Original Research Article

Significance of serum-pleural effusion albumin gradient in differentiating transudative and exudative pleural effusions in comparison to light’s criteria

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ABSTRACT

Background: Approximately one million patients develop pleural effusion every year. It is a common clinical disorder and is either a manifestation or a complication of one or other respiratory or non-respiratory disorders. It leads to serious prognosis, if not diagnosed and treated properly. To calculate SEAG and Light’s criteria and to compare SEAG with Light’s criteria in analyzing pleural effusions.

Methods: A total of hundred patients were selected for the study. Pleural fluid of patients who met the inclusion and exclusion criteria were collected, when pleural fluid is being tapped for diagnostic thoracocentesis. Venous blood sample was collected along with diagnostic thoracocentesis or within 24 hours of thoracocentesis. Written informed consent was obtained from them for thoracocentesis.

Results: In our study we compared the clinical outcome with outcome as per Pleural fluid/Serum protein ratio (p value of <0.0001), pleural fluid/serum LDH (p value of <0.0001) and pleural fluid LDH (p value of <0.0001) separately and the p values were statistically significant. The sensitivity, specificity, PPV and NPV of Light’s criteria were 77.2%, 100%, 100%, 93.9% respectively. We compared Light’s criteria outcome with clinical outcome and the difference was statistically significant (p value of <0.0001). SEAG showed 100% sensitivity, 97.43% specificity, 91.6% PPV and is 91.66% and NPV is 100%. We compared the clinical outcome with SEAG and there was statistically significant difference (p value of <0.0001). We compared SEAG with Light’s criteria and the difference was statistically significant (p <0.0001). We compared Light’s plus pleural fluid protein gradient with SEAG and the difference is statistically significant (p value of <0.0001).

Conclusions: SEAG is more sensitive for classifying transudates and more specific for exudates than Light’s criteria.

Keywords: Exudate, Effusion, Pleural effusion, Transudate

INTRODUCTION

It is estimated that every year one million people have pleural effusion.¹ Pleural effusion is very common. It results as a complication of respiratory disorder or non respiratory disorder. It can also result as a manifestation of respiratory disorder or non respiratory disorder.² If pleural effusion is not diagnosed and treated at an early stage, it can lead serious complication and prognosis may be hampered.
Whenever a physician sees a patient with pleural effusion, he should try to find out the cause in terms of whether it is transudate or exudates. The altered systemic factors can lead to transudate pleural effusion that influence the pleural fluid formation and absorption. Left ventricular failure and cirrhosis of liver are considered as important causes of transudate pleural effusion. The altered local factors can lead to exudates pleural effusion that influence the pleural fluid absorption and formation. Bacterial pneumonia, viral infection etc. are considered as important causes of exudates pleural effusion.

Hence classification of pleural effusion as transudate or exudates is important from treatment point of view. Light’s criteria is used to classify the pleural effusion. As on whole, the exudates type of pleural effusion should fulfil at least one criteria and the transudate type of pleural effusion should not fulfil any criteria for proper classification.

Sometimes transudates can be classified as exudates as the origin is uncertain. Pleural capillaries are considered as the source of pleural effusion. The fluid gets transferred from across the pleural space. This is due to the semi permeable nature of endothelium in the pleural area. The diffusion is due to components like globulin and albumin in the serum and the sub pleural lymphatic vessels clear them. The causes of exudates pleural effusion are swelling and reduced diameter of microvasculature. The in case of transudate pleural effusion there is no swelling and reduced diameter of microvasculature. Thus increased fluid leakage is seen in exudates type of pleural effusion. But in transudate pleural effusion, there is loss of balance of hydrostatic forces and loss of balance of oncotic forces.

Roth et al stated that this principle can be applied to distinguish between transudate and exudates type of pleural effusion.

Hence present study was undertaken to calculate SEAG and Light’s criteria and to compare SEAG with Light’s criteria in analysing pleural effusions.

METHODS

The sources of data are the patients with pleural effusion based on clinical and radiological basis from the departments of General medicine, Pulmonology, Gastroenterology and Nephrology, Kamineni Hospitals, LB Nagar, Hyderabad, from October 2012 to October 2014.

A total of hundred patients were selected for the study. Pleural fluid of patients who met the inclusion and exclusion criteria was collected, when pleural fluid is being tapped for diagnostic thoracentesis. Venous blood sample was collected along with diagnostic thoracentesis or within 24 hours of thoracentesis. Written informed consent was obtained from them for thoracentesis.

The patients were followed up to their discharge and classified as exudates or transudates based on the clinical features, microscopy, cytology, biopsy, pleural fluid culture, radiography & response to treatment and were included in the study.

Inclusion criteria

Patients with clinical and radiological evidence of pleural effusion

Exclusion criteria

- Age less than 14 years
- Pregnant females
- Old diagnosed cases of Pleural effusion

Informed consent was obtained from all the subjects included in the study. Blood Samples were collected by venipuncture under aseptic conditions in red capped vacutainers. Pleural fluid is collected in sterile containers from the patient when they are undergoing diagnostic thoracentesis observing standard safety & aseptic precautions. The blood was allowed to clot.

Blood and pleural fluid were centrifuged for the estimation of total protein & LDH on a fully automated system within 3-4 hours of sample collection. Total proteins were estimated by Biuret method and serum albumin was measured by BCG method. LDH was estimated by modified IFCC method in which rate of oxidation of NADH to NAD was measured as a decrease in absorbance that was proportional to the LDH activity in the sample.

Chest X rays were taken for all the subjects. Ultrasound chest and CT chest were asked in selected patients. By sputum examination [sputum for AFB], Bronchoscopy and BAL, ADA level in the pleural fluid more than 40 U/L, more than 70 U/L (highly suggestive of TB) we diagnosed a case as Tuberculosis.

Malignancy was diagnosed based on the malignant cells in the pleural fluid, Paramalignant effusions based on the underlying malignancy, CECT chest and CT guided biopsy. Para pneumatic effusions were diagnosed based on the sputum examination [gram stain] and cultures for organisms, USG or CT chest, and resolution with antibiotics.

Pancreatitis was diagnosed based on Serum amylase and lipase levels, CT abdomen and Pleural fluid/Serum amylase ratio of 1.0. PPF is diagnosed based on the pleural fluid amylase levels and MRCP. Congestive cardiac failure is diagnosed based on the clinical presentation, 2D ECHO, past history and resolution of effusions with diuretics. Cirrhosis of liver with ascites is
diagnosed based on the history, clinical details and Ultrasound abdomen. Nephrotic syndrome was diagnosed based on 24 hour urine protein and serum albumin levels. Patients without clinical diagnosis were excluded from the study.

Ethics committee of our institution has reviewed the protocol and approved the study. Informed consent was taken from all the patients in the study group.

RESULTS

The present study was conducted on 100 patients with Pleural effusion from the Departments of General medicine, Pulmonology, Nephrology and Gastroenterology, Kamineni hospital, L. B. Nagar, Hyderabad between October 2012 and October 2014.

The mean age of patients in our study group was 51.85±18.53 years. 57(57%) were males and 43(43%) were female subjects.

Out of 78 subjects, 25 [32%] were Para-pneumonic effusions, 21 [27%] were due to Tuberculosis, 19 [25%] were Para-malignant effusions, 7 [9%] were Malignant effusions, 4 [5%] were due to Pancreatitis, 1 [1%] was due to pancreatico-pleural fistula and the other one [1%] was due to esophageal rupture (Figure 1).

Out of 22 subjects with transudative effusions 15 [68%] were due to congestive cardiac failure, 2 [9%] each with cirrhosis of liver with ascites, chronic kidney disease, nephrotic syndrome and 1 [5%] with hypoalbuminemia rupture (Figure 2).

The mean of serum protein, serum albumin and serum LDH in our study group are 5.74±1.149 g/dl, 2.96± g/dl, 283.29 U/L respectively (Table 1).

The mean values of Pleural fluid protein, albumin and LDH are 3.78±1.662 g/dl, 2.13±0.988 g/dl, 361.42±246.330 U/L (Table 2).

The mean values for pleural fluid protein/serum protein, pleural fluid LDH/Serum LDH are 0.49±0.249 and 0.91±0.970 respectively (Table 3).

Table 1: Distribution of serum variables.

| Statistics       | Serum total protein g/dl | Serum albumin g/dl | Serum LDH U/L |
|------------------|--------------------------|--------------------|---------------|
| N                | 100                      | 100                | 100           |
| Mean             | 5.74                     | 2.96               | 283.29        |
| Median           | 5.50                     | 2.50               | 261.50        |
| Std. deviation   | 1.149                    | 0.706              | 126.408       |
| Minimum          | 4                        | 2                  | 75            |
| Maximum          | 9                        | 6                  | 900           |

Table 2: Distribution of pleural fluid variables.

| Statistics       | Pleural fluid protein g/dl | Pleural fluid LDH U/L | Pleural fluid albumin g/dl |
|------------------|---------------------------|-----------------------|-----------------------------|
| No. of observations | 100                       | 100                   | 100                          |
| Mean             | 3.78                      | 361.42                | 2.13                         |
| Median           | 3.50                      | 340.00                | 2.00                         |
| Std. deviation   | 1.662                     | 246.330               | 0.988                        |
| Minimum          | 2                        | 58                   | 0                            |
| Maximum          | 9                        | 1600                 | 7                            |

Table 3: Distribution of light’s criteria ratios.

| Statistics       | Pleural fluid protein/ Serum protein | Pleural fluid LDH/ Serum LDH |
|------------------|--------------------------------------|-----------------------------|
| No of observations | 100                                  | 100                         |
| Mean             | 0.49                                 | 0.91                        |
| Median           | 0.50                                 | 0.50                        |
| Std. deviation   | 0.249                                | 0.970                       |
| Minimum          | 0                                    | 0                           |
| Maximum          | 2                                    | 5                           |
Table 4: Distribution of pleural fluid/serum protein ratio.

|                | No of patients | % of patients |
|----------------|----------------|---------------|
| Transudate     | 24             | 24            |
| Exudate        | 76             | 76            |

In our study we found out that taking pleural fluid protein/serum protein cut off as 0.5 (>0.5 as exudate and <0.5 as transudate) there are 76% exudates and 24% transudates (Table 4).

We compared the clinical outcome with Pleural fluid protein/Serum protein ratio outcome and the P value of <0.0001 was significant (Table 5).

Table 5: Pleural fluid/serum protein versus clinical outcome.

| Category-exudates or transudate | No. of cases as per clinical outcome | No. of cases differentiated by pleural fluid/Serum protein | No. of cases truly classified | No. of cases misclassified classified | P value       |
|----------------------------------|-------------------------------------|----------------------------------------------------------|-----------------------------|--------------------------------------|---------------|
| Exudate                          | 78                                  | 76                                                       | 73                          | 3 (3.9%)                             | <0.0001       |
| Transudate                       | 22                                  | 24                                                       | 22                          | 2 (8.3%)                             | Significant   |

In present study we found out that taking pleural fluid protein/serum protein cut off as 0.6 (>0.6 as exudate and <0.6 as transudate) there are 83% exudates and 17% transudates (Table 6). Comparing Pleural fluid protein/serum protein ratio, P value of <0.0001 is significant (Table 7).

Pleural fluid LDH of more than 220 U/L is taken as an exudative effusion and below that as transudative effusion. Thus the patients with transudate were 28% and patients with exudate were 72% (Table 8).

Table 6: Distribution of pleural fluid/serum LDH outcome.

|                | No of patients | % of patients |
|----------------|----------------|---------------|
| Transudate     | 17             | 17            |
| Exudate        | 83             | 83            |

Table 7: Pleural fluid/serum LDH Vs clinical outcome.

| Category- exudate or transudate | No. of cases as per clinical outcome | No. of cases differentiated by pleural fluid/serum LDH | No. of cases truly classified | No. of cases misclassified classified | P value       |
|----------------------------------|-------------------------------------|------------------------------------------------------|-----------------------------|--------------------------------------|---------------|
| Exudate                          | 78                                  | 83                                                   | 83                          | 0                                    | <0.0001       |
| Transudate                       | 22                                  | 17                                                   | 12                          | 5(29.4%)                             | Significant   |

Pleural fluid LDH of more than 220 U/L is taken as an exudative effusion and below that as transudative effusion (Table 9). Light’s criteria classified 83 patients under exudative effusions and 17 patients under transudative effusions (Table 10).

Table 8: Distribution of pleural fluid LDH outcome.

|                | No of patients | % of patients |
|----------------|----------------|---------------|
| Transudate     | 28             | 28            |
| Exudate        | 72             | 72            |

Table 9: Pleural fluid versus clinical outcome.

| Category- exudate or transudate | No. of cases as per clinical outcome | No. of cases differentiated by Pleural fluid LDH>220U/L | No. of cases truly classified | No. of cases misclassified classified | P value       |
|----------------------------------|-------------------------------------|------------------------------------------------------|-----------------------------|--------------------------------------|---------------|
| Exudate                          | 78                                  | 72                                                   | 65                          | 7(9.7%)                              | <0.0001       |
| Transudate                       | 22                                  | 28                                                   | 27                          | 1(3.5%)                              | Significant   |

P value of <0.0001 is significant.
The sensitivity and specificity of Light’s criteria for the separation of transudates is 77.2% and 100% respectively. Positive predictive value and Negative predictive value are 100% and 93.97% respectively. And for exudates the sensitivity, specificity, positive and negative predictive value are 100%, 77.2%, 93.97% and 100%. P value of <0.0001 is significant. We compared Light’s criteria outcome with Clinical outcome and the p value was statistically significant (Table 11).

Table 10: Distribution of Light’s criteria outcome.

|       | No. of patients | % of patients |
|-------|----------------|---------------|
| Transude | 17            | 17.0          |
| Exudate | 76            | 83.0          |

SEAG classified 24 [24%] subjects as transudates, 76 [76%] as exudates (Table 12).

Table 11: Light’s criteria versus clinical outcome.

| Light’s criteria outcome | Clinical outcome | Total |
|-------------------------|------------------|-------|
| Transude                | Exudate          |       |
| Transude                | 17 (TP)          | 0 (FP) |
| Exudate                 | 5 (FN)           | 78 (TN) |
| Total                   | 22               | 100   |

The commonest cause of transudative effusions was Congestive heart failure (68%). Our results are comparable to the study of Roth et al,11 found a male to female ratio of 1.32:1. Roth et al 3 found a ratio of 1.68:1.11 Gongati P et al found a male to female ratio 2:1.12

Table 12: Distribution of SEAG outcome.

|       | No. of patients | % of patients |
|-------|----------------|---------------|
| Transude | 24            | 24.0          |
| Exudate | 76            | 76.0          |

Table 13: SEAG versus clinical outcome.

| Light’s criteria outcome | Transude | Exudate | Total |
|-------------------------|----------|---------|-------|
| SEAG criteria           | Transude | Exudate |       |
| Transude                | 17       | 7       | 24    |
| Exudate                 | 0        | 76      | 76    |
| Total                   | 17       | 83      | 100   |

Table 14: SEAG versus light’s criteria.

| Light’s criteria outcome | Transude | Exudate | Total |
|-------------------------|----------|---------|-------|
| SEAG criteria            | Transude | Exudate |       |
| Transude                | 17       | 7       | 24    |
| Exudate                 | 0        | 76      | 76    |
| Total                   | 17       | 83      | 100   |

For classifying transudates SEAG is 100% sensitive and 97.43% specific. Positive predictive value is 91.66%; Negative predictive value is 100%. For exudates the sensitivity is 97.3%, specificity is 100%, positive predictive value is 100%, and negative predictive value is 91.66%. P value of <0.0001 is significant. SEAG outcome is compared with clinical outcome and the p value of <0.0001 is statistically significant (Table 13).

P value of <0.0001 is significant. In our study we compared SEAG outcome with that of Light’s criteria and the p value was statistically significant (Table 14).

DISCUSSION

The mean age of study population was 51.3±18.53 years. Para-pneumonic effusions were seen in all age groups maximum between 20 and 50 years. Tuberculous effusion was equally seen in all age groups. Roth et al found that the average age group was 61 years.11 Mean ages of the patients was 55.64±17.081 years in the study done by Gongati P et al.12

We found that a male to female ratio of 1.32:1. Roth et al 3 found a ratio of 1.68:1.11 Gongati P et al found a male to female ratio 2:1.12

Out of 100 pleural effusions analyzed the maximum (78%) are exudative effusions, out of which the most commonly seen are due to Pneumonia, i.e. Para-pneumonic effusions (27%) followed by Tuberculosis (27%) followed by Para-malignant (25%) effusions. These results are comparable to the study of Gongati P et al, Roth et al, Dhar et al reported in his study that the commonest cause of exudative effusion was tuberculosis (42%).11-13

The commonest cause of transudative effusions was Congestive heart failure (68%). Our results are comparable to the study of Roth et al.11

3 out of 76 exudates (3.94%) were misclassified, one para-pneumonic effusion, one para-malignant effusion and one pancreatico-pleural fistula. 2 (CHF) out of 24 transudates (8.33%) were misclassified. Total misclassification rate is 5%. Gupta KB et al 1 found that 4 out of 12 transudates (33.3%) and 7 out of 48 exudates (14.5%) were misclassified.1 Das AK et al observed that 5 of the exudates & 3 transudates were falsely classified. Total misclassification of 20% occurred.14

In our study pleural fluid LDH/serum LDH > 0.6 (i.e. >0.6 as exudates and < 0.6 as transudates) separated 17 as transudates and 83 as exudates. 5 transudates (four with CHF and one cirrhosis of liver) were misclassified as exudates (29.41%). All the exudates were correctly classified. The difference was statistically significant (p<0.0001) when the LDH ratio was compared to the clinical outcome. Our results are comparable to the study done by Gupta KB et al, Mangaraj M et al, Das AK et al, Sunanda V et al.1,14-16

Sensitivity, Specificity, Positive Predictive value and Negative predictive value of Lights criteria for classifying transudates are 77.2%, 100%, 100%, 93.9% respectively. In classifying exudates the sensitivity and
specify are 100% and 77.2%, Positive and Negative predictive values are 93.97% and 100% respectively. There was a statistically significant difference (p<0.0001) between the light’s criteria and the clinical outcome. Our results are comparable to the study by Roth et al, and Dhar et al.11,13

For classifying transudates SEAG is 100% sensitive and 97.43% specific. Positive predictive value is 91.66%, Negative predictive value is 100%. For exudates the sensitivity is 97.3%, specificity is 100%, positive predictive value is 100%, and negative predictive value is 91.66%.

SEAG is more sensitive for classifying transudates and more specific for exudates than Light’s criteria. There was a statistically significant difference (p<0.0001) between the SEAG criteria and the clinical outcome. Our results are comparable to the study done by Roth et al, and Dhar et al.11,13

SEAG correctly classified all the transudates but misclassified two exudates (para malignant effusions) as transudates. SEAG is more sensitive for transudates and more specific for exudates than Light’s criteria.

**CONCLUSION**

It was found that SEAG is a good parameter to differentiate the groups. SEAG is more sensitive than Light’s criteria for classifying transudates and is more specific for exudates. SEAG was found to be a better criterion than Light’s for classifying transudates. Also only single parameter of pleural fluid is used in SEAG criteria which is easy to apply when compared to Light’s criteria where three parameters are needed. Light’s criteria with pleural fluid protein gradient is better than SEAG and very promising for classifying pleural effusions.

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