for identifying exudates and transudates with albumin gradient was 100%.

The advantage of using SEAG as criteria is that there is reduction in the number of patients with pleural effusion due to congestive heart failure being misclassified as exudates. There are certain studies which show that there are increased protein levels in pleural effusion of patients with congestive heart failure treated with diuretics. Chakko et al.\[29-31\] showed that treatment of patients with congestive heart failure and pleural effusions with diuretics leads to a concentration of pleural fluid protein which can be in the exudative range. Romero-Candeira et al. have found that the concentrations of the biochemical components commonly measured in pleural fluid increase progressively.
during diuretic therapy. Calculation of the serum-pleural fluid gradients for protein and albumin may be the most useful way to distinguish transudates from exudates in patients with congestive heart failure who have undergone diuresis. The underlying mechanism for protein leakage into pleural fluid from pleural microvasculature in patients with congestive heart failure on diuretics could not be established properly.

Pleural effusion in congestive heart failure is because of increased leakage of fluid into the pulmonary interstitium due to increased systemic venous pressure, which decreases lymphatic flow and therefore decreases pleural fluid. Diuretics are used for resolution of this fluid. There are different underlying mechanisms of action for diuretics. They decrease left atrial pressure so that less fluid would leak from the pulmonary microvasculature leading to decreased fluid formation and at the same time by decreasing systemic venous pressure, the lymphatic drainage would be increased. Finally, by decreasing systemic arterial pressure, a favorable pressure gradient could be established so that fluid may resolute via the pleural capillaries. Hence, in this process, there may be leakage of protein from the pleural microvasculature which is not due to primary lung or pleural pathology but secondary to diuretic usage which may be falsely considered as exudates. Eventually the diagnosis and treatment also get altered.

Therefore, to avoid this unnecessary mismanagement, SEAG has been adopted which is superior to Light as it is based on the calculation of gradient between serum and effusion rather than absolute values or ratios. Its superiority in avoiding misclassifications has been demonstrated in this study.

Table 7: Data for calculating sensitivity, PPV, and accuracy of SEAG

| SEAG Transudate | SEAG Exudate | Final diagnosis |
|-----------------|--------------|-----------------|
| 20 (TP)         | 3 (FN)       | 22 Transudates  |
| 2 (FN)          | 41 (TP)      | 44 Exudates     |
| 3 (FP)          | 2 (FP)       |                 |

Table 8: Data for calculating sensitivity, PPV, and accuracy of Light’s criteria

| Light’s Transudate | Light’s Exudate | Final Diagnosis |
|--------------------|-----------------|-----------------|
| 14 (TP)            | 8 (FP)          | 22 Transudate   |
| 0 (FP)             | 44 (TP)         | 44 Exudate      |
| 8 (FN)             | 0 (FN)          |                 |

Table 9: Sensitivity, PPV, and accuracy of SEAG and Light’s criteria (comparison)

|                  | SEAG            | Light’s Criteria |
|------------------|-----------------|------------------|
| Sensitivity      | 90.90%          | 70%              |
| PPV              | 93.18%          | 100%             |
| Accuracy         | 92.42%          | 87.87%           |

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Conflicts of interest
There are no conflicts of interest.

References
1. Gupta KB, Aggarwal SK, Kumar S, Manchanda M. Evaluation of plasma-pleural effusion albumin gradient for differentiating between pleural transudate and exudate. Ind J Tub 2003;50:23-8.
2. Chubb SP, Williams RA. Biochemical analysis of pleural fluid and ascites. Clin Biochem Rev 2018;39:39-50.
3. Beaudoin S, Gonzalez AV. Evaluation of the patient with pleural effusion. CMAJ 2018;190:E291-5.
4. Milevoj Kopcinovic L, Culej J, Jokic A, Bozovic M, Kocijan J. Laboratory testing of extravascular body fluids: National recommendations on behalf of Croatian society of medical biochemistry and laboratory medicine. Part 1- Serous fluids. Biochem Med (Zagreb) 2020;30.
5. Sahi N, Dwivedi NK. Role of various biochemical markers for the differential diagnosis of exudative and transudative pleural effusion and its comparison with traditional lights criteria. J Med Sci Clin Res 2019;7:407-11.
6. Hamm H, Brohan U, Bohmer R, Missmahl HP. Cholesterol in pleural effusions: A diagnostic aid. Chest 1987;92:296-302.
7. Valdes L, Pose A, Suarez J, Gonzalez-Juanatey JR, Sarandeses A, San José E, et al. Cholesterol: A useful parameter for distinguishing between pleural exudates and transudates. Chest 1991;99:1097-102.
8. Romero-Candeira S, Fernández C, Martín C, Sánchez-Paya J, Hernández L. Influence of diuretics on the concentration of proteins and other components of pleural transudates in patients with heart failure. Am J Med 2001;110:681-6.
9. Gupta KB, Ghelau V, Gupta PP, Arora P, Tandon S. Efficacy of pleural fluid alkaline phosphatase and its ratio to serum levels in distinguishing exudates from transudates. Lung India 2004;21:46-9.
10. Garcia-Pachon E, Padilla-Navas I, Sanchez JF, Jimenez B, Custardoy J. Garcia-Pachon E, et al. Pleural fluid to serum cholinesterase ratio for the separation of transudates and exudates. Chest 1996;110:97-101.
11. Meisel S, Shamis A, Thaler M, Nussinovitch N, Rosenthal T. Pleural fluid to serum bilirubin concentration ratio for the separation of transudates from exudates. Chest 1999;98:141-4.
12. Light RW, Mac Gregor I, Luelisinger PC, Bail WC. Pleural effusions: The diagnostic separatations of transudates and exudates. Ann Intern Med 1972;77:507-73.
13. Roth BJ, O’Meara TF, Cragan WH. The serum effusion albumin gradient in the evaluation of pleural effusion. Chest 1999;98:546-9.
14. Dhar MC, Chaudhary S, Basu K, Sau TJ, Pal D, K Mitra K. Serum effusion albumin gradient in the differential diagnosis of pleural effusion. Ind J Tub 2000;18:241-5.
15. Sahm SA. The pleura: State of the art. Am Rev Respir Dis 1988;138:184-234.
16. Black LF. The pleural space and pleural fluid. Mayo Clin Proc 1972;47:493-506.
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17. Broaddus VC, Light RW. What is the origin of pleural transudates and exudates. Chest 1992;102:658-9.
18. Pistolesi M, Miniati M, Giuntini C. Pleural liquid and solute exchange. Am Rev Respir Dis 1989;140:825-47.
19. Zinneman HH, Johnson JJ, Lyon RH. Proteins and microproteins in pleural effusions. Am Rev Respir Dis 1957;76:247-55.
20. Shallenberger DW, Daniel TM. Quantitative determination of several pleural fluid proteins. Am Rev Respir Dis 1972;106:1212.
21. Broaddus VC, Staub NC. Pleural liquid and protein turnover in health and disease. Semin Respir Med 1987;9:7-12.
22. Light RW. Pleural Disease. 3rd Baltimore: Williams and Wilkins; 1995.
23. Jay SJ. Diagnostic procedures for pleural disease. Clin Chest Med 1985;6:33-4.
24. Light RW. Pleural Diseases. 2nd ed. Philadelphia: Lea and Febiger; 1990. p. 9-19.
25. Palanikumaran V, Kasipandian S, Natarajan M. Evaluation of serum pleural fluid albumin gradient for differentiation of transudate and exudate. J Evol Med Dent Sci 2017;6:3711-6.
26. Sujatha G, Vindhya P, Kalyan Kumar K. Significance of serum pleural effusion albumin gradient in differentiating transudative and exudative pleural effusions. Int J Adv Med 2017;4:457-62.
27. Das AK, Krishna B. A study on significance of serum effusion albumin gradient in the differential diagnosis of pleural effusion. J Med Educ Res 2009;11.
28. Burgess LJ, Maritz FJ, Taljaard FFJ. Comparative analysis of the biochemical parameters used to distinguish between pleural transudates and exudates. Chest 1995;107:1604-9.
29. Chakko SC, Caldwell SH, Sforza PP. Treatment of congestive heart failure: Its effect on pleural fluid chemistry. Chest 1989;95:798-802.
30. Chakko S. Pleural effusion in congestive heart failure. Chest 1990;95:521-2.
31. Pillay VKG. Total proteins in serous fluids in cardiac failure. S Afr Med J 1965;39:142-3.