Original Article

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.

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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.[2] The initial assessment of the patient with pleural effusion should include an ultrasonography-guided thoracocentesis to categorize the effusion as transudate or an exudate.[3] 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.*[4] 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.[5] 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).[8]

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,[9] 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.[12]

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	68	16	32
Females	16	10	62.5	6	37.5

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	0.8249±0.44	.000
	Transudate	22	1.8491±0.81	.000
Protein Ratio	Exudate	44	0.7312±0.10	.000
	Transudate	22	0.4422±0.20	.000
LDH Ratio	Exudate	44	1.6692±1.37	.010
	Transudate	22	0.8231±0.76	.002
Pleural Fluid LDH	Exudate	44	1080.3±1485.49	.041
	Transudate	22	405.86±362.64	.007

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

Exudates		Transudates	
Tuberculosis	29	CHF	9
Malignancy	8	Cirrhosis of liver	8
Synpneumonic effusion	6	Anemia and hypoproteinemia	4
Empyema	1	Constrictive Pericarditis	1
Total	44 (66.66%)	Total	22 (33.33%)

In this study, the mean albumin gradients were significantly ($P < 0.001$) raised in transudates (1.85 ± 0.82 g/dl) as compared to exudates (0.82 ± 0.44 g/dl) [Table 3]. The SEAG was used for the classification of pleural effusions with a cut-off value of 1.2 g/dl. In 1990, Roth *et al.*[13] assessed the diagnostic value of serum-pleural effusion albumin gradient and found that this gradient was significantly higher in patients with transudative than exudative pleural effusions. To identify exudative from transudative, it is now well-accepted that SEAG of <1.2 g/dl can be interpreted as an exudate.

It is a known fact that pleural effusion arises from pleural capillaries.[15] There is always an exchange of fluid between pleural space and capillaries maintaining a steady flux between extravascular and intravascular compartment. The protein content of pleural fluid is lower when compared to serum as the membrane is semipermeable so that the required gradient can

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.[19-22] 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 righty 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%). 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 Dhar *et al.*,[14] 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

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	28	Tuberculosis	29
Malignancy	08	Malignancy	06	Malignancy	08
Synmpneumonic effusion	06	Synpneumonic effusion	06	Synpneumonic effusion	06
Empyema	01	Empyema	01	Empyema	01
Total	44	Total	43	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	CHF	04
Cirrhosis of liver	08	Cirrhosis of liver	08	Cirrhosis of liver	06
Anemia and hypoproteinemia	04	Anemia and hypoproteinemia	04	Anemia and hypoproteinemia	04
Constrictive pericarditis	01	Constrictive pericarditis	01	Constrictive pericarditis	0
Total	22	Total	20	Total	14

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

SEAG Transudate	SEAG Exudate	Final diagnosis
20 (T.P)	3 (F.N)	22 Transudates
2 (F.N)	41 (T.P)	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 (T.P)	8 (F.P)	22 Transudate
0 (FP)	44 (T.P)	44 Exudate
8 (FN)	0 (FN)	

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

		SEAG	Light's Criteria
Sensitivity	Transudate	90.90%	70%
	Exudate	93.18%	100%
PPV	Transudate	90.90%	100%
	Exudate	100%	84.61%
Accuracy		92.42%	87.87%

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.

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Conflicts of interest

There are no conflicts of interest.

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