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Comparison Of Serum-pleural Fluid Albumin Gradient And Alkaline Phosphatase Against Light's Criteria For Distinguishing Transudates From Exudates

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Abstract

Background: The delineation of pleural effusions as being either transudate or exudate is the initial and crucial step in the diagnosis of pleural effusions. The aim is to ascertain the role of serum-pleural fluid albumin gradient and pleural fluid alkaline phosphatase in segregating the exudative and transudative pleural effusions and to compare with the gold standard Light's criteria. **Methods:** Thirty four patients with pleural effusion admitted over a period of one and half years were studied. Light's criteria, serum-pleural fluid albumin gradient and pleural fluid alkaline phosphatase were used to separate transudates and exudates. **Results:** According to the Light's criteria, there were 23 exudates and 11 transudates. Out of the 23 exudates, 5 exudates were found to be transudates and among the 11 transudates, 5 cases were found to be exudates by serum-pleural fluid albumin gradient (cut off value 1.2g/dL). With pleural fluid alkaline phosphatase 7 cases were classified as exudate and 27 cases were classified as transudates. All the 7 exudates were correctly classified with respect to the Light's criteria. Pleural fluid alkaline phosphatase is 54% sensitive and 78% specific with respect to the Light's criteria for differentiating exudative and transudative effusions. At the cut off value of 75 U/L, the pleural fluid alkaline phosphatase is 34% sensitive but 100% specific for classifying exudates. **Conclusion:** In conclusion, though light's criteria is mostly recommended, coalesced use of other criteria like albumin gradient and alkaline phosphatase improve the diagnostic confidence in distinguishing exudates and transudates.

Key Words: Albumin gradient, alkaline phosphatase, Light's criteria, pleural effusion.

INTRODUCTION

Pleural effusions are quite common and are of highly manifold etiologies. The excessive collection of fluid is accumulated in the pleural space, which lies between the parietal pleura and visceral pleura. Tuberculosis, malignancy, renal and cardiac failures are the main etiologies for the pleural effusion which require immediate diagnosis and treatment. The relative annual incidence of pleural effusion globally is estimated to be 320 per million people in industrialized countries.[1] Normally, every one hour 10 µl per kgof fluid enters constantly to pleural space from the capillaries in the parietal pleura. However, almost all the fluid drains by lymphatic system.[2]

The excess pleural liquid accumulates due to excessive production or decreased lymphatic drainage. Distinguishing between the transudate and exudate is necessary to determine the origin (local or systemic) of effusion. The primary reason to differentiate transudate and exudate is that if the fluid is transudate no further diagnostic procedure is necessary. Contrary to this, advanced diagnostic effort is required if the fluid is exudate. The criteria proposed by Light et al., in 1972,[3] remains robust in differentiating exudates from transudates. With Light's criteria, a pleural effusion is exudate if one or more of the following criteria is met and transudate if none of the criteria is present. i) Ratio of pleural fluid protein to serum protein greater than 0.5. ii) Ratio of pleural fluid LDH (Lactate dehydrogenase) to serum LDH greater than 0.6. iii) Pleural fluid LDH greater than 2/3rd the upper limit of normal for the serum LDH (usually cut off level for pleural fluid is 200 IU/L).

Here, the protein expresses the permeability of vessels where the fluid was formed and the lactate dehydrogenaseexpresses the level of inflammation in the pleural space.[4] Light's criteria is more accurate in identifying exudates.However,it may confound about 25% of transudative effusion cases as exudatives.Dharet al.,[5] established that whenthe serum - effusion albumin gradient and Light's criteria were compared, Light's criteria correctly identified all the exudates but misdiagnosed 2 of 5 transudates (cases of heart failure). Owing to this reason, several other parameters have also been recommended todiscriminate transudates and exudates viz.difference in cut offvalue of 1.2 g/dl of serum-pleural fluid albumin gradient,[6] pleural fluid to serum bilirubin ratio of 0.6,[7] pleural fluid cholesterol cut off value 60mg/dl,[8] soluble leukocyte selectin,[9] uric acid,[10] cytokines,[11,12] difference in cut off level of 0.23 of pleural fluid to serum cholinesterase ratio,[13] pleural fluid adenosine deaminase level,[14] alkaline phosphatase value.[15] Guptaet al.,[16] demonstrated the usefulness of plasma-pleural effusion albumin gradient (PPEAG) parameter to differentiate between exudates and transudates, especially in the cases misclassified by Light's criteria. Hence, this prospective study was designed to determinethe role of serum-pleural fluid albumin gradient and pleural fluid alkaline phosphatase in differentiating the exudative and transudative pleural effusions and to compare with the gold standard Light's criteria.

MATERIALS AND METHODS

This Institutional based prospective observational study was conducted between August 2007 and January 2009 at the Department of Pulmonology,MediCiti hospital, Hyderabad. The study protocol was approved by Institutional Ethics committee of the MediCiti Institute of Medical Sciences. All the patients attending the pulmonology department with history and clinical examination suggestive of pleural effusions were included. Patients with Frank empyema,hemothorax, post pleurodesis and chylothorax were excluded from the study.

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Table: 1 Distribution of patients with (according to, based on) Co-morbidites

Co-morbidities	Number of patients
Diabetes	14(41.11%)
Hypertension	14(41.11%)
Asthma	3(8.82%)
COPD	0(0%)
PTB	3(8.82%)
Renal disease	4(11.76%)
Connective tissue disease	0(0%)
Malignancy	0(0%)
Hypothyroidism	1(2.94%)
Coronary artery disease	3(8.82%)

Table: 2 Distribution of cases according to the sex and etiology

Etiology	Males n (%)	Females n (%)	Total n (%)
Pneumonic	9 (26.47)	3(8.82)	12 (35.3)
Tuberculosis	6 (17.64)	2 (5.88)	8 (23.52)
Malignancy	1(2.94)	5 (14.70)	6 (17.64)
CKD/Renal Failure	5(14.70)	0 (0)	5 (14.70)
CCF	2 (5.88)	1 (2.94)	3 (8.82)
TOTAL	23 (67.64)	11 (32.35)	34 (100)

Table: 3 Distribution of cases according to the etiology and Light's criteria

Group	Etiology (n)	Serum protein g/dl mean	Pl fluid protein g/dl mean	Fluid /serum protein ratio mean	Serum LDH U/L mean	Fluid LDH U/L mean	Fluid/ Serum LDH ratio mean
Exudate	Tuberculosis(8)	6.6	4.41	0.66	207.62	571.25	3.46
	Parapneumonic(9)	6.52	4.83	0.72	237.77	1030.2	5.84
	Malignancy(6)	6.91	5.43	0.78	272.83	940.16	4.71
AVG		6.67	4.89	0.72	239.40	847.20	4.67
Transudate	CCF(3)	5.50	1.53	0.28	383	109.66	0.27
	Synpneumonic (3)	6.33	1.9	0.30	498	120.33	0.25
	CKD/Renal failure(5)	6.06	1.88	0.29	353.2	127.4	0.36
AVG		5.96	1.77	0.29	411.4	119.13	0.29

Table: 4 Distribution of cases according to serum and pleural fluid albumin gradient

Group	Etiology (n)	Serum albumin mean (gm/dl)	Fluid albumin mean (gm/dl)	Serum-fluid albumin gradient mean (gm/dl)
Exudate	Tuberculosis (5)	2.46	2.2	0.26
	Parapneumonic (9)	2.21	1.77	0.43
	Malignancy (6)	2.68	2.75	-0.4
	CKD/Renal failure (2)	1.95	0.85	0.6
	CCF (1)	1.8	0.8	1
Avg		2.22	1.67	0.37
Transudate	CCF(2)	3.25	0.85	2.4
	Tuberculosis (3)	3.8	1.6	2.2
	Synpneumonic (3)	2.8	0.7	2.12
	CKD/Renal failure (3)	2.53	0.96	1.56
Avg		3.09	1.02	2.07

Table: 5 Distribution of cases according to the etiology and pleural fluid alkaline phosphatase

Group	Etiology (n)	Fluid ALP U/L mean
Exudates	Parapneumonic (3)	105.66
	Malignancy (4)	200.75
Avg		153.2
Transudate	CCF (3)	31.66
	Tuberculosis (8)	54.37
	Synpneumonic (9)	41.88
	CKD/Renal failure (5)	27.4
	Malignancy (2)	27
Avg		36.46

Table: 6 Comparison of sensitivity and specificity of S-P albumin gradient and alkaline phosphatase with respect to Light's criteria

Groups	S-P albumin gradient	Alkaline phosphatase
Transudates	11	27
Exudates	23	7
Total	34	34
Sensitivity	54%	34%
Specificity	78%	100%
PPV	54%	100%
NPV	78%	30%

A total of 34 study subjects were enrolled and were interviewed with detail history and undergone complete general and systemic examination. Written informed consent was obtained from each patientand investigated according to the preset proforma.

Besides, routine investigations of hemogram with ESR and serum biochemistry, all the patients were subjected to the chest radiography (PA view),sputum gram stain, sputum AFB stain, pleural fluid analysis for total count and differential count, pleural fluid chemistry, pleural fluid AFB stain, pleural fluid gram stain and pleural fluid cytology.

Pleural fluid and venous blood were simultaneously drawn to investigate biochemical parameters such as protein, albumin, LDH, alkaline phosphatase and others. Biochemical analysis was done by multichannel analyzer (Siemen's DADE Behring Dimension Xpand Plus) after thorough calibration. Total count and differential count of pleural fluid were done manually. Pleural fluid pH estimation was done on arterial blood gas machine.Pleural biopsy was done by using Abram's pleural biopsy needle in appropriate patients. Bronchoscopy was done in and subjected to biopsy wherever needed and evaluated for histopathological examination. Complete hemogram was done on Siemen's Diana-5 Evolution cell counter.

RESULTS

Thirty four patients were included in the study. There were 23 male (67.64%) and 11 female (32.36%) in the study group. The mean age of patients was 55.64±17.081. The majority (47.1%) of study subjects were aged > 60 years, 41.17% of patientswere in age group 30-60, and 11.70% were in the age group ≤30. Out of 34 subjects, 12 patients had no co-morbidities and 22 patients had one or more than one co-morbidities. Patients with co-morbidities are as follows, 41.11% each of diabetes and hypertension, 11.76% patients of renal disease, 8.82% each of asthma, pulmonary tuberculosis and coronary artery disease, 2.94% patients with hypothyroidism (Table 1). At the time of study, majority (58.82%) of the study subjects had normal BMI, underweight was 2.94%, and overweight was 38.23%.

Based on the etiology of the total patients, 35.3% (male-26.47%: female-8.82%) had paraneumonic effusion, 23.52% (male-17.64%: female-5.88%) had tuberculosis, 17.64% (male-2.94%: female-14.70%) had malignancy, 14.70% (male-14.70%: female-0%) had renal failure and 8.82% (male-5.88%: female-2.94%) had congestive cardiac failure (Table 2).

In this observational study of 34 patients, according to gold standard light's criteria, 23 patients were classified as exudates and 11 were transudates (Table 3). The exudates have mean serum protein, pleural protein of 6.67g/dl and 4.89g/dl respectively. The mean fluid to serum ratio was found out to be 0.72. The mean values of serum LDH, fluid LDH and fluid to serum LDH ratio were 239.40U/L, 847.20U/L and 4.67U/L respectively. The transudates have mean serum protein, pleural protein and fluid to serum ratio of 5.96g/dl,1.77 g/dl and 0.29g/dl respectively. The mean values of serum LDH, fluid LDH and fluid to serum LDH ratio were 411.4U/L,119.13U/L and 0.29 respectively.

Based on the work done by Roth et al, patients were classified as exudates and transudates according to the cut off value 1.2g/dl of serum-pleural fluid albumin gradient. Samples having serum-pleural fluid albumin gradient ≤1.2g/dl were classified as exudates and >1.2g/dl were classified as transudates.

In our study, according to the above criteria, 23 pleural effusions were exudates and 11 pleural effusions were transudates (Table 4).Theexudates hadmean values of serum albumin, pleural fluid albumin and serum-pleural fluid albumin gradient of 2.22 g/dl, 1.67 g/dl and 0.37 g/dl respectively. The transudate group had mean serum albumin, mean pleural fluid albumin of 3.09 g/dl and 1.02 g/dl respectively. The mean serum-pleural fluid albumin gradient was 2.07 g/dl.

Thirty foursubjects of pleural effusion in our study were again classified into exudates and transudates by absolute value of pleural fluid alkaline phosphatase with a cut off value of 75 U/L. As 75 U/L was used as cut off value in most of the standard studies, 7 patients were classified as exudates and 27 patients as transudates. The 7 exudates had mean pleural fluid alkaline phosphatase of 153.2 U/L. 27 transudates had mean pleural fluid alkaline phosphatase of 36.46 U/L. The results were shown in table 5.

As shown in table 6, using the cut off value of 1.2 g/dl for differentiating exudative and transudative effusions the sensitivity, specificity, positive predictive value, and negative predictive value of the serum-pleural fluid albumin gradient were 54%, 78%, 54% and 78% respectively. Using the pleural fluid alkaline phosphatase method for classifying the exudative and transudative effusions substantiated the sensitivity, specificity, positive predictive value and negative predictive valuesas 40%, 100%, 100% and 30% respectively.

DISCUSSION

Despite numerous studies, physiology of pleural effusion formation and absorption is still a matter of debate. In most of the conditions, Light's criteria are still widely used to distinguish exudates and transudates. This prospective study compared the serum-pleural fluid albumin gradient and pleural fluid alkaline phosphatasewith the Light's criteria to discriminate transudates and exudates.In the current study, Light's criteria was considered as the gold standard against the other two parameters. The gold standard referred to have 100% sensitivity and 100% specificity (assuming it does not falsely identify) in diagnosing the disease.

In our study, male to female ratio was 2.1:1. Mean age of the patients was 55.64±17.08. Similar studies have also reported the age distribution, 47% of the patients were between 41-60 years with 63 males and 38 females [14], out of 59 patients, 37 were male and 22 were female with mean age of 61years (age range=19 to 84) [6].

In our study the commonest cause of exudative effusion was parapneumonic effusions 35.29% followed by tuberculosis 23.52%, and malignancy 17.64%, and the commonest cause transudates was renal failure 14.70% followed by CCF 8.82%.Dharet al., [5] reported in his study that the commonest cause of exudative effusion was tuberculosis 42% and others were neoplasm (22%), parapneumonia (4%), and rheumatoid arthritis (2%). Among the transudative effusions cirrhosis of liver was 12%, heart failure (10%) and nephritic syndrome (8%).

The mean levels of serum protein, pleural fluid protein and the pleural fluid to serum protein ratio in the present study were almost comparable with that observed by the Dharet al [5]. The highest and lowest serum protein levels were 8.5 g/dl, and 4.7 g/dl respectively. The highest pleural fluid protein level of 6.2 g/dl which was seen in case of mesothelioma and lowest pleural fluid protein of 1.2g/dl was seen in 2 cases, one of which has biventricular failure, and the other was suffering from bilateral

bronchopneumonia with acute respiratory distress syndrome (ARDS).

The mean serum LDH levels were lower than those observed by the Dharet al., [5] but the pleural fluid LDH levels were closely comparable in both the studies. The highest pleural fluid LDH of 4320 U/L was seen with a case of parapneumonic effusion and lowest pleural fluid LDH of 48 U/L was seen in a case of biventricular failure. The pleural fluid to serum LDH ratio was considerably higher in our study compared to the study byDharet al[5].

In this present study, the mean serum and pleural fluid albumin levels as well as the serum-pleural fluid albumin gradient were less, compared to those observed by the Dharet al[5]. The highest pleural fluid albumin was 3.9 g/dl in a case of mesothelioma and the lowest pleural fluid albumin was 0.5 g/dl, as observed in two cases, one of which was having biventricular failure as well as hypoalbuminemia, the other had bilateral bronchopneumonia with ARDS and ventilator associated pneumonia (VAP).

Apparently,in our study the sensitivity and specificity for identifying exudates and transudates with albumin gradient were 54% and 78%.A study Roth et al., [6] revealed that the sensitivity and specificity for identifying the exudates with the Light's criteria were 100% and 72% respectively. The corresponding sensitivity, specificity for identifying exudates with the albumin gradient was 95% and 100% respectively with the cutoff of 1.2 g/dl for the albumin gradient. Recently, a study by Bielsaet al.,[17]substantiated the prevalence of mislabelled transudates by light's criteria andrevealed that the sensitivity and specificity of albumin gradient (cut off level 1.2g/dL) parameter were 83% and 62%.

The study done by FusunSahinet al [18]analyzed the diagnostic utility of albumin gradient, alkaline phosphatase, total cholesterol, total bilirubin and uric acid in differentiating pleural exudates from transudates, and shown that the sensitivity and specificity for the serum-effusion albumin gradient were 94% and 100% with cut off of 1.2 g/dl and concluded that Light's criteria remains the best criteria for classifying exudates and transudates.

In another research work by Gupta et al[16], by using the albumin gradient of 1.2 g/dLit was observed that the sensitivity, specificity, PPV and NPV were of 97.9%, 100%, 100% and 92.3% respectively. From this study, they have established that the serum effusion albumin gradient was better than the Light's criteria and inferred that this parameter can be used as supplementary parameter.

In the present study of 34 patients for classifying exudates from transudates by using pleural fluid, only 7 patients were classified as exudate and 27 patients were classified as transudates with mean pleural fluid alkaline phosphatase (ALP) of 153.2 U/L and 36.46 U/L respectively. Out of 7 exudates, 3 patients had parapneumonic effusions and 4 patients had malignancy. Out of the 23 transudates, 3 patients had CCF, 8 patients had tuberculosis, 9 patients had synpneumonic effusions, 5 patients had CKD, remaining 2 were suffering from malignancy.

At the cut of value of 75 U/L for ALP, we have obtained the sensitivity of 34%. i.e., among the 27 transudates by pleural fluid alkaline phosphatase criteria, 11 were correctly classified as transudates, but the remaining 16 transudates were exudates by applying Light's criteria. Furthermore, specificity value was found to be 100% i.e., the samples which were classified as transudates according to light's criteria remained as transudates even after the classification based on ALP. In a similar study by Mushtaqet al.,(15) the sensitivity for the diagnosis of exudates was 100% and specificity was 85.71%; PPV and NPV were 58.62% and 100% respectively. FusunSahinet al., [18]by using the cut off value of 42 U/L for ALP found that the sensitivity and specificity were 77% and 95% respectively.Both the above studies have concluded that the alkaline phosphatase as an efficacious parameter to differentiate exudates from transudates.

CONCLUSION

Though earlier studies established the Light's criteria as “gold standard” for segregating transudative and exudative effusions, often misclassifications occur due to the combination of multiple parameters in parallel manner under a single test. Due to various etiological factors like modernization (life style, food habits), emergence of various diseases, etc. much deviation from Light's criteria is being observed in differentiating transudates and exudates. Hence, it is mandatory to revisit the light's criteria by using other criteria like serum albumin gradient and alkaline phosphatase, which demonstrated the usefulness in classifying the exudates and transudates as complementary criteria. This strategy improves diagnostic confidence and benefits the management of exudative pleural effusion.

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